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NDA 020386

FIRM:

MERCK

1 OF 10

TRADE NAME:

COZAAR (LOSARTAN POTASSIUM) 25/50 MG TAB

GENERIC NAME:

LOSARTAN POTASSIUM

Summary Basis of Approval
Cover Form

~~Appl # 020386~~

~~Firm: MERCK~~

Reviewing Div: 110

~~Trade Name: COZAAR (LOSARTAN POTASSIUM) 25/50 MG TAB~~

~~Generic Name:~~

LOSARTAN POTASSIUM

Approval Letter: Y

Statistician Review: Y

SBA Form: N

Bio/Dissolution Review: Y

Final Printed Labeling: Y

Microbiologist Review: N

Medical Officer Review: Y

NAG/NRC Review: N

Chemist Review: Y

Pharmacologist Review: Y

Federal Register Notice: N

Completion Date: 13-MAR-96

APPROVAL

LETTER



Food and Drug Administration
Rockville MD 20857

NDA 20-386

APR 14 1995

Merck Research Laboratories
Attention: Larry P. Bell, M.D.
Sumneytown Pike
West Point, PA 19486

Dear Dr. Bell:

Please refer to your December 3, 1993 new drug application submitted on December 3, 1993 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cozaar (losartan potassium) 25 and 50 mg Tablets.

We acknowledge receipt of your amendments dated March 1, 7, 13, 14, 17 and 22, and April 5, 7 and 14, 1995.

The information contained in your amendment dated February 14, 1995 is currently under review. We note that you have agreed to submit a supplemental NDA to address this issue.

This new drug application provides for the use of Cozaar (losartan potassium) Tablets in the treatment of hypertension.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit fifteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-386. Approval of this labeling by FDA is not required before it is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any deficiencies that may occur.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Kathleen Bongiovanni
Consumer Safety Officer
(301) 594-5300

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

cc:

Original NDA

HF-2/MedWatch (with labeling)

HFC-130/JAllen

HFD-2/MLumpkin

HFD-5/Hassall (If user fee application)

HFD-80 (with labeling)

HFD-100 (with labeling)

HFD-110

HFD-110/CSO

HFD-240 (with labeling)

HFD-613 (with labeling)

HFD-735/DBarash (with labeling)

HFD-110/KBongiovanni

sb/4/12/95; 4/13/95; 4/14/95

R/D: RMittal

RWolters/4/13/95

GJagadeesh

AProakis/4/13/95

CResnick/4/13/95

APPROVAL

CSO OVERVIEW OF NDA REVIEW PACKAGE
NDA 20-386 Cozaar (losartan potassium) Tablets
Merck Research Laboratories

1S

CSO: Kathleen Bongiovanni

Chemistry

Primary reviewer: Carl Berninger, Ph.D.; Ram Mittal, Ph.D.

Issues: Environmental Assessment: response submitted 3-13-95. Under review (Nancy Sager)

EER: Acceptable 3-7-95.

Methods Validation: on-going

Labeling: Merck has sent in a counterproposal for labeling 3-14-95.

Conclusion: approvable.

Pharmacology

Primary reviewer: Anthony Proakis, Ph.D., and G. Jagadeesh, Ph.D.

Labeling: see pgs 165-6 of 12-7-94 review.

Conclusion: approvable. Labeling changes included in Dr. Lipicky's mark-up.

Biostatistics (pre-clinical)

Primary reviewer: Mohammad Rahman, Ph.D.

Conclusion: approvable.

Medical

Primary reviewer: Charles Ganley, M.D.

Conclusion: approvable. Labeling changes included in Dr. Lipicky's mark-up.

Biostatistics (clinical)

Primary reviewer: Walid Nuri, Ph.D

Conclusion: approvable.

Biopharm

Primary reviewer: Emmanuel Fadiran, Ph.D.

Conclusion: approvable. Labeling changes included in Dr. Lipicky's mark-up.

Safety Updates: dated 4-4-94 and 1-31-95.

Labeling: See Dr. Lipicky's marked-up draft (in package)

Patent info: included in package

Department Certification: included in package

Labeling & Nomenclature Committee: review Feb 9, 1994. Some minor concerns.

Overview revised 3-23-95

ALE

LTR



Food and Drug Administration
Rockville MD 20857

NDA 20-386

MAR 2 1995

Merck Research Laboratories
Attention: Larry P. Bell, M.D.
Sumneytown Pike
West Point, PA 19486

Dear Dr. Bell:

Please refer to your December 3, 1993 new drug application submitted on December 3, 1993 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cozaar (losartan potassium) 25 and 50 mg Tablets.

We acknowledge receipt of your amendments and correspondence dated December 10, 1994; January 6 and 31, February 9, 23 and 28, March 25, April 4, 11, 12, 14 and 15, May 2, 4 (two), 18 and 20, June 17, 29 and 30, July 15, 21, 25 (two), 26 (two), and 28 (two), August 12, 17, 18, 19 and 26, September 1, 13 and 19, October 3, 5 (two), 7, and 21 (two), and December 8 and 21, 1994; and January 11, 25, 27 and 31 and February 7, 8, 9, 10, 14 (two), 16 and 23, 1995.

We have completed the review of this application as submitted with draft labeling. Before the application may be approved, however, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed marked-up draft. If additional information relating to the safety or effectiveness of this drug becomes available, revision of the FPL may be required.

Please submit fifteen copies of the printed labels and other labeling, ten of which are individually mounted on heavy weight paper or similar material.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Cardio-Renal Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

We remind you that a satisfactory inspection of your manufacturing facilities for conformance with current good manufacturing practices (CGMP) is required before this application may be approved.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any deficiencies that may occur.

We note that you have responded to our letter of December 9, 1994 that asked for additional information on the Environmental Assessment portion of this application with two amendments, dated January 30 and February 8, 1995. We have completed our review and have the following requests:

The following information should be provided. It is not necessary to provide a complete update of your confidential and non-confidential environmental assessments as the requested information may be submitted in an addendum to your environmental assessments dated February 1, 1995. The two addenda should be titled:

Confidential Addendum to February 1, 1995
Environmental Assessment for Cozaar

Non-Confidential Addendum to February 1, 1995
Environmental Assessment for Cozaar

The Non-Confidential Addendum should be self explanatory since it will be attached directly to your non-confidential environmental assessment of February 1, 1995 and made available for public inspection once the application is approved.

1. The following information should be included in the non-confidential EA Addendum:
 - a. The contract packaging sites including specific addresses;
 - b. Information in Appendix 1, sections 1 and 2 (nomenclature and description); and
 - c. Site permit information (Attachment 3).
2. The basis (detailed calculations) for the estimated concentrations from production at the _____ facilities should be provided.
3. The request for information regarding the methods used in the *Daphnia magna* and *Pimephales promelas* studies was not adequately addressed. The testing information provided does not, for example, report the no observed effects level, if observed, the length and weight of the fathead minnows, etc. Please review the reporting requirements for these tests which are located in either 40 CFR § 797, parts 1300 and 1400 or Environmental Assessment Technical Assistance Documents 4.08 and 4.11 and provide the missing information.

Please change the dissolution specifications from "not less than _____ of the labeled amount of losartan potassium dissolved in 45 minutes" to "not less than _____ of the labeled amount of losartan potassium dissolved in 30 minutes."

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

Under section 736(a)(1)(B)(ii) of the Prescription Drug User Fee Act of 1992, this letter triggers the remaining 50% of the fee assessed for this application. You will receive an invoice for the amount due within the next month. Payment will be due within 30 days of the date of the invoice.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Ms. Kathleen Bongiovanni
Consumer Safety Officer
Telephone: (301) 594-5300

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Draft Labeling

cc:

Original NDA

HF-2/Medwatch (with draft labelling)

HFC-130/JAllen

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HFD-5/THassall (If user fee application)

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HFD-110/CSO

HFD-240 (with draft labelling)

HFD-638 (with draft labelling)

HFD-735/DBarash (with draft labelling)

HFD-110/KBongiovanni

sb/1/31/95;2/8/95;2/14/95

R/D: RMittal/2/9/95

RWolters/2/9/95

AProakis

GJagadeesh

CResnick/2/10/95

EFadrihan/2/10/95

WNuri/2/13/95

CGanley/2/13/95

NMorgenstern/2/13/95

APPROVABLE

COZAAR
(LOSARTAN POTASSIUM TABLETS)
USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death in the developing fetus. When pregnancy is detected, COZAAR should be discontinued as soon as possible. See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

COZAAR* (losartan potassium), the first of a new class of antihypertensives, is an angiotensin II receptor (type AT1) antagonist. Losartan potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[*p*-(*o*-1 *H*-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt.

Its empirical formula is $C_{22}H_{22}ClKN_6O$, and its structural formula is:

Losartan potassium is a white to off-white free-flowing crystalline powder with a molecular weight of 461.01. It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone. Oxidation of the 5-hydroxymethyl group on the imidazole ring results in the active metabolite of losartan.

COZAAR is available for oral administration containing either 25 mg or 50 mg of losartan potassium and the following inactive ingredients: microcrystalline cellulose, lactose hydrous, pregelatinized starch, magnesium stearate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, titanium dioxide, D&C yellow No. 10 aluminum lake and FD&C blue No. 2 aluminum lake.

COZAAR 25 mg and 50 mg contain potassium in the following amounts: 2.12 mg (0.054 mEq) and 4.24 mg (0.108 mEq), respectively.

CLINICAL PHARMACOLOGY

Mechanism of Action

Angiotensin II [formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase I)], is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system and an important component in the pathophysiology of renin-related hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting

effects of angiotensin II by interfering with the binding of angiotensin II to the AT₁ receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland). There is also an AT₂ receptor found in many tissues but it is not known to be associated cardiovascular homeostasis. Both losartan and its principal active metabolite do not exhibit any partial agonist activity of the AT₁ receptor and have much greater affinity (about 1000-fold for the AT₁ receptor than for the AT₂ receptor). *In-vitro* binding studies indicate that losartan is a reversible, competitive inhibitor of the AT₁ receptor. The active metabolite is 10 to 40 times more potent by weight than losartan and appears to be a reversible, non-competitive inhibitor of the AT₁ receptor.

Neither losartan nor its active metabolite inhibits ACE (kininase I), the enzyme that converts angiotensin I to angiotensin II, and degrades bradykinin, other hormone receptors, or ion channels known to be important in cardiovascular regulation.

Pharmacokinetics

Losartan is an orally active agent that undergoes substantial first pass metabolism by cytochrome P-450 enzymes. It is converted, in part, to an active carboxylic acid metabolite that is responsible for most of the angiotensin II receptor antagonism that follows losartan treatment. The terminal half life of losartan is about 1-2 hours and of the metabolite is about 6-9 hours. The pharmacokinetics of losartan and its metabolite are generally dose-proportional and constant over time and neither the drug nor its metabolite accumulate on replicated dosing.

Following oral administration, losartan is well absorbed (based on absorption of radiolabelled losartan) and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and several inactive metabolites. The absolute bioavailability of losartan is approximately 33%. Losartan's low bioavailability is due to its high presystemic first pass metabolism. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours respectively. Maximum plasma concentrations of losartan and its metabolite are approximately equal, but because of the longer half life, the exposure (AUC) of the metabolite is about 5 times as great as that of losartan. A meal slows absorption of losartan and decreases its C_{max} but has only minor effects on losartan AUC or on the AUC of the metabolite (about 10% decreased).

Both losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2% respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed. Following oral and intravenous administration of ¹⁴C-labeled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and its active metabolite. *In vitro* studies indicate that cytochrome P450C9 and 3A4 are involved in the biotransformation of losartan to its

metabolites. Minimal conversion of losartan to the active metabolite (less than 1% of the dose compared to 14% of the dose in normal subjects) was seen in about one percent of individuals studied.

The volume of distribution of losartan is about 47 liters and of the active metabolite is about 12 liters. Total plasma clearance of losartan and the active metabolite is about 600 ml/min and 50 ml/min, respectively, with renal clearance of about 75 ml/min and 25 ml/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% excreted in urine as active metabolite. Biliary excretion contributes to the elimination of losartan and its metabolites. Following oral ¹⁴C-labeled losartan, about 35% of radioactivity is recovered in the urine and about 60% in the feces. Following an intravenous dose of ¹⁴C-labeled losartan, about 45% of radioactivity is recovered in the urine and 50% in the feces.

Special Populations

Pediatric

Losartan pharmacokinetics have not been investigated in patients < 18 years of age.

Geriatric and Gender

Losartan Pharmacokinetics have been investigated in the elderly (65-75 years) and in both genders. Renal clearance of losartan is decreased by about 50% in elderly male hypertensives when compared to young healthy males, but clearance of the active metabolite is little altered. The AUC of the metabolite is about 50% greater in elderly men and women than in young males. Plasma concentrations of losartan were about twice as high in female hypertensives as male hypertensives, but concentrations of the active metabolite were similar in males and females.

Race

Pharmacokinetic differences due to race have not been studied.

Renal Insufficiency

Plasma concentrations of losartan are not altered in patients with creatinine clearance above 30 ml/min. Below that clearance, AUCs are increased by about 50% and are doubled in hemodialysis patients. Plasma concentrations of the active metabolite are not significantly altered in patients with renal impairment or in hemodialysis patients. Neither losartan nor its active metabolite can be removed by hemodialysis.

Hepatic Insufficiency

Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were respectively, 5-times and about 1.7-times those in young male volunteers. Compared to normal subjects the volume of distribution of losartan in patients with hepatic insufficiency decreased by about 50% but the oral bioavailability increased by about 100%.

Drug Interactions

Losartan, administered for 12 days, did not affect the pharmacokinetics of a single dose of warfarin. This does not rule out the possibility of a pharmacodynamic interaction of losartan and warfarin and there is no chronic experience with co-administration of the two drugs. Losartan did not affect the pharmacokinetics of oral or intravenous digoxin. Co-administration of losartan and cimetidine led to an increase of about 20% in AUC of losartan but did not affect the pharmacokinetics of its active metabolite. Co-administration of losartan and phenobarbital led to a reduction of about 20% in the AUC of losartan and that of its active metabolite. There is no interaction between losartan and hydrochlorothiazide.

Pharmacodynamics and Clinical Effects

Losartan inhibits the pressor effect of angiotensin II (as well as angiotensin I) infusions. A dose of 100 mg inhibits the pressor effect by about 85% at peak with 25-40% inhibition persisting for 24 hours. Aldosterone plasma concentrations fall. Removal of the negative feedback of angiotensin II causes a rise in plasma renin activity and consequent rise in angiotensin II plasma concentration. Losartan does not affect the response to bradykinin, whereas an ACE inhibitor increased the response to bradykinin. In spite of its effect on aldosterone secretion, very little effect on serum potassium was observed.

Losartan has no effects on glomerular filtration rate, renal plasma flow or filtration fraction. There were no notable effects on systemic prostaglandin concentrations, fasting triglycerides, total cholesterol or HDL-cholesterol or fasting glucose concentrations. There was a clear, but small uricosuric effect leading to a small decrease in serum uric acid (mean decrease < 0.4 mg/dL) during chronic oral administration. [Address possibility of flank pain, renal failure syndrome - suprofen, ticrynafen, etc.]

[NOTE: Plasma concentration data, effects on proteinuria and effects of hemodynamics in heart failure have been left out deliberately, pending further data.]

The antihypertensive effects of Cozaar were demonstrated principally in 4 placebo-controlled 6-12 week trials of dosages from 10 to 150 mg per day in patients with baseline diastolic blood pressures of 95-115. The studies allowed comparisons of two doses (50 and 100 mg) as once daily or twice daily regimens, comparisons of peak and trough effects, and comparisons of response by gender, age, and race. Three studies examined the interaction of losartan and diuretic.

The 4 studies of losartan monotherapy included a total of 1075 patients randomized to several doses of losartan and 334 to placebo. The 10 and 25 mg doses produced some effect at peak (6 hours after dosing) but small and inconsistent trough (24 hour) responses. Doses of 50, 100, and 150 mg once daily gave decreases in blood pressure, compared to placebo, of 5-9.5/4-6 mmHg, with the 150 mg dose giving no greater effect than 50-100 mg. Twice daily dosing at 50-100 mg/day gave consistently larger trough responses, 8.5-9.5/6-6.3 mmHg, than once daily dosing at the same total dose. Peak (6 hour) effects were uniformly larger than trough effects, with the trough to peak ratio for systolic and diastolic responses 45-70% and 60-90% respectively.

[Describe, briefly, the losartan/HCTZ data.]

Analysis of age, gender, and race subgroups of patients showed that men and women, and patients over and under 65, had generally similar responses. Black patients, however, had notably smaller responses, generally less than 50% of the effect in whites, and with no detectable effect in two of the 3 studies where this could be assessed.

The effect of losartan is substantially present within one week but in some studies the maximal effect occurred in 3-6 weeks. In long-term follow-up studies (without placebo control) the effect of losartan appeared to be maintained for up to a year. There is no apparent rebound effect after abrupt withdrawal of losartan. There was essentially no change in average heart rate in losartan-treated patients in controlled trials.

INDICATIONS AND USAGE

COZAAR is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

In considering the use of COZAAR monotherapy, it should be noted that in controlled trials COZAAR had an effect on blood pressure that was less in black patients than in non-blacks, sometimes showing no effect at all, a finding similar to the small effect of angiotensin converting enzyme inhibitors in blacks.

CONTRAINDICATIONS

COZAAR is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS:

Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, COZAAR should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester.

Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of losartan potassium as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, losartan potassium should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Losartan potassium has been shown to produce adverse effects in rat fetuses and neonates, including decreased body weight, delayed physical and behavioral development, mortality and renal toxicity. These findings are attributed to drug exposure in late gestation and during lactation. With the exception of neonatal weight gain (which was affected at doses as low as 10 mg/kg/day), doses associated with these effects exceeded 20 mg/kg/day (approximately twice the maximum recommended human dose of 100 mg on a mg/m² basis). Significant levels of losartan and its active metabolite were shown to be present in rat fetal plasma and rat milk.

Hypotension-Patients on Diuretic Therapy

Patients receiving diuretic therapy or who are salt and volume depleted from other causes can be expected to have a greater antihypertensive effect from any dose of losartan. Therapy with COZAAR should be initiated at no greater than 25 mg in such patients, and patients should be monitored for 4 to 6 hours after the first dose of COZAAR.

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. COZAAR would be expected to behave similarly. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increased in serum creatinine or BUN were observed in 20% of patients. There has been no known use of COZAAR in patients with unilateral or bilateral renal artery stenosis, but a similar effect should be anticipated.

PRECAUTIONS

General

In patients who are intravascularly volume-depleted (e.g., those treated with high-dose diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of COZAAR, or a lower starting dose should be used (see DOSAGE AND ADMINISTRATION).

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with impaired liver function (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY, Pharmacokinetics).

Information for Patients

Pregnancy. Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions

Compounds that have been studied in clinical pharmacokinetic trials include hydrochlorothiazide, digoxin, warfarin, cimetidine and phenobarbital. (See CLINICAL PHARMACOLOGY: Drug Interactions.) Significant inhibitors of cytochrome P4503A4 (ketoconazole, for example) have not been studied clinically but *in vitro* studies of ketoconazole, troleandomycin and gestodene have shown substantial inhibition of formation of the active metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Losartan potassium was not carcinogenic when administered at maximally tolerated dosages to rats and mice for 105 and 92 weeks, respectively. Female rats given the highest dose (270 mg/kg/day) had a slightly higher incidence of pancreatic acinar adenoma. The maximally tolerated dosages (270 mg/kg/day in rats, 200 mg/kg/day in mice) provided systemic exposures for losartan and its pharmacologically active metabolite that were approximately 110- and 90-times (rats) and 30- and 7-times (mice) the exposure of a 50 kg human given 100 mg per day.

Losartan potassium was negative in the microbial mutagenesis and V-79 mammalian cell mutagenesis assays and in the *in vitro* alkaline elution and *in vitro* and *in vivo* chromosomal aberration assays. In addition, the active metabolite showed no evidence of genotoxicity in the microbial mutagenesis, *in vitro* alkaline elution, and *in vitro* chromosomal aberration assays.

Fertility and reproductive performance were not affected in studies with male rats given oral doses of losartan potassium up to approximately 150 mg/kg/day. Doses of 300/200 mg/kg/day in females resulted in significantly ($p \leq 0.05$) fewer corpora lutea/female,

implants/female and live fetuses/female. In the 100 mg/kg/day group there was a slight but significant effect on the number of corpora lutea/female. In nonpregnant rats dosed at 135 mg/kg/day for 7 days, systemic exposure (AUCs) for losartan and its active metabolite were approximately 66 and 26 times the exposure achieved in man at the maximum recommended human daily dosage (100 mg).

Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters).
See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers

It is not known whether losartan is excreted in human milk, but significant levels of losartan and its active metabolite were shown to be present in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Use in the Elderly

Of the total number of patients receiving COZAAR in controlled clinical studies, 391 patients (19%) were 65 years and over, while 37 patients (2%) were 75 years and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

COZAAR has been evaluated for safety in more than 2500 [UPDATE] patients treated for essential hypertension and _____ patients overall. _____ patients were treated for over 6 months and _____ for over one year. In general, treatment with COZAAR was well tolerated. The overall incidence of adverse experiences reported with COZAAR was similar to placebo. In controlled clinical trials, discontinuation of therapy due to clinical adverse experiences was required in 2.3 percent of patients, treated with COZAAR and 3.7% of patients given placebo. Although angioedema was not reported by name, one patient treated with COZAAR was withdrawn from study because of swelling of the lips and eyelids, which returned to normal 5 days after therapy was discontinued.

The following table of adverse events is based on four 6-12 week placebo controlled trials [011, 050, 065, 021] involving over 1000 patients on various doses (10-150 mg) of losartan and over 300 given placebo. All doses of losartan are grouped because none of the adverse events appeared to have a dose-related frequency. The table includes all adverse events, whether or not attributed to the treatment, occurring in at least 0.5% of losartan patients and that were numerically more frequent on losartan than placebo.

Event (by body system)	Losartan n=1075	Placebo n=334
Event 1		
Event 2		
Etc.		

The following adverse events occurred at $\geq 0.5\%$ but were at least as frequent on placebo: headache, asthenia/fatigue, etc.

Adverse events occurred at about the same rates in men and women, older and younger patients, and black and non-black patients.

Lab Findings:

Vital Signs:

In addition to the events in the table above, the following potentially important events were observed at least twice in the (total exposure) patients exposed to losartan in all studies. It cannot be determined whether these events were casually related to losartan.

[List by body system; omit if they are already in the table or in the paragraph that follows the table. Leave out anything not occurring at least twice, anything too vague (pain, thyroid disorder, arrhythmia) or very improbable (cancer early in treatment). Also include brief discussion of the single case of hemolytic anemia and exfoliation of the palms.]

OVERDOSAGE

Significant lethality was observed in mice and rats after oral administration of 1000 mg/kg and 2000 mg/kg, respectively, about 44 and 170 times the maximum recommended human dose on a mg/m² basis.

Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan nor its active metabolite can be removed by hemodialysis.

DOSAGE AND ADMINISTRATION

COZAAR can be administered once or twice daily with total daily doses ranging from 25 to 100 mg. The usual starting dose is between 25 and 50 mg once daily, with 25 mg preferred for patients with possible depletion of intravascular volume because of preceding diuretic therapy (see PRECAUTIONS, General) and patients with a history of hepatic impairment (see PRECAUTIONS, General). The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy.

If the antihypertensive effect measured at trough using once-a-day dosing is inadequate, a twice-a-day regimen may give a more satisfactory response.

HOW SUPPLIED

No. 3612 - Tablets COZAAR, 25 mg, are light green, teardrop-shaped, film-coated tablets with code MRK on one side and 951 on the other. They are supplied as follows:

- NDC 0006-0951-31 unit of use bottles of 30
- NDC 0006-0951-54 unit of use bottles of 90
- NDC 0006-0951-58 unit of use bottles of 100
- NDC 0006-0951-28 unit dose packages of 100
- NDC 0006-0951-82 bottles of 1000.

No. 3613 - Tablets COZAAR, 50 mg, are green, teardrop-shaped, film-coated tablets with code MRK on one side and 952 on the other. They are supplied as follows:

- NDC 0006-0952-31 unit of use bottles of 30
- NDC 0006-0952-54 unit of use bottles of 90
- NDC 0006-0952-58 unit of use bottles of 100
- NDC 0006-0952-28 unit dose packages of 100
- NDC 0006-0952-82 bottles of 1000.

Storage190

Store at temperatures below 30°C (86°F). Keep container tightly closed. Protect from light

Manuf by:

MERCK & CO., INC., West Point, PA 19486, USA

by:

Wilmington, DE 19380, USA

Issued XXXXX

Printed in U.S.A.

** Based on a patient weight of 50 kg.

COZAAR (Losartan Potassium)

DIVISION
DIRECTOR
AND

OFFICE
DIRECTOR
MEMOS

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: MAR 2 1995

FROM: Director, Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: NDA 20-386, Cozaar (losartan potassium)

TO: Director, Office of Drug Evaluation I, HFD-100

We are returning losartan for final signature on the approvable letter. We have incorporated all revisions to the labeling noted on your marked-up draft and memorandum of February 27, 1995 and those discussed at our March 1, 1995 internal meeting into a clean draft.

The approvable letter contains Dr. Vincent's latest environmental assessment deficiencies.

The firm has been informed that some type of phase IV study regarding the effect of 3A4 inhibitors on the effectiveness of losartan may be forthcoming.

Raymond J. Lipicky, M.D.

cc
Orig.
HFD-110
HFD-110/GBuehler
sb/3/1/95

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: FEB 27 1995
FROM: Director, Office of Drug Evaluation I, HFD-100
SUBJECT: Losartan (Cozaar, NDA 20-386)
TO: Dr. Raymond Lipicky, HFD-110

Losartan clearly is an antihypertensive agent with an effect size, over the 50-100 mg range, that is typical of what we have seen with other agents (ACEI's, beta-blockers), net diastolic change of 4-8 mmHg, and 5-9 mmHg systolic. It was pretty similar to enalapril 10-20 where these were studied, although generally a little behind enalapril. Trough/peak rates were variable, 50-90%, showing some drop-off; it is therefore not too surprising that the b.i.d. regimens were better than the same dose o.d. and labeling should make that clear. There is little effect in blacks and it does not seem to be a good monotherapy candidate in blacks.

I have only a few issues to raise:

1. Cough

The "less-cough than ACEIs" is a critical claim and should be a replicated finding. Study 056 is reasonably convincing as far as cough goes but the pooled trials analysis (MOR p. 19) doesn't really show a significant difference (I would have accepted this approach as a second study, I believe). I also believe any comparison should have a valid estimate of antihypertensive effect size; that's important to define implications of any difference. For example, if cough is less but BP effect is also much less (as suggested by 056), then L could be important for people with intolerable cough but might not be a good first choice (or again, it might be if you were willing to add a second drug or switch if effect was inadequate).

2. Interactions/metabolism

It is important to see just what the effect of 3A4 inhibitors is on the effectiveness of losartan. Given 30 x potency of E3174 and at least 4 times greater half life (and steady state plasma peak concentration after 40 mg of 180 ng/ml E3174 vs 30 ng/ml parent), not forming E3174 could lead to lack of effect (just as codeine doesn't work in poor 2D6 metabolizers because they don't form morphine). This should at least be determined post-marketing. The cimetidine results probably give an adequate answer for weak 3A4 antagonists (erythromycin, grapefruit

juice), but not for the antifungals.

3. Trough/Peak

Systolic pressure should "count" too. For potentially pertinent doses, the following table gives these results:

Sup D. Syst/Diast T/P Ratio (%)					
	25	50	100 + Others	150	Enal 20
Study 111	35/23	66/60	44/72	54/49	61/47
Study 050	--	/78	(50-100 mg) /73	--	--
Study 065	84/85	73/87	25 b.i.d. 68/90		

I calculated systolic values from means given in the review. This gives somewhat different values from MOR calculations, which only use people with both peak and trough measurements (p. 42, 65 of MOR). Despite the somewhat better b.i.d. results in study 065, the trough/peak ratio is not really higher for the b.i.d., as one might have expected. All in all, these results are not so bad.

4. Biopharm

I am puzzled by the absolute bio figure of 30%. If I understand study 022, where the absolute bio of losartan was 23%, the absolute bio of E3174 was about 100%. That suggest to me that considerable E3174 is formed and absorbed in the gut.

Perhaps, however, I don't understand the calculations/normalization. This is how I reach the above conclusion. Figures given are:

	L		E 3174	
	100 mg Tablet	30 mg IV	100 mg Tablet	30 mg IV
Cmax	486.2	--	584	112.5
AUC	722.4	925.6	3561	1066

Cmax and AUC are said to be normalized to nominal doses of 100 mg and 30 mg but those were the doses given, so I don't follow this. If you take 30% of the L AUC (216.7), which is "normalizing" to a 30 mg dose, 216.7 is 23% of 925.6, the calculated absolute bioavailability. A similar

procedure for E3174 would give 30% of AUC (.3 x 3561) or 1068, which is almost identical to the AUC for the metabolite after IV, suggesting an absolute bioavailability of about 100%. As the bioavailability of L itself is considerably less than 100%, this would imply gut metabolism to E3174 and absorption of E 3174. What's wrong with what I did?

5. Labeling

I worked from the latest Division mark-up, noting some of Merck's proposals as well. Apart from what is obvious on the text:

- a. I presume the 2nd/3rd trimester warning is to be boxed.
- b. Pharmacokinetics needs a short introduction. How's this:

Pharmacokinetics

Losartan is an orally active agent that undergoes substantial first pass metabolism by cytochrome P-450 enzymes. It is converted, in part, to an active carboxylic acid metabolite that is responsible for most of the angiotensin II receptor antagonism that follows losartan treatment. The terminal half life of losartan is about 1-2 hours and of the metabolite is about 6-9 hours. The pharmacokinetics of losartan and its metabolite are generally dose-proportional and constant over time and neither the drug nor its metabolite accumulate on replicated dosing.

- c. Labeling says that E-3417 is, by binding studies, 20-40 x as potent as L (p. 2, paragraph 2) and 5-10 x as potent (p. 2, paragraph 6). We will need to decide.
- d. I have substantially rewritten PK. The ADME format is not very useful (it caused you to omit the half-life, for example) and forces inclusion of lots of not too helpful stuff. See what you think.
- e. I have a suggested revision of the clinical Studies section.

The antihypertensive effects of COZAAR were demonstrated principally in 4 placebo-controlled 6-12 week trials of dosages from 10 to 150 mg per day in patients with baseline diastolic blood pressures of 95-115. The studies allowed comparisons of two doses (50 and 100 mg) as once daily or twice daily regimens, comparisons of peak and trough effects, and comparisons of response by gender, age, and race. _____ studies examined the interaction of losartan and diuretic.

The 4 studies of losartan monotherapy included a total of 1075 patients randomized to several doses of losartan and 334 to placebo. The 10 and 25 mg doses produced some effect at peak (6 hours after dosing) but small and inconsistent trough (24 hour) responses. Doses of 50, 100, and 150 mg once daily gave decreases in blood pressure, compared to placebo, of 5-9.5/4-6 mmHg, with the 150 mg dose giving no greater effect than 50-100 mg. Twice daily dosing at 50-100 mg/day gave consistently larger trough responses, 8.5-9.5/6-6.3 mmHg, than once daily dosing at the same total dose. Peak (6 hour) effects were uniformly larger than trough effects, with the trough to peak ratio for systolic and diastolic responses 45-70% and 60-90%, respectively, [I have omitted the blood pressure comparison data for the present. I would consider putting in the comparative data, but probably if any goes in, at all goes in, as you have done in the draft, although it would be possible to include only the enalapril comparison, which is probably best studied. Most of the other studies are really too small to merit inclusion.]

[Describe, briefly, the losartan/HCTZ data]

Analysis of age, gender, and race subgroups of patients showed that men and women, and patients over and under 65, had generally similar responses. Black patients, however, had notably smaller responses, generally less than 50% of the effect in whites, and with no detectable effect in two of the 3 studies where this could be assessed.

The effect of losartan is substantially present within one week but in some studies the maximal effect occurred in 3-6 weeks. In long-term follow-up studies (without placebo control) the effect of losartan appeared to be maintained for up to a year. There is no apparent rebound effect after abrupt withdrawal of losartan. The average change in heart rate in controlled trials was _____.

- f. Is the warning on Impaired Renal Function based on losartan data or carried over from ACEI's? If the latter, it should say so; I've assumed this was the case and changed it.
- g. The effects of major 3A4 inhibitors should be studied. You would expect little or no active metabolite and increased losartan parent in the presence of, say, ketoconazole.
- h. Adverse reactions (version, starting on p. 9)

The following table of adverse events is based on four 6-12

week placebo controlled trials [011, 050, 065, 021] involving over 1000 patients on various doses (10-150 mg) of losartan and over 300 given placebo (this is similar to Dr. Ganley's table on p. 13, but I see no reason not to include study 021 also). All doses of losartan are grouped because none of the adverse events appeared to have a dose-related frequency. The table includes all adverse events, whether or not attributed to the treatment, occurring in at least 0.5% of losartan patients and that were numerically more frequent on losartan than placebo.

Event (by body system)	Losartan n=1075	Placebo n=334
Event 1		
Event 2		
Etc.		

The following adverse events occurred at $\geq 0.5\%$ but were at least as frequent on placebo: headache, asthenia/fatigue, etc.

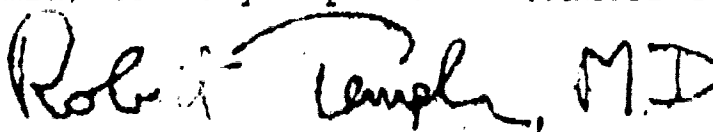
Adverse events occurred at about the same rates in men and women, older and younger patients, and black and non-black patients.

Lab findings:

Vital Signs:

In addition to the events in the table above, the following potentially important events were observed at least twice in the (total exposure) patients exposed to losartan in all studies. It cannot be determined whether these events were causally related to losartan.

[List by body system; omit if they are already in the table or in the paragraph that follows the table. Leave out anything not occurring at least twice, anything too vague (pain, thyroid disorder, arrhythmia) or very improbable (cancer early in treatment).]



Robert Temple, M.D.

Bonagiovanni

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION Public Health Service
Division of Cardio-Renal Drug Products

Memorandum

DATE : ~~MAR 2 1995~~ Feb 15, 1995

FROM : Director, Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: Approval (approvable) of NDA 20-386, Cozaar (losartan potassium) Tablets,
Merck Research Laboratories

TO : Director, Office of Drug Evaluation I, HFD-100

Introduction

Losartan is the first of a new class of angiotensin receptor blockers that has been developed, initially for use as an antihypertensive therapy. The NDA, in addition to acute and chronic animal toxicology, manufacturing and controls, environmental assessment and patient information, contained the results of 26 clinical pharmacology studies, 5 active-control trials, 9 open-label studies, 2 studies in patients with congestive heart failure and 6 placebo-controlled trials of up to 12 weeks in duration. The initial submission contained data obtained from 3628 losartan-treated patients and periodic safety updates have increased that number to a final (as of 6/30/94) number to a total of 4,753 losartan-treated patients. This is among the largest data bases I have seen (if not the largest) from the point of view of total exposure and contains a wealth of information.

In addition to the many controlled trials of as long as three months duration, the dose of losartan was varied over a 15-fold range (10 to 150 mg), it was studied in both once-a-day and twice-a-day regimens, and black and white patients in 2 trials were stratified by race so a clean analysis of effect by race could be performed. There was even one trial where not only was there stratification by race but also by severity of hypertension. There is no question that losartan is an antihypertensive drug. It is antihypertensive in both once-a-day and twice-a-day regimens, its safety profile is as reasonable as any we have seen and all-in-all, it is not a very interesting matter. Consequently, even though this is a new chemical entity, considering the work load of the Cardio-Renal Drugs Advisory Committee and the timing of its regular meetings, in order to meet user fee deadlines and conform to project management goals, I have elected not to take this to the Advisory Committee. There are more important issues for them to devote their time to.

The reviews in the attached documentation are complete, are comprehensive and well written. Therefore, in this transmittal memorandum (and secondary review) I will only touch upon highlights and can offer no new insights.

Major Placebo Controlled Trials

All of the placebo-controlled trials were randomized, parallel-group, double-blind trials where casual cuff blood pressure (except for the ABPM trial; study 021) was the principal measurement. Blood pressure was measured at trough (before the next dose was taken) and sometimes at peak (e.g., sometime arbitrarily defined) also. The crude features are summarized in the following table. The Number of Patients column is listed as Number of Patients Randomized/Number of patients completing the trial.

<u>Trial Number</u>	<u>Duration Blinded</u>	<u>Number Patients</u>	<u>Major Endpoints</u>	<u>Special Features</u>
005	5 days	100/96	Diastolic Blood Pressure	Withdrawal Blood Pressures, All White
011	8 Weeks	576/521	10,25, 50, 100, 150, Enal	Stratified on basis of race
050	12 Weeks	366/322	50, 50 to 100	Peak and Trough, Race Stratified
065	12 Weeks	428/365	bid vs qd	Stratified by race
021	6 Weeks	122/91	bid vs qd	ABPM

The overall results, trough blood pressures, as a function of dose are shown in Figures 1 and 2 (attached). The lines connecting the points connect results obtained within the same trial.

All decreases in diastolic or systolic blood pressure were statistically significantly different from placebo (p values ranging from 0.024 to <0.001) except for the 25 mg, once-a-day dose in study 011 for either systolic or diastolic blood pressure. It is reasonably clear that the trough blood pressure response is a function of dose, that for a given dose (e.g., 25 or 50 mg) the response to bid is greater than qd (even though within each individual trial there was no statistically significant difference between qd and bid (with reasonable sample sizes, about 30 for study 021 and about 80 for study 065), and that both systolic and diastolic blood pressures are affected by treatment.

The shape of the curve that relates change of trough blood pressure to dose is not so clear. If one considers only the results of study 011, a 7-arm, parallel-group trial (placebo and 5 doses losartan (and enalapril, not shown)), the plateau occurs between 50 and 100 mg, when administered once-a-day. Study 021, also a parallel-group trial, shows that there is still a dose response going from 50 to 100 mg once-a-day. Although study 050 did not show an increasing effect going from 50 to 100 mg, the group that went from 50 to 100 mg got to 100 by titration if 50 did not change blood pressure. In sum, it appears to me that the apparent plateau from 50 onward is only apparent and not real. Indeed the logistic model (Figure 3 of Dr. Nuri's review) appears to give the best fit and would predict that the next increment in dose that would produce a clearly differentiable effect would be in the range of several hundred mg, so this is another example where varying the dose by 50% (e.g., 100 to 150 mg) is not very useful. Retrospectively, doses that should have delineated the shape of the dose-response curve would have been 5, 15, 50, 150 and 500 mg.

The effect of losartan in blacks and whites is clearly described by the results. Blacks and whites were stratified, so one can take these results as pretty definitive and not just tentative or suggestive. The dose response for these two populations are shown in Figure 3 (attached).

It is clear that over the entire range of doses studied, blacks have less of a response to losartan than do whites. Bid dosing in whites sticks out rather prominently with respect to its greater effect on trough, diastolic blood pressure in whites and less clearly in blacks.

Other demographic features, such as age or sex (each being analyzed for each study) showed less obvious differences in response, although patients over the age of 65 appear to have a little less of an effect. None of the differences observed as a function of age or sex are as consistent, as obvious nor as great as the black/white difference observed. The best summary of these data are found on pages 4 through 6 in Dr. Ganley's review.

Some Pharmacology and Clinical Pharmacology

General. Losartan (MK-954, DuP 753) is an angiotensin II receptor blocking agent (about 10,000 more

selective for AT₁ angiotensin receptors than for AT₂ angiotensin receptors). Judging from experiments in pithed rats, isolated aortic strips, and receptor binding techniques, its mechanism of action is that of competitive antagonism. In receptor binding studies the IC₅₀ was about 20 nanoMolar. Of passing note is that it inhibits platelet aggregation at concentration of 40 microMolar (2000 times that of the IC₅₀ for the AT₁ receptor).

An active metabolite (E-3174, L 158,641, EXP3174, a carboxylic acid metabolite, formed via an oxidative pathway) is known to be formed, presumably in the liver (at least human liver slices produce it, in both animals and man; P450, CYP2C9 AND CYP3A4). E-3174, in contrast to losartan, shows features of non-competitive antagonism (non-parallel shifts in dose-response curves in the same animal systems that losartan shifts in parallel fashion) and is about 30 times as potent as losartan. About 14% of administered losartan is converted to the E-3174 metabolite, so most of the effect comes from E-3174.

There were 29 studies that described various aspects of the clinical pharmacology of losartan. The absolute bioavailability of losartan is about 30% (estimates range from 22.9 to 32.6%); C_{Max}, AUC, etc. are dose proportional over a range of 10 to 300 mg administered orally, reach peak concentrations about 1 hour after dosing; it has a volume of distribution of about 47 Liters and shows a plasma half-life of about between 1 and 2 hours. Less than 4% of an administered dose, in man, is recovered in the urine. Not surprisingly, the pharmacokinetic constants which describe losartan are unaffected by renal insufficiency, except for AUC.

The absolute bioavailability of E-3174 has not been determined; following oral administration of losartan C_{Max}, AUC, etc. of E-3174 are dose proportional over a range of 10 to 300 mg losartan administered orally, reach a peak 3 to 4 hours after administration; it has a volume of distribution of about 16 Liters and has a plasma half-life of 6 to 9 hours. About 50% of an intravenously administered dose is recovered in the urine. The pharmacokinetic description of E-3174 seems to change as function of renal disease, as shown in Figure 4 (attached).

The study (012) that defined effects of renal disease was not large and the variability was great so this is not well defined, but it seems reasonable to conclude that losartan is little affected and that E-3174 has a longer half-life as the creatine clearance decreases. Overall not much happens.

The effects of food and hepatic disease.

Food delays and decreases the absorption of losartan. The production of the E-3174 metabolite is also delayed and very slightly decreased. Since the metabolite is the major player, the effect of food is not very important.

Hepatic insufficiency increases the absolute bioavailability of losartan from about 33% to about 65% with AUC and C_{Max} increasing about 5 fold, decreases its clearance (without much change in t_{1/2}) because a smaller volume of distribution is apparently also present (n=9 Protocol 067). Although the formation of E-3174 is also affected, it is not affected much. It is difficult to know what one would predict, but I predict very little change in effect as a function of hepatic disease.

Time course of drug action and interval between dose. The time course of drug action appears longer than a few hours, which is all it should be if losartan were the molecule responsible for its principal antihypertensive effects (a competitive, reversible antagonist with a half-life of a couple of hours). So, E-3174 must be important to the antihypertensive effects in man and animals. E-3174 is complicated in that it appears to be a non-competitive antagonist and its reversibility has not been well characterized. Prediction of the effects of orally administered losartan seems difficult, based upon the description of basic properties of either losartan or E-3174.

Protocol 069 (a placebo-controlled, 4-hour IV infusion of E-3174) did a reasonable job of characterizing the relationship between plasma concentration and antihypertensive effect. That relationship is shown in the accompanying Figure labelled Protocol 069 (Figure 5). There is a very broad, clock-wise hysteresis. Peak antihypertensive effects occurred about 3 hours after peak plasma concentrations.

It is clear that neither losartan nor E-3174 have agonist or partial agonist properties; these have been carefully looked for in man and animals and do not appear to be present. It is also clear that upon discontinuing losartan after weeks of therapy, the antihypertensive effect decreases over the course of a day or so.

Dosing regimens of once-a-day (studies 005, 011 and 050) as well as once-a-day and twice-a-day (studies 065 and 0210) show a larger effect on trough blood pressure for the bid regimens (when analyzed for all patients by intent-to-treat or completers, or when looked at for black patients or white patients), partially depicted in the figures of dose-response (Figures A and B). Additionally, although there is no formal analysis (only graphs to look at, pages 72 and 73 of Dr. Ganley's review), I see two humps in the bid regimen (each at its peak at about the number 1 on the time axis) and cannot see anything like that in the once-a-day regimens. So, although once-a-day regimens clearly are superior to placebo at trough, have reasonable peak/trough ratios and exhibit dose-response, twice-a-day administration is a superior regimen. Labelling should indicate that once or twice-a-day regimens are acceptable but that, before adding other drugs, twice-a-day should be tried.

Safety

General.

Overall, the 5 placebo-controlled trials randomized 1592 patients and 1395 (88%) completed the trials (the bulk of which were 8 to 12 weeks duration). Of the 1592 randomized patients, 357 were randomized to placebo, so 1235 were randomized to losartan. Drop outs due to adverse effects were (number dropped and in parentheses the %) 7 (1.96%), 1 (0.53%), 3 (0.83%), 8 (3.07%), 3 (2.88%), 3 (2.88%) and 1 (3.2%) in the placebo, 10, 25, 50, 100, 150 mg qd and 25, 50 mg bid groups, respectively. The pattern of adverse effects (incidence of any adverse event) were similarly relatively evenly distributed involving 54.06%, 47.50%, 52.63%, 47.51%, 54.81%, 56.60% and 45.16% in the placebo, 10, 25, 50, 100 150 mg qd and 25 and 50 mg bid groups, respectively. There were no overall statistically significant differences between placebo and any of the randomized losartan groups with respect to drop-outs nor to overall incidence of any side effect. After review of tables constructed by Dr. Ganley and by the sponsor (in their integrated summary of safety and efficacy), I cannot tell what side effects are drug related (meaning, highly likely to be due to losartan) and which are not.

Of note in the lists (pages 211-216 of Dr. Ganley's review) are, alphabetically, burning/stinging of the eye (0.3%, placebo = 0.0%), congestion, nasal (2.0%, placebo = 1.3%), congestion, pulmonary (0.2%, placebo = 0.0%), congestion, respiratory (0.65, placebo = 0.7%), conjunctivitis (0.1%, placebo = 0.0%), edema eyelid (0.1%, placebo = 0.0%), edema, facial (0.1%, placebo = 0.0%), inflammation, eyelid (0.2%, placebo = 0.3%), laryngitis (0.2%, placebo = 0.3%), obstruction, airway, upper (0.1%, placebo = 0.0%), pharyngitis (1.8%, placebo = 3.0%), urticaria (0.2%, placebo = 0.7%), wheezing (0.1%, placebo = 0.0%). The word angioedema appears not once anywhere I have looked. It is hard to make a case for any of the immediately preceding being angioedema but not diagnosed. It is also hard to make the case for edema, facial, edema, eyelid not being angioedema by another name. General concept has angioedema and bradykininase inhibition by ACE inhibitors going hand in hand. So an angiotensin receptor blocker that has no bradykininase inhibition properties should not cause angioedema. One patient was withdrawn from a study because of swelling of the lips and eyelids (which were gone 2 days after losartan was withdrawn). I am not sure that angioedema was not observed, am not sure that it was and do not know what action to take. I suggest that the labelling make the assertion that swelling of the lips, face and

eyelids, reversible upon discontinuation of losartan have been reported, and were a cause of one study withdrawal, but that the diagnosis of angioedema has not been reported.

As a consequence of angiotensin blockade (AT_1), circulating plasma renin activity increases and angiotensin II increases (both, about an order of magnitude and their increase is dose-related) and aldosterone decreases or remains normal. Plasma ACE activity is unchanged. Losartan appears to be uricosuric, for unknown reasons. This phenomenon had no clinical consequences recognized.

Alkaline phosphatase, AST and ALT elevations were sporadically reported more often (not statistically significantly) for losartan treated patients than for those receiving placebo. One of these patients had a proven viral hepatitis. Tracking down those patients that had both AST and ALT elevations (not one alone) led to no obvious hepatic injury being present (some had sporadic elevations, some had elevations persist long after drug was withdrawn, etc.). Red cells in the urine (hematuria, measured several different ways) similarly did not lead to finding cases where it appeared that losartan had induced any renal disease.

Cough. As a consequence of mechanism of action, like angioedema, one would not expect cough to be a part of losartan's effects. We specified that such a claim would require 2 studies that clearly demonstrated the lack of cough as a side effect. The current application contains the results of one study (protocol 056, page 156 of Dr. Ganley's review), the second study is in progress. Protocol 056 recruited patients who had ACE type cough while being treated with 20 mg lisinopril, orally, once-a-day. The study was well designed and found a greater incidence of cough ($p < 0.01$) in patients randomized to lisinopril than in patients randomized to losartan or HCTZ. Although it is reasonably clear that losartan and lisinopril are distinguishable with respect to the incidence of cough, almost 30% of patients receiving losartan redeveloped cough after losartan was started (having been cough free on placebo) and the blood pressure reduction produced by lisinopril was greater than that produced by losartan (so the two therapies were not at equieffective doses). This single study should not be considered sufficient to allow a claim of "no cough" associated with losartan therapy.

Renal Cell Carcinoma.

In the entire data-base (this NDA and the Losartan/HCTZ NDA), including open-label follow-on long term use, there were 6 cases of renal cell carcinoma observed, occurring in patients receiving losartan (2 others were observed in patients receiving control agents; 1 placebo and 1 captopril/HCTZ). At the time of NDA filing (see table SS.9, page 20 of Dr. Ganley's review), only one patient with renal cell carcinoma was reported; the remaining 5 on losartan or losartan/HCTZ (2 losartan alone, 3 losartan/HCTZ, 1 losartan/HCTZ/felodipine) became known during the review as a consequence of Merck's careful follow-up and reporting system; because documents were submitted during the course of review (and our review documents were restricted to the time period of documents as they were submitted), numbers of cases vary depending upon where one looks. At the time of constructing table SS.9 there were 12 other malignancies reported in addition to the one renal cell carcinoma. Of the 13 reported malignancies, one (intestinal) was observed while the patient was receiving placebo. Of the 12 patients receiving losartan, one was receiving HCTZ, losartan and felodipine, and 6 were receiving HCTZ and losartan. So, there were 5 patients receiving losartan alone.

I do not think the incidence of renal cell carcinoma would have been noticed at all during the course of our review, except that very early in the development of losartan an investigator (Dr. Remuzzi, independent of Merck, to whom Merck had supplied losartan) reported that rats treated with streptozotocin appeared to have a high incidence of grossly detected renal cell tumors. This finding suggested that losartan might act as a tumor promoter (streptozotocin is a known tumorigen) and therefore the index of suspicion (on our part) was very high.

It is clear (see reviews by Drs. Jagadeesh and Proakis, our Pharmacology reviewers; Dr. Rahman, our

statistical consultant, and the Carcinogenicity Assessment Committee meeting minutes) that there is no reasonable suggestion of carcinogenicity (other than pancreatic acinar adenoma in female rats, 3/75 in the high dose group vs 0/75 to 0/130 in each of the other 3 groups) in standard mouse and rat assays that were adequately designed, implemented and analyzed, nor any suggestion of mutagenicity in standard tests. Thus, in standard testing systems, losartan would not be regarded as a tumorigen (although including the pancreatic acinar adenoma in female rats will be included in labelling to conform to the wishes of the Carcinogenicity Assessment Committee, I do not regard that finding as a signal).

Moreover, at the suggestion of the Division, Merck undertook an extensive battery of animal tumorigenicity testing (in addition to the standard assays) in an attempt to evaluate the tumor promoter suggestion of the Remuzzi study. In short, the original observation could not be repeated and extensive tests (well beyond that conducted by Dr. Remuzzi ; this effort was subject to a laboratory field inspection that Dr. Proakis participated in) failed to suggest any tumor promoting potential of losartan. It is worth noting that evaluating the notion of evaluating tumor promotion is not something that anyone requires of any drug. We suggested doing it because of the original Remuzzi observations. The results of the Merck extensive laboratory evaluation were not known until December, 1994. Thus, the clinical cases of renal cell carcinoma and the Remuzzi study were heavy influences on degree of suspicion.

As it turns out, with respect to the clinical data (see review by Dr. Burkhart, our epidemiology consultant), there are 4 things one may regard as fact. The incidence of renal cell carcinoma in a hypertensive patient population is greater than that in a non-hypertensive population. The incidence of renal cell carcinoma in the patient population studied in NDAs 20-386 and 20-387 and receiving losartan is greater than any incidence reported in the literature in hypertensive patients. The relative risk for developing renal cell carcinoma estimated from the losartan data-base and the relative risk for developing renal cell carcinoma in hypertensive patients receiving enalapril or lisinopril (the latter data coming from the Merck who have a sophisticated follow-up and data reporting system) are not differentiable and the point estimates are similar. The relative risk for developing renal cell carcinoma in patients with congestive heart failure taking enalapril (data also from the same data collection and reporting system) does not even suggest that enalapril alters the risk of development of renal cell carcinoma in a congestive heart failure population. In sum, there is no theoretical (or empirical human, animal or *in-vitro*) data that are persuasive and require the conclusion that losartan is tumorigenic or a tumor promoter. Although its use was associated with a high incidence of renal cell carcinoma, the observations must be considered to be a function of the increased incidence of such tumors in patients who have hypertension and the more competent than usual Merck system of data collection and reporting. The data do not support a conclusion that losartan is related to renal cell carcinoma.

Dr. Knudsen in his review (dated 12/20/94), of NDA 20-387 (losartan/HCTZ) reaches another conclusion. Unfortunately, as a consequence of lack of communication within the Division, Dr. Knudsen apparently was unaware of the Division's activities regarding this matter and formulated a different point of view. In his review, he rejects the rationale of the immediately preceding paragraph. He thinks the only fact that matters is that the high incidence of renal cell carcinoma in the patient population studied in NDAs 20-386 and 20-387. I, and all other reviewers of this matter disagree with his reasoning.

Rat and Rabbit Reproduction

In the attached review package is a letter that the Division sent to each angiotensin receptor blocking agent developers, stating that the angiotensin converting enzyme Inhibitor class labelling for pregnancy would be needed unless that animal reproduction studies differentiated angiotensin receptor blocking agents from angiotensin converting enzyme inhibitors in this regard. Since there is no current animal model for the effects of ACE inhibitors on the human fetus during the late stages of pregnancy and since the submitted animal studies showed fetal harm from administration of losartan to pregnant animals, the ACE inhibitor warning should appear. There is no way of knowing that the effects of losartan would be the

same as ACE inhibitors in pregnant humans, but it is reasonable to assume that the known deleterious effects in pregnant women are mediated through interference with the renin-angiotensin system and that losartan does interfere with the renin-angiotensin system. The warning is avoid empirical confirmation of the suspicion that losartan would produce the same effects.

Summary

It is clear that losartan lowers blood pressure over the dose ranges studied and that its use is relatively side-effect free. Consequently, losartan is approvable. Although one can argue that the doses studied show that increasing dose beyond 100 mg is of no value, the argument rests heavily upon not differentiating between doses of 100 and 150 mg (there were only 129 patients who received doses of 150 mg for 30 days or longer; table D-69, page D157 of Merck's 5/6/94 submission of clinical efficacy and safety summary, volume 1.101). I do not regard that as a very adequate argument (although it has sufficed in the past) particularly since there is no evidence that increasing dose is limited by the occurrence of dose-dependent side effects.

The antihypertensive effect of 50 mg of losartan was compared to that of 5 mg of felodipine ER, 20 mg of enalapril, 20 of lisinopril, 50 mg of captopril, and to HCTZ, all being administered once-a-day, in controlled trials. The antihypertensive effect of 50 mg of losartan was greater than that of 50 mg of captopril given once-a-day (the usual dose, in the treatment of hypertension, being 50 mg tid) and also greater than that of 12.5 mg HCTZ. Otherwise, the other comparators produced diastolic blood pressure effect 2 to 3 mm Hg greater than that seen with losartan (always not statistically significantly less; but reproducibly less). So, it is not clear to me whether an angiotensin receptor blocking agent is inherently less effective or the dosing has not been well enough worked out. In any event, although clearly able to lower blood pressure (in those with mild hypertension or those with severe hypertension; two protocols clearly show that), the performance of losartan does not appear to be as good as that able to be produced by other agents.



Raymond J. Lipicky, M.D.

cc:

NDA 20-386

HFD-110

HFD-110/CGanley/CResnick/AProakis/GJagadeesh

HFD-426/AParekh/EFadran

HFD-713/GChi/WNuri

HFD-111/KBongiovanni

Table 2, Dr. Nuri' s statistical review

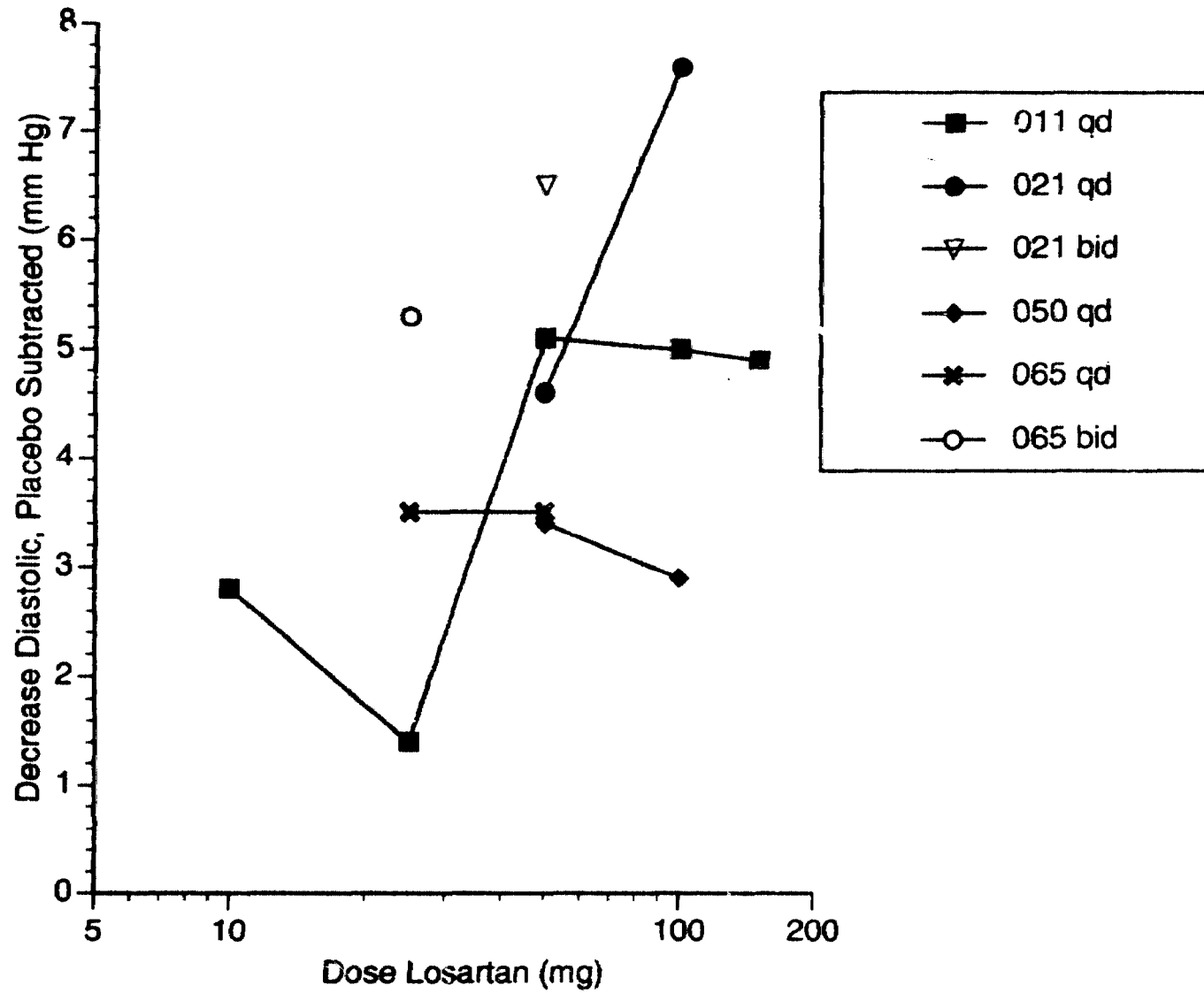


FIGURE 1. Losartan, trough, diastolic blood pressure, all placebo controlled trials.

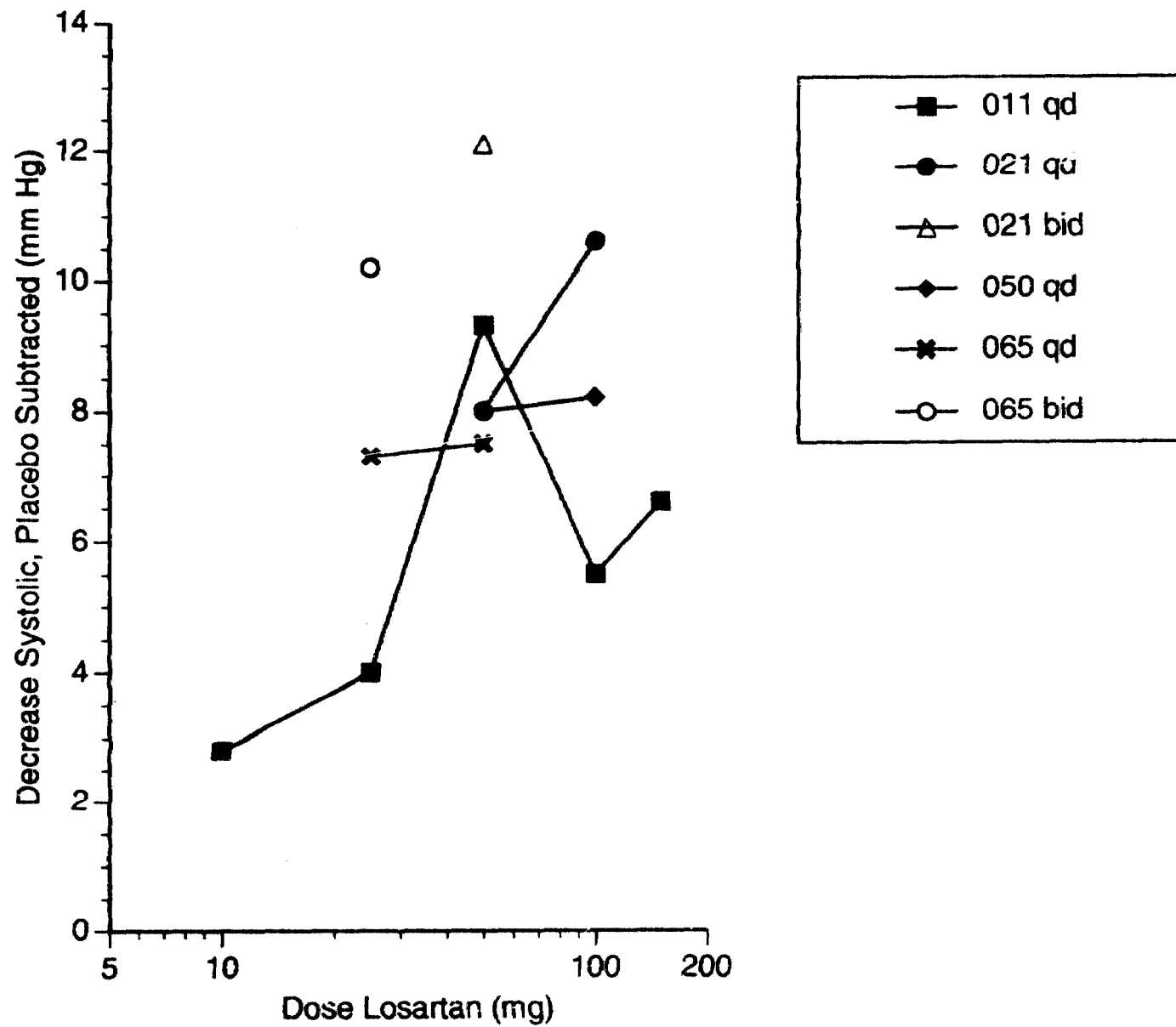


FIGURE 2. Losartan, trough, systolic blood pressure, all placebo controlled trials.

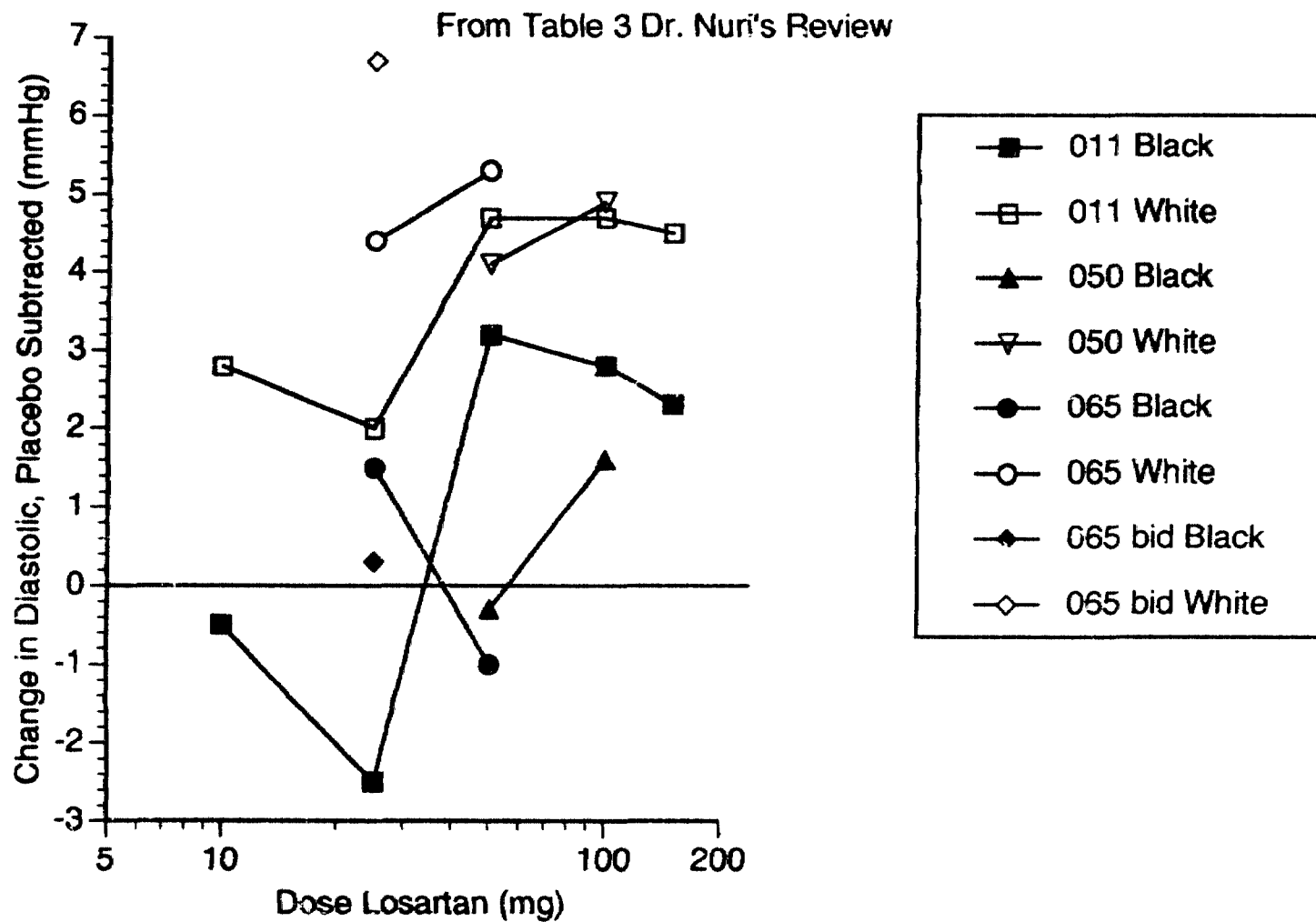


FIGURE 3. Losartan, trough, diastolic blood pressure, all placebo controlled trials. Comparison of race (black and non-black patient's response).

From Table 12.4, Page 138, Dr. Ganley's Review

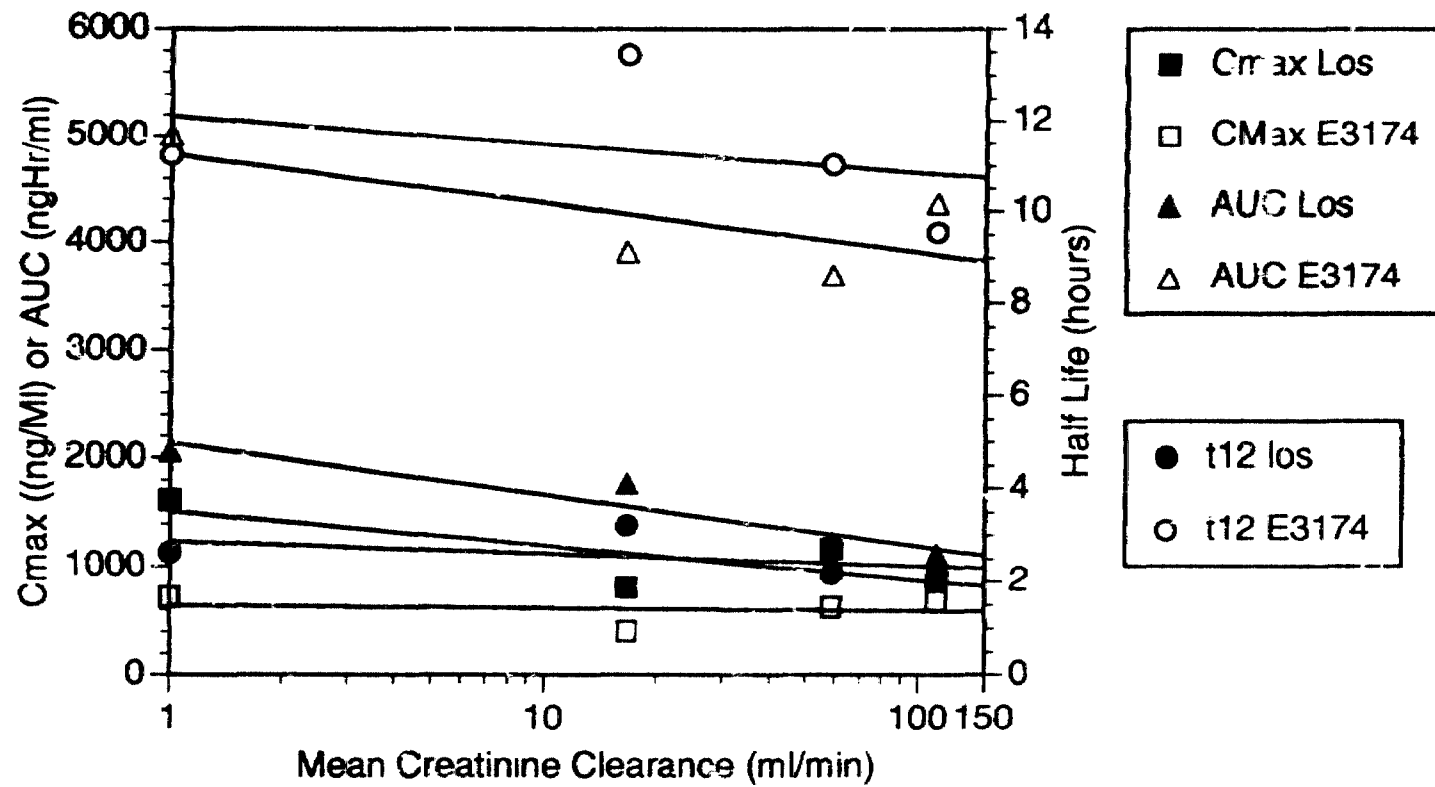


FIGURE 4. Summary of the effects of renal disease on the pharmacokinetic parameters of losartan (los) and its major, active, metabolite (E-3174). t12 = the plasma half-life.

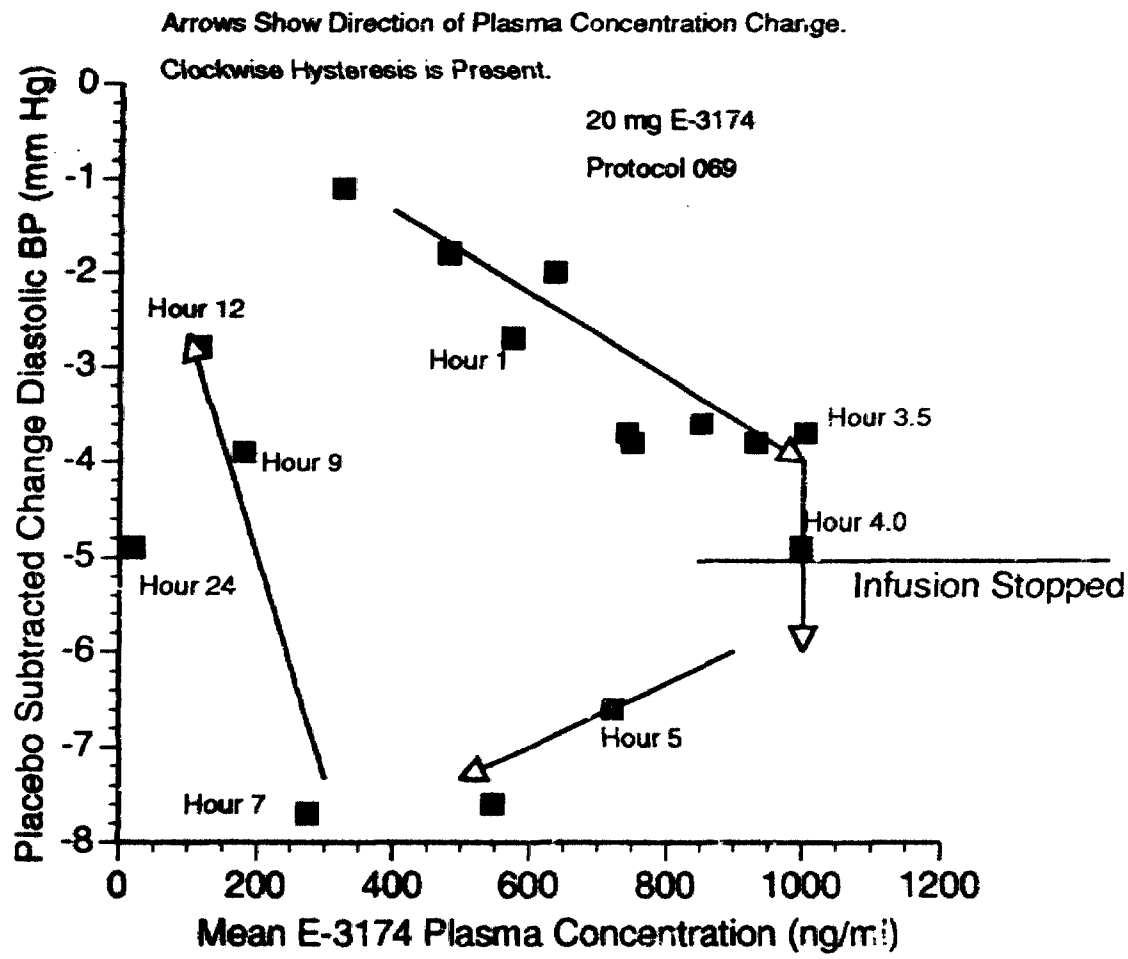


FIGURE 5. E-3174, plasma concentration-effect description.

LABELING

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MRL COMMENTS/SUPPORT

 **MERCK & CO., INC.**
West Point, PA 19486, USA

XXXXXXX

COZAAR®

(LOSARTAN POTASSIUM TABLETS)

Agreement with FDA (Teleconference 4/4/95) to retain
parenthesis placement following "Tablets".

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, COZAAR should be discontinued as soon as possible. See WARNINGS: *Fetal/Neonatal Morbidity and Mortality.*

DESCRIPTION

COZAAR® (losartan potassium), the first of a new class of antihypertensives, is an angiotensin II receptor (type AT₁) antagonist.

Losartan potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt.

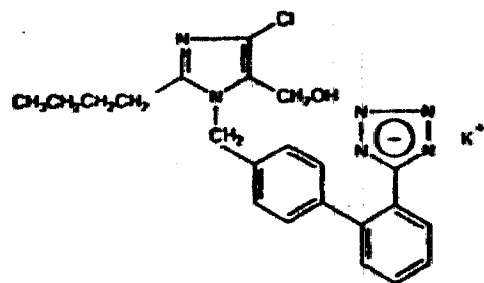
Its empirical formula is C₂₂H₂₂ClKN₄O, and its structural formula is:

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MRL COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)



Losartan potassium is a white to off-white free-flowing crystalline powder with a molecular weight of 461.01. It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone. Oxidation of the 5-hydroxymethyl group on the imidazole ring results in the active metabolite of losartan.

COZAAR is available for oral administration containing either 25 mg or 50 mg of losartan potassium and the following inactive ingredients: microcrystalline cellulose, lactose hydrous, pregelatinized starch, magnesium stearate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, titanium dioxide, D&C yellow No. 10 aluminum lake and FD&C blue No. 2 aluminum lake.

COZAAR 25 mg and 50 mg contain potassium in the following amounts: 2.12 mg (0.054 mEq) and 4.24 mg (0.108 mEq), respectively.

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MRL COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

CLINICAL PHARMACOLOGY

Mechanism of Action

Angiotensin II [formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II)], is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT₁ receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland). There is also an AT₂ receptor found in many tissues but it is not known to be associated with cardiovascular homeostasis. Both losartan and its principal active metabolite do not exhibit any partial agonist activity at the AT₁ receptor and have much greater affinity (about 1000-fold) for the AT₁ receptor than for the AT₂ receptor. *In vitro* binding studies indicate that losartan is a reversible, competitive inhibitor of the AT₁ receptor. The active metabolite is 10 to 40 times more potent by weight than losartan and appears to be a reversible, non-competitive inhibitor of the AT₁ receptor.

Accepted.

Neither losartan nor its active metabolite inhibits ACE (kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin); nor do they bind to or block other hormone receptors, or ion channels known to be important in cardiovascular regulation.

Accepted.

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COZAAR® (Losartan Potassium Tablets)

Pharmacokinetics
General
~~*Pharmacokinetics*~~

Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. It is converted, in part, to an active carboxylic acid metabolite which contributes significantly to that is responsible for most of the angiotensin II receptor antagonism that follows losartan treatment. The terminal half-life of losartan is about 2 hours and of the metabolite is about 6-9 hours. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan doses up to 200 mg and do not change over time. Neither losartan nor its metabolite accumulate in plasma upon repeated once-daily dosing.

Following oral administration, losartan is well absorbed (based on absorption of radiolabeled losartan) and undergoes substantial first-pass metabolism; the systemic bioavailability of losartan is approximately 33%. About 14% of an orally administered dose of losartan is converted to the active metabolite. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. While maximum plasma concentrations of losartan and its active metabolite are approximately equal, the AUC of the metabolite is about 4 times greater than as great as that of losartan. A meal slows absorption of losartan and decreases its C_{max} but has only minor effects on losartan AUC or on the AUC of the metabolite (about 10% decreased).

Both losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2% respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Agreement with FDA (Teleconference 4/4/95) to retain FDA-requested wording.

Accepted.

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Losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed. Following oral and intravenous administration of ¹⁴C-labeled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and its active metabolite. *In vitro* studies indicate that cytochrome P450 2C9 and 3A4 are involved in the biotransformation of losartan to its metabolites. Minimal conversion of losartan to the active metabolite (less than 1% of the dose compared to 14% of the dose in normal subjects) was seen in about one percent of individuals studied.

The volume of distribution of losartan is about 34 liters and of the active metabolite is about 12 liters. Total plasma clearance of losartan and the active metabolite is about 600 mL/min and 50 mL/min, respectively, with renal clearance of about 75 mL/min and 25 mL/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% is excreted in urine as active metabolite. Biliary excretion contributes to the elimination of losartan and its metabolites. Following oral ¹⁴C-labeled losartan, about 35% of radioactivity is recovered in the urine and about 60% in the feces. Following an intravenous dose of ¹⁴C-labeled losartan, about 45% of radioactivity is recovered in the urine and 50% in the feces.

Special Populations

Pediatric: Losartan pharmacokinetics have not been investigated in patients < 18 years of age.

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Geriatric and Gender: Losartan pharmacokinetics have been investigated in the elderly (65-75 years) and in both genders. Plasma concentrations of losartan and its active metabolite are similar in elderly and young hypertensives. Plasma concentrations of losartan were about twice as high in female hypertensives as male hypertensives, but concentrations of the active metabolite were similar in males and females. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).

Race: Pharmacokinetic differences due to race have not been studied.

Renal insufficiency: Plasma concentrations of losartan are not altered in patients with creatinine clearance above 30 mL/min. AUCs below that creatinine clearance appear to be in patients with lower creatinine clearance, AUCs are about 50% greater and they are doubled in hemodialysis patients. Plasma concentrations of the active metabolite are not significantly altered in patients with renal impairment or in hemodialysis patients. Neither losartan nor its active metabolite can be removed by hemodialysis. No dosage adjustment is necessary for patients with renal impairment unless they are volume-depleted (see WARNINGS, Hypotension - Volume-Depleted Patients and DOSAGE AND ADMINISTRATION).

Accepted.

Accepted.

Accepted.

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COZAAR® (Losartan Potassium Tablets)

Hepatic Insufficiency: Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-times and about 1.7-times those in young male volunteers. Compared to normal subjects the total plasma clearance of losartan in patients with hepatic insufficiency was about 50% lower and the oral bioavailability was about 2-fold times higher. A lower starting dose is recommended for patients with a history of hepatic impairment (see DOSAGE AND ADMINISTRATION).

Accepted.

Accepted.

Drug Interactions

Losartan, administered for 12 days, did not affect the pharmacokinetics or pharmacodynamics of a single dose of warfarin. Losartan did not affect the pharmacokinetics of oral or intravenous digoxin. Coadministration of losartan and cimetidine led to an increase of about 18% in AUC of losartan but did not affect the pharmacokinetics of its active metabolite. Coadministration of losartan and phenobarbital led to a reduction of about 20% in the AUC of losartan and that of its active metabolite. There is no pharmacokinetic interaction between losartan and hydrochlorothiazide.

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COZAAR® (Losartan Potassium Tablets)

Pharmacodynamics and Clinical Effects

Losartan inhibits the pressor effect of angiotensin II (as well as angiotensin I) infusions. A dose of 100 mg inhibits the pressor effect by about 85% at peak with 25-40% inhibition persisting for 24 hours. Removal of the negative feedback of angiotensin II causes a 2-3 fold rise in plasma renin activity and consequent rise in angiotensin II plasma concentration in hypertensive patients. Losartan does not affect the response to bradykinin, whereas an ACE inhibitor increased the response to bradykinin. Aldosterone plasma concentrations fall following losartan administration. In spite of the effect of losartan on aldosterone secretion, very little effect on serum potassium was observed.

In a single-dose study in normal volunteers, losartan had no effects on glomerular filtration rate, renal plasma flow or filtration fraction. In multiple dose studies in hypertensive patients, there were no notable effects on systemic or renal prostaglandin concentrations, fasting triglycerides, total cholesterol or HDL-cholesterol or fasting glucose concentrations. There was a small uricosuric effect leading to a minimal decrease in serum uric acid (mean decrease < 0.4 mg/dL) during chronic oral administration.

The antihypertensive effects of COZAAR were demonstrated principally in 4 placebo-controlled 6-12 week trials of dosages from 10 to 150 mg per day in patients with baseline diastolic blood pressures of 95-115. The studies allowed comparisons of two doses (50 and 100 mg/day) as once-daily or twice-daily regimens, comparisons of peak and trough effects, and comparisons of response by gender, age, and race. Three additional studies examined the antihypertensive efficacy effects of losartan and hydrochlorothiazide in combination.

Accepted.

Editorial revision for clarity and accuracy and for consistency with twice-daily dosing range mentioned in next paragraph (i.e., "Twice-daily dosing at 50-100 mg/day").

Accepted.

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MRL COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

~~The 4 studies of losartan monotherapy included a total of 1075 patients randomized to losartan and 334 to placebo. The 10 and 25 mg doses of losartan produced some effect at peak (6 hours after dosing) but small and inconsistent trough (24 hour) responses. The blood pressure response of losartan in the range of 50 to 150 mg once daily was statistically significant compared to placebo. However, there was little additional effect when the dose was increased above 50 mg. The range of placebo-adjusted systolic and diastolic antihypertensive responses in these four studies at doses of 50-150 mg once daily were 5.5-10.8/3.4-7.8 mmHg, respectively. Although peak (6 hours) effects were uniformly larger than trough effects following once daily dosing, the reductions at trough were not the result of excessive reductions at peak; the trough to peak ratios for systolic and diastolic blood pressure were 50-95% and 60-90% at doses of 50-100 mg, respectively. Twice-daily dosing at total daily doses of 50-100 mg generally gave larger numerical placebo-adjusted reductions in blood pressure when compared to once-daily dosing.~~

MRL text submitted to FDA 3/14/95.

The 4 studies of losartan monotherapy included a total of 1075 patients randomized to several doses of losartan and 334 to placebo. The 10 and 25 mg doses produced some effect at peak (6 hours after dosing) but small and inconsistent trough (24 hour) responses. Doses of 50, 100, and 150 mg once daily gave statistically significant systolic/diastolic mean decreases in blood pressure compared to placebo in the range of 6-9.6/4-8 5.5-10.5/3.5-7.5 mmHg, with the 150 mg dose giving no greater effect than 50-100 mg. Twice-daily dosing at 50-100 mg/day gave consistently larger trough responses than once daily dosing at the same total dose. Peak (6 hour) effects were uniformly, but moderately larger than trough effects, with the trough to peak ratio for systolic and diastolic responses 45-70% 50-95% and 60-90% respectively.

Agreement with FDA (Teleconference 4/4/95) to accept FDA-requested language with MRL numbers (see attached for supporting documentation).

Addition of a low dose of hydrochlorothiazide (12.5 mg) to losartan 50 mg once daily resulted in placebo-adjusted blood pressure reductions of 15.5/9.2 mmHg.

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COZAAR® (Losartan Potassium Tablets)

Analysis of age, gender, and race subgroups of patients showed that men and women, and patients over and under 65, had generally similar responses. Black patients, however, had notably smaller responses to losartan monotherapy; ~~generally less than 50% of the effect in whites, with no detectable effect in two of the three studies where this could be assessed.~~

The effect of losartan is substantially present within one week ~~and~~ but in some studies the maximal effect occurred in 3-8 weeks. In long-term follow-up studies (without placebo control) the effect of losartan appeared to be maintained for up to a year. There is no apparent rebound effect after abrupt withdrawal of losartan. There was essentially no change in average heart rate in losartan-treated patients in controlled trials.

MRL COMMENTS/SUPPORT

Agreement with FDA (Teleconference 4/4/95) to reword section as shown.

Agreement with FDA (Teleconference 4/4/95) to accept FDA-requested wording.

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COZAAR® (Losartan Potassium Tablets)

INDICATIONS AND USAGE

COZAAR is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

~~In controlled clinical trials, monotherapy with COZAAR had less effect on blood pressure in black patients than in non-black patients.~~

In considering the use of COZAAR monotherapy with COZAAR, it should be noted that in controlled trials COZAAR had an effect on blood pressure that was notably less in black patients than in non-blacks, sometimes showing no effect at all; a finding similar to the small effect of angiotensin converting enzyme inhibitors in blacks.

CONTRAINDICATIONS

COZAAR is contraindicated in patients who are hypersensitive to any component of this product.

MRL COMMENTS/SUPPORT

MRL text submitted to FDA 3/14/95.

Agreement with FDA (Teleconference 4/4/95) to accept FDA wording with modification as shown.

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MRL COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

WARNINGS:

Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, COZAAR should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester.

Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of COZAAR as soon as possible.

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MRL COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, COZAAR should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Losartan potassium has been shown to produce adverse effects in rat fetuses and neonates, including decreased body weight, delayed physical and behavioral development, mortality and renal toxicity. With the exception of neonatal weight gain (which was affected at doses as low as 10 mg/kg/day), doses associated with these effects exceeded 25 mg/kg/day (approximately three times the maximum recommended human dose of 100 mg on a mg/m² basis). These findings are attributed to drug exposure in late gestation and during lactation. Significant levels of losartan and its active metabolite were shown to be present in rat fetal plasma during late gestation and in rat milk.

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COZAAR® (Losartan Potassium Tablets)

Hypotension – Volume-Depleted Patients

In patients who are intravascularly volume-depleted (e.g., those treated with high-dose diuretics), symptomatic hypotension may occur after initiation of therapy with COZAAR. These conditions should be corrected prior to administration of COZAAR, or a lower starting dose should be used (see DOSAGE AND ADMINISTRATION).

Agreement with FDA (Teleconference 4/4/95) to delete "high dose" from statement.

PRECAUTIONS

General

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with impaired liver function (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY, Pharmacokinetics).

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. COZAAR would be expected to behave similarly. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or BUN have been reported. There has been no known use of COZAAR in patients with unilateral or bilateral renal artery stenosis, but a similar effect should be anticipated.

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MRL COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

Information for Patients

Pregnancy. Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions

~~Compounds that have been studied in clinical pharmacokinetic trials include~~ No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, cimetidine and phenobarbital. (See CLINICAL PHARMACOLOGY, Drug Interactions.) Significant Potent inhibitors of cytochrome P450 3A4 and 2C9 have not been studied clinically but in vitro studies show significant inhibition of the formation of the active metabolite by inhibitors of P450 3A4 (ketoconazole, itraconazole, gestodene), or P450 2C9 (sulfaphenazole) and nearly complete inhibition by the combination of sulfaphenazole and ketoconazole. The pharmacodynamic consequences of concomitant use of losartan and these inhibitors have not been examined.

Agreement with FDA (Teleconference 4/4/95) to revise section as shown.

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MRL COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

Carcinogenesis, Mutagenesis, Impairment of Fertility

Losartan potassium was not carcinogenic when administered at maximally tolerated dosages to rats and mice for 105 and 92 weeks, respectively. Female rats given the highest dose (270 mg/kg/day) had a slightly higher incidence of pancreatic acinar adenoma. The maximally tolerated dosages (270 mg/kg/day in rats, 200 mg/kg/day in mice) provided systemic exposures for losartan and its pharmacologically active metabolite that were approximately 180- and 90-times (rats) and 30- and 15-times (mice) the exposure of a 50 kg human given 100 mg per day.

Agreement with FDA (Teleconference 4/4/95) to retain FDA statement regarding pancreatic acinar adenoma in female rats with commitment from FDA to look again at MRL data.

Losartan potassium was negative in the microbial mutagenesis and V-79 mammalian cell mutagenesis assays and in the *in vitro* alkaline elution and *in vitro* and *in vivo* chromosomal aberration assays. In addition, the active metabolite showed no evidence of genotoxicity in the microbial mutagenesis, *in vitro* alkaline elution, and *in vitro* chromosomal aberration assays.

Fertility and reproductive performance were not affected in studies with male rats given oral doses of losartan potassium up to approximately 150 mg/kg/day. The administration of toxic dosage levels in females (300/200 mg/kg/day) was associated with a significant ($p < 0.05$) decrease in the number of corpora lutea/female, implants/female, and live fetuses/female at C-section. At 100 mg/kg/day only a decrease in the number of corpora lutea/female was observed. The relationship of these findings to drug-treatment is uncertain since there was no effect at these dosage levels on implants/pregnant female, percent post-implantation loss, or live animals/litter at parturition. In nonpregnant rats dosed at 135 mg/kg/day for 7 days, systemic exposure (AUCs) for losartan and its active metabolite were approximately 66 and 26 times the exposure achieved in man at the maximum recommended human daily dosage (100 mg).

**MRL TEXT SUBMITTED 3/14/95 WITH
FDA-REQUESTED REVISIONS OF 4/3/95**

MRL COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters).

See WARNINGS, *Fetal/Neonatal Morbidity and Mortality*.

Nursing Mothers

It is not known whether losartan is excreted in human milk, but significant levels of losartan and its active metabolite were shown to be present in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

**MR. TEXT SUBMITTED 3/14/95 WITH
FDA-REQUESTED REVISIONS OF 4/3/95**

MRL COMMENTS/SUPPORT

4/13/95

Use in the Elderly

Of the total number of patients receiving COZAAR in controlled clinical studies, 391 patients (19%) were 65 years and over, while 37 patients (2%) were 75 years and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

COZAAR has been evaluated for safety in more than 3300 patients treated for essential hypertension and 4058 patients/subjects overall. Over 1200 patients were treated for over 6 months and more than 800 for over one year. In general, treatment with COZAAR was well tolerated. The overall incidence of adverse experiences reported with COZAAR was similar to placebo.

In controlled clinical trials, discontinuation of therapy due to clinical adverse experiences was required in 2.3 percent of patients treated with COZAAR and 3.7 percent of patients given placebo.

The following table of adverse events is based on four 6-12 week placebo controlled trials involving over 1000 patients on various doses (10-150 mg) of losartan and over 300 patients given placebo. All doses of losartan are grouped because none of the adverse events appeared to have a dose-related frequency. The table includes all adverse events, whether or not attributed to the treatment, occurring in at least 1% of patients treated with losartan (or at a lower rate for selected events) and that were more frequent on losartan than placebo.

Agreement with FDA (Teleconference 4/4/95) to delete text as shown.

**MF EXT SUBMITTED 3/14/95 WITH
FDA-REQUESTED REVISIONS OF 4/3/95**

MRL COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

	Losartan (n=1075) Incidence	Placebo (n=334) Incidence
Digestive		
Diarrhea	2.4	2.1
Dyspepsia	1.3	1.2
Musculoskeletal		
Cramp, muscle	1.1	0.3
Myalgia	1.0	0.9
Pain, back	1.8	1.2
Pain, leg	1.0	0.0
Nervous System/Psychiatric		
Dizziness	3.5	2.1
Insomnia	1.4	0.6
Respiratory		
Congestion, nasal	2.0	1.2
Cough	3.4	3.3
Infection, upper respiratory	7.9	6.9
Sinus disorder	1.5	1.2
Sinusitis	1.0	0.3

Agreement with FDA (Teleconference 4/4/95) to retain table as shown.

The following adverse events were also reported at a rate of 1% or greater in patients treated with losartan, but were as or more frequent, in the placebo group: asthenia/fatigue, edema/swelling, abdominal pain, chest pain, nausea, headache, pharyngitis.

Adverse events occurred at about the same rates in men and women, older and younger patients, and black and non-black patients.

REVISION OF PARAGRAPH AS REQUESTED BY FDA ON 4/14/95.

Relocated per FDA Teleconference 4/13/95.

**TEXT SUBMITTED 3/14/95 WITH
FDA REQUESTED REVISIONS OF 4/3/95**

MRL COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

A patient with known hypersensitivity to aspirin and penicillin, when treated with COZAAR, was withdrawn from study due to swelling of the lips and eyelids and facial rash, reported as angioedema, which returned to normal 5 days after therapy was discontinued.

Relocated per FDA Teleconference 4/13/95.

Superficial peeling of palms and possible hemolysis was reported in one subject.

Relocated per FDA Teleconference 4/13/95.

~~The following adverse events occurred without regard to causality, at ≥0.5% in patients treated with losartan: Body as a Whole: abdominal pain, asthenia/fatigue, chest pain, edema/swelling, fever, orthostatic effects; Cardiovascular: palpitation, tachycardia; Digestive: anorexia, constipation, dental pain, nausea, vomiting; Metabolic: gout; Musculoskeletal: arm pain, hip pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness; Nervous System/Psychiatric: anxiety, depression, headache, libido decreased, paresthesia, vertigo; Respiratory: dyspnea, bronchitis, epistaxis, pharyngeal discomfort, pharyngitis, rhinitis, respiratory congestion; Skin: flushing, pruritus, rash; Special Senses: tinnitus; Urogenital: impotence, urinary frequency, urinary tract infection.~~

**TEXT SUBMITTED 3/14/95 WITH
FDA-REQUESTED REVISIONS OF 4/3/95**

MRL COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

In addition to the adverse events in the table above, potentially important events, without regard to causality, that occurred in at least twice in the two patients/subjects exposed to losartan or other adverse events that occurred in <1% of patients in clinical studies are listed below. It cannot be determined whether these events were causally related to losartan. Body as a Whole: facial edema, fever, orthostatic effects, syncope; Cardiovascular: angina pectoris, second degree AV block, CVA, hypotension, myocardial infarction, arrhythmias including atrial fibrillation, palpitation, sinus bradycardia, tachycardia, ventricular tachycardia, ventricular fibrillation; Digestive: anorexia, constipation, dental pain, dry mouth, flatulence, gastritis, vomiting; Hematologic: anemia; Metabolic: gout; Musculoskeletal: arm pain, hip pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, fibromyalgia, muscle weakness; Nervous System/Psychiatric: anxiety, anxiety disorder, ataxia, confusion, depression, dream abnormality, hypesthesia, decreased libido, memory impairment, migraine, nervousness, paresthesia, peripheral neuropathy, panic disorder, sleep disorder, somnolence, tremor, vertigo; Respiratory: dyspnea, bronchitis, pharyngeal discomfort, epistaxis, rhinitis, respiratory congestion; Skin: alopecia, dermatitis, dry skin, ecchymosis, erythema, flushing, photosensitivity, pruritus, rash; sweating, urticaria; Special Senses: blurred vision, burning/stinging in the eye, conjunctivitis, taste perversion, tinnitus, decrease in visual acuity; Urogenital: impotence, nocturia, urinary frequency, urinary tract infection.

Laboratory Test Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of COZAAR.

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 0.1 percent of patients with essential hypertension treated with COZAAR alone. No patient discontinued taking COZAAR alone due to increased BUN or serum creatinine. (See PRECAUTIONS, Impaired Renal Function.)

Agreement with FDA (Teleconference 4/4/95 and request 4/7/95) to revise paragraph as shown. Paragraph has been revised to include those adverse events that were previously included on page 19, as well as those potentially important events from all studies. Those four adverse events that FDA had requested be included (orthostatic effects, vertigo, epistaxis, tinnitus) are included in this section since they meet the incidence criteria.

Agreement with FDA (Teleconference 4/4/95) to revise subsection as shown.

**. TEXT SUBMITTED 3/14/95 WITH
FDA-REQUESTED REVISIONS OF 4/3/95**

MRL COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.11 grams percent and 0.09 volume percent, respectively) occurred frequently in patients treated with COZAAR alone, but were rarely of clinical importance. No patients were discontinued due to anemia.

Liver Function Tests: Occasional elevations of liver enzymes and/or serum bilirubin have occurred. In patients with essential hypertension treated with COZAAR alone, one patient (<0.1%) was discontinued due to these laboratory adverse experiences.

OVERDOSAGE

Significant lethality was observed in mice and rats after oral administration of 1000 mg/kg and 2000 mg/kg, respectively, about 44 and 170 times the maximum recommended human dose on a mg/m² basis.

**MRL TEXT SUBMITTED 3/14/95 WITH
FDA-REQUESTED REVISIONS OF 4/3/95**

MRL COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan nor its active metabolite can be removed by hemodialysis.

**MRL TEXT SUBMITTED 3/14/95 WITH
FDA-REQUESTED REVISIONS OF 4/3/95**

MRL COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

DOSAGE AND ADMINISTRATION

~~The usual starting dose for most patients is 50 mg once daily. The dosage range is 25 to 100 mg. For patients with possible depletion of intravascular volume (e.g., those treated with high dose diuretics) (see WARNINGS, Hypotension—Intravascular Volume Depletion) and for patients with a history of hepatic impairment (see PRECAUTIONS, General), a starting dose of 25 mg is recommended. Some patients may receive an additional benefit by an increase in the dose (100 mg). If blood pressure is not controlled by COZAAR alone, a low dose of a diuretic may be added. Hydrochlorothiazide has been shown to have an additive effect (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects).~~

~~COZAAR can be administered once or twice daily with total daily doses ranging from 25 mg to 100 mg. The usual starting dose is 50 mg once daily, with 25 mg used in patients with possible depletion of intravascular volume (e.g., patients treated with diuretics) (see PRECAUTIONS, General) and patients with a history of hepatic impairment (see PRECAUTIONS, General).~~

~~If the antihypertensive effect measured at trough using once a day dosing is inadequate, a twice a day regimen may give a more satisfactory response.~~

~~Some patients may receive an additional benefit by an increase in the dose (100 mg). If blood pressure is not controlled by COZAAR alone, a low dose of a diuretic may be added. Hydrochlorothiazide has been shown to have an additive effect (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects).~~

MRL text submitted to FDA 3/14/95.

FDA-requested text of 4/3/95.

**MRL TEXT SUBMITTED 3/14/95 WITH
FDA-REQUESTED REVISIONS OF 4/3/95**

MRL COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

The usual starting dose of COZAAR is 50 mg once daily, with 25 mg used in patients with possible depletion of intravascular volume (e.g., patients treated with diuretics) (see WARNINGS, Hypotension - Volume-Depleted Patients) and patients with a history of hepatic impairment (see PRECAUTIONS, General). COZAAR can be administered once or twice daily with total daily doses ranging from 25 mg to 100 mg.

Text agreed to by FDA and MRL at teleconference 4/4/95.

If the antihypertensive effect measured at trough using once-a-day dosing is inadequate, a twice-a-day regimen at the same total daily dose or an increase in dose may give a more satisfactory response.

If blood pressure is not controlled by COZAAR alone, a low dose of a diuretic may be added. Hydrochlorothiazide has been shown to have an additive effect (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects).

No initial dosage adjustment is necessary for elderly patients or for patients with renal impairment, including patients on dialysis.

COZAAR may be administered with other antihypertensive agents.

COZAAR may be administered with or without food.

HOW SUPPLIED

No. 3612 — Tablets COZAAR, 25 mg, are light green, teardrop-shaped, film-coated tablets with code MRK on one side and 951 on the other. They are supplied as follows:

NDC 0006-0951-54 unit of use bottles of 90

NDC 0006-0951-58 unit of use bottles of 100

NDC 0006-0951-28 unit dose packages of 100.

**MRL TEXT SUBMITTED 3/14/95 WITH
FDA-REQUESTED REVISIONS OF 4/3/95**

MRL COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

No. 3613 — Tablets COZAAR, 50 mg, are green, teardrop-shaped, film-coated tablets with code MRK 952 on one side and COZAAR on the other. They are supplied as follows:

NDC 0006-0952-31 unit of use bottles of 30

NDC 0006-0952-54 unit of use bottles of 90

NDC 0006-0952-58 unit of use bottles of 100

NDC 0006-0952-28 unit dose packages of 100.

Storage

Store at controlled room temperature, 15-30°C (59-86°F).
Keep container tightly closed. Protect from light.

Manuf for:

⊕ **MERCK & CO., INC., West Point, PA 19486, USA**

by:

**DUPONT
PHARMA**

Wilmington, DE 19880, USA

Issued XXXXX.

Printed in U.S.A.

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MEDICAL

OFFICER'S

REVIEW

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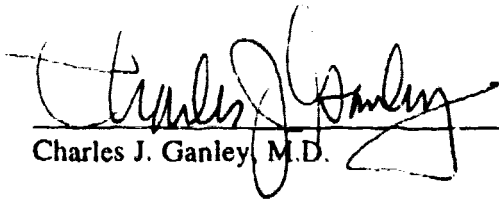
APR 12 1995

MEDICAL OFFICER REVIEW

NDA #: 20-386/
NDA Volume:
DRUG NAME: losartan
SPONSOR: Merck
TYPE OF DOCUMENT: Response to FDA approval letter
DATE RECEIVED:
DATE REVIEW COMPLETED: 3/30/95
MEDICAL OFFICER: Charles J. Ganley, M.D.

Merck's response to proposed labeling is included in this submission along with explanations of changes. There are only three issues that require comment.

- 1) Changes in labeling will be finalized by Dr. Temple and will not be included in this review. Documentation of changes are included in the division and cso file.
- 2) The losartan-warfarin issue is not resolved. Chronic Prothrombin Times (PT) for patients on warfarin/losartan from study 68 are included. It is difficult to make any comment from this data since the PT increase in some, decreases in others and remains unchanged in others. The major question is can losartan cause displacement of warfarin from protein binding sites leading to an increased PT and increased risk of bleeding. The sponsor has not adequately ruled out this possibility. [NOTE: Merck performed a norfloxacin-warfarin interaction study similar in design to the losartan-warfarin interaction study performed in the NDA. The norfloxacin-warfarin interaction study claimed there was no pharmacokinetic and pharmacodynamic interaction. There are reports, however, that link norfloxacin to an increase in PT in patients on warfarin. The American Hospital Formulary states that this interaction may be due to warfarin displacement from protein caused by norfloxacin. Could this happen with losartan?]
- 3) The sponsor does not feel that losartan will cause a syndrome of renal dysfunction, flank pain and hematuria as described with suprofen and ticrynafen. They base this opinion on the following:
 - a) losartan does not adversely affect, GFR, renal blood flow or prostaglandin synthesis;
 - b) it is not clear that uricosuria is a contributing factor;
 - c) losartan is not structurally similar to suprofen or ticrynafen; and
 - d) the syndrome was not reported in the losartan database (which is quite extensive).


Charles J. Ganley, M.D.

cc: orig.
HFD-110
HFD-110 / CSO / C. GANLEY / S.CHEN

Larry P. Bell, M.D.
Director
Regulatory Affairs

DESK COPY

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215 652 5000



March 14, 1995

Raymond J. Lipicky, M.D., Director
Division of Cardio-Renal Drug Products
HFD-110, Room 16B-45
Office of Drug Evaluation I (CDER)
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

Dear Dr. Lipicky:

NDA 20-386: Tablets COZAAR (Losartan Potassium)

Reference is made to the above New Drug Application submitted on December 3, 1993, an approvable letter dated March 2, 1995 from the FDA, which contained the Agency's comments on the submitted draft labeling, additional requested information on the Environmental Assessment portion of the above application, and a request to change the dissolution specifications for COZAAR prior to approval of the application. Specific reference is made to telephone conversations between Ms. K. Bongiovanni and Dr. L. Bell on March 6, 1995, Dr. E. Fadiran and Dr. L. Bell on March 8, 1995, Mr. M. Jones and Dr. L. Bell on March 8, 1995, and Dr. R. Wolters and Dr. L. Bell on March 8, 1995. Specific reference is also made to an approvable letter for COZAAR (NDA 20-387), received from the FDA on March 10, 1995.

A response to the Agency's request to modify the dissolution specification will be provided in a subsequent submission.

By copy of this letter we are submitting a revised draft package circular. Attached are two separate documents to facilitate review. Attachment I is formatted as a two column document: The left hand column provides the draft labeling text as revised by the Agency in the March 2, 1995 approvable letter. Deletions to this draft are shown by strike-through and additions are shown in double-underline. The right hand column provides Merck Research Laboratories (MRL) comments along with supporting annotation. In addition, supporting documentation is included within this Attachment. Attachment II provides the entire text of the draft package circular, incorporating all proposed revisions.

MRL is also providing the entire text of the draft package circular, incorporating all proposed revisions in electronic format as individual disks. This information is formatted as a Macintosh Word Perfect 3.1 document.

Medical Officer Review

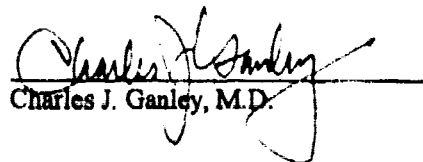
NDA #: 20-366/BM
Volume: 18.1
Drug Name: Losartan
Sponsor: MSDRL
Date of Receipt: 3/2/94
Review Start Date: 3/8/95
Medical Reviewer: Charles J. Ganley, M.D.

Re: Prothrombin Times of Patient #1031 from study 47

Patient #1031 had gingival bleeding and an elevated prothrombin time (PT) while receiving losartan 2.5 mg. Pre-study prothrombin time was 11.1 seconds on 4/24/92. The patient started losartan therapy on 5/18/92. The prothrombin time on 5/19/92 was 16.3 seconds. The prothrombin time on day 10 was 11.9 seconds. The prothrombin time on day 33 was 29.4 seconds. The dose of warfarin was the same for all of these dates. Subsequent prothrombin times on the same dose of warfarin and losartan 10 and 25 mg did not appear elevated.

Conclusion:

The increase in PT on day 33 can not be explained although the role of losartan appears questionable. The data suggests that a pharmacokinetic interaction is not likely although information regarding other therapies is not provided. The information does not rule out an interaction during the first days of losartan (e.g. related to displacement from albumin) therapy.


Charles J. Ganley, M.D.

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MAR 7 1995

MEDICAL OFFICER REVIEW

IND #: 20-386/BM
IND Volume: 16.1
DRUG NAME: losartan
SPONSOR: Merck
TYPE OF DOCUMENT: Response to request for information
DATE RECEIVED: 2/15/95
DATE REVIEW COMPLETED: 3/6/95
MEDICAL OFFICER: Charles J. Ganley, M.D.

This submission provides answers to questions concerning various studies in the NDA. All questions have been answered in a satisfactory manner. Additional information has been provided for patient #12 in study 075. This patient had barely detectable L-158,641 (E-3174) after losartan 50 mg. A metabolic profile was performed under study 060 for cytochrome P-450 activity. CYP1A2, CYP2D6 and CYP3A4 were evaluated by the administration of caffeine, dextromethorphan and dapsone.

In vitro studies with isoform-specific inhibitors of CYP450 indicated that CYP3A4 and at least one isoform of the CYP2C family can catalyze the conversion of losartan to L-158,641. CYP3A4 specific inhibitors, gestodene and ketoconazol, and a CYP2C9-10 inhibitor, sulphaphenazole, decreased the formation of L-158,641 and 2 hydroxylated metabolites. The CYP2D6 inhibitor, quinidine, did not inhibit formation of L-158,641.

Table 1. lists the results of the metabolic ratios after single doses of caffeine, dextromethorphan and dapsone.

Table 1. Metabolic Ratios for Patient 12 (#07 in study 60).

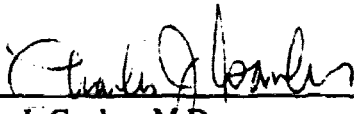
Probe Drug	Metabolic Ratio (MR)	Result	Conclusion
Caffeine	$MR = \ln\{\ln[(AFMU + 1U + 1X)/1,7X]\}$	.018	Slow Metabolism
Dextromethorphan	$MR = [DM]/[DT]$	.7841	Poor metabolism
Dapsone	$MR = [NHD]/(dapsone + [NHD])$	.796	Normal Activity

NHD = N-hydroxydapsone; DM = dextromethorphan; DT = dextromethorphan; 1U = 1-methyluric acid; AFMU = 5-acetyl-amino-6-formylamino-3-methyluracil; 1X = 1-methylxanthine; 1,7X = paraxanthine

Patient 12 received losartan 30 mg i.v., losartan 100 mg p.o. and L-158,641 20 mg i.v. After losartan dosing, L-158,641 was barely detectable. After L-158,641 dosing, the elimination half-life of L-158,641 was approximately 8 hours.

Conclusions:

Decreased activity of CYP3A4 was not apparent in this patient as one might expect from the in vitro CYP data. CYP2C9 activity was not evaluated in this patient.


Charles J. Ganley, M.D.

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HFD-110 / CSO / C. GANLEY / S. CIEN
HFD-100 / R. Temple

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Medical Officer Review

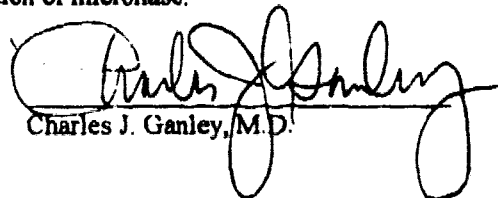
NDA #: 20-386/BM
Volume: 15.1 - 15.4
Drug Name: Losartan
Sponsor: MSDRL
Type of Document: Request to FDA request for information
Date of Receipt: 2/13/95
Review Start Date: 3/2/95
Medical Reviewer: Charles J. Ganley, M.D.

MAR 1 1995

This submission contains requested case report forms. There is little additional information to be derived from the CSRs. As with the CSRs included in the NDA, the CSRs are computerized recreations of the original data. They have been signed by the investigators.

Summary/Conclusions

- 1) Twelve of the thirteen patients with either eyelid edema, orbit edema or face edema can be ruled out as having angioedema. Patient #2365 (losartan 50 mg) in study 050 cannot. This patient had edema of the face and eyes and a photosensitivity rash while working in the yard on 4/24/92. Reportedly a photo is available (this has been requested from Dr. Bell, MSDRL). A similar reaction apparently occurred on 3/12/85 while the patient was receiving chlorthalidone. Thus, there are two patients (the other being patient # 488 in study 011) on losartan therapy who had face or eyelid edema. Angioedema cannot be ruled out from the information provided.
- 2) Ataxia was used as a code for adverse events such as "physically clumsy" and "slight imbalance in the head". The patients did not have ataxia.
- 3) Patient #4551 (losartan 100 mg/HCTZ 25 mg) in study 64 had elevations in ALT and AST and hepatomegaly. Other than fatigue, starting 14 days prior to detection of LFT abnormalities, there were no other symptoms suggesting hepatitis. The patient also had hyperglycemia possibly related to the discontinuation of micronase.


Charles J. Ganley, M.D.

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HFD-110/cso/ganley/chen/r.lipicky

Medical Officer Review

MAR 1 1995

NDA #: 20-386/BM
 Volume: 17.1-17.3
 Drug Name: Losartan
 Sponsor: MSDRL
 Type of Document: Request to FDA request for information
 Date of Receipt: 2/15/95
 Review Start Date: 3/1/95
 Medical Reviewer: Charles J. Ganley, M.D.

Due to malfunctioning of the CANDAs, queries of the database could not be performed in a timely manner. Queries of liver function tests, electrolytes, urine blood and renal function tests were requested from the sponsor. This submission includes the results of the queries except for those involving urine blood.

Liver Function Test Abnormalities

Liver function test abnormalities were queried by several criteria: AST and ALT > 2 times the upper limit of normal, AST and ALT > 80 U/L, AST or ALT increased, alk. phosphatase, or total bilirubin or GGT increased and hyperbilirubinemia. For the most part, abnormalities followed several patterns. Many patients had elevations of AST and ALT on one or several labs only to have them return to normal with continued losartan therapy. Some had mild abnormalities at baseline that increased after the initiation of treatment. Others had increases in ALT and AST that returned toward normal after discontinuation of therapy. Several patients had elevation in ALT or AST on the final reported lab with no additional follow-up. Three patients in the CHF trial (study 47) had abnormal tests. It was not clear whether this was due to underlying disease or losartan. Two losartan treated patients withdrew from studies due to LFT abnormalities. Patient #548 in study 011 had hepatitis A. Patient #2230 in study 050 had mild baseline abnormalities that worsened with therapy. Table 1 lists liver function test results for several patients where losartan therapy could not be ruled out as a factor in increases in LFTs. Patient #1008 had increasing edema on day 127 (?worsening heart failure). Additional information is needed to document that LFT abnormalities were due to worsening heart failure. In conclusion, asymptomatic abnormal liver function tests occurred occasionally. Their clinical significance is unknown. Clinical hepatitis (symptomatic) does not appear to be a problem.

Table 1. Liver Function Test Results for Selected Patients

	Day	ALT (U/L)	AST (U/L)	Alk. Phos. (U/L)	Total Bilirubin (U/L)
Patient #4561, Study 064					
	-4	41	24	72	
Losartan 100 mg	29	49	30	70	
Losartan 100 mg/HCTZ 25 mg	43				
Losartan 100 mg/HCTZ 25 mg/Felodipine 10mg	88	38	26	68	
Losartan 100 mg/HCTZ 25 mg/Felodipine 10mg	97				
Losartan 100 mg/HCTZ 25 mg/Felodipine 5 mg	201	63	43	82	
Losartan 100 mg/HCTZ 25 mg/Felodipine 5 mg	271	113	86	81	
Patient #0685, Study 054					
	-15	29	24	73	
Losartan 50 mg/HCTZ 6.25 mg	21	52	35	84	
Losartan 50 mg/HCTZ 6.25 mg	85	45	28	79	
Losartan 50 mg/HCTZ 6.25 mg	201	89	72	77	
Losartan 50 mg/HCTZ 12.5 mg	378	168	94	91	
off-drug	532	105	83	103	
Patient #5689, Study 059					
	1	18	19	170	
Losartan 100 mg	29	32	28	86	
Losartan 100 mg/HCTZ 12.5 mg	44	49	33	89	
Losartan 100 mg/HCTZ 25 mg	58	92	47	94	
Losartan 100 mg/HCTZ 25 mg/Atenolol 100 mg	86	87	35	118	
Losartan 100 mg/HCTZ 25 mg/Atenolol 100 mg	148	221	93	89	
Losartan 100 mg/HCTZ 25 mg/Atenolol 100 mg	268	91	39	68	
Patient #7102, Study 049					
	-43	32	21	83	
	-1	21	23	77	
Losartan 50 mg/HCTZ 25 mg	10	101	81	137	
off-drug	18	76	21	116	

Table 1. (Cont)

	Day	ALT (U/L)	AST (U/L)	Alk. Phos. (U/L)	Total Bilirubin (U/L)
Patient #4551, Study 064					
	-6	57	51	90	
Losartan 100 mg	8	65	39	100	
Losartan 100 mg/HCTZ 25 mg	15				
Los. 100 mg/HCTZ 25 mg/Diltiazem 240mg	29				
Los. 100 mg/HCTZ 25 mg/Diltiazem 300 mg	92	170	101	150	
off-drug	102	163	99	134	
off-drug	131	97	58	115	
Patient #6007, Study 048					
	-11	18	12	40	.8
Losartan 50 mg	29	18	14	42	.7
Losartan 50 mg/HCTZ 6.25 mg	53	14	14	62	1.0
Losartan 50 mg/HCTZ 6.25 mg	113	37	33	9.1	
Losartan 50 mg/HCTZ 12.5 mg	184	33	86	1.8	.9
Losartan 50 mg/HCTZ 12.5 mg	344	37	22	2.1	3.7
Patient #1008, Study 47					
	-8	42	36	93	.8
Losartan 2.5 mg	10	40	28	86	.9
Losartan 2.5 mg	32	56	42	85	1.2
Losartan 2.5 mg	66		56	113	1
Losartan 2.5 mg	95	80	58	116	1.1
Losartan 2.5 mg	109	72	59	143	1.5
Losartan 10 mg	115	86	69	137	1.5
Losartan 10 mg	125	91	76	163	1.7
Losartan 10 mg	130	216	220	266	4.4
off-drug	137	119	68	313	8.5
off-drug	144	43	40	238	6.1
off-drug	151	26	36	169	4.6
off-drug	157	22	29	143	3.5
off-drug	172				3.1
off-drug	194				4.0
Patient #1185, Study 47					
	-7	16	29		
	-1	18	21	65	
Losartan 10 mg	9	16	33	63	
Losartan 10 mg	30	29	57	56	
Losartan 10 mg	63				
Losartan 10 mg	75	16	17	48	
Losartan 10 mg	103	197	189	75	
Patient #1070, Study 047					
	-24	13	19	61	
	-1	18	23	71	
Losartan 25 mg	1				
Losartan 25 mg	10	57	30	36	
Losartan 25 mg	17	99	101	80	
off-drug	32	21	25	89	

Table 1. (cont)

	Day	ALT (U/L)	AST (U/L)	Alk. Phos. (U/L)	Total Bilirubin (U/L)
Patient #834, Study 011					
	-15	24	29	92	.5
Losartan 10 mg	14	18	26	87	.7
Losartan 10 mg	31	20	30	98	1
Losartan 10 mg	56	19	27	83	.8
Losartan 100 mg/HCTZ 12.5 mg	108	15	22	96	.6
Losartan 150 mg/HCTZ 12.5 mg	129	17	23	82	.6
Losartan 150 mg/HCTZ 12.5 mg	157	24	35	87	.7
Losartan 150 mg/HCTZ 12.5 mg	179	25	31	88	.8
Losartan 150 mg/HCTZ 12.5 mg	235	20	27	82	.9
Losartan 150 mg/HCTZ 25 mg	270	24	27	95	.4
Losartan 150 mg/HCTZ 25 mg	340	28	27	87	.7
Losartan 150 mg/HCTZ 25 mg	405	25	30	79	.6
Losartan 150 mg/HCTZ 25 mg	461	28	38	93	1
Losartan 150 mg/HCTZ 25 mg	524	29	39	72	.8
Losartan 150 mg/HCTZ 25 mg	580	25	31	68	.7
Losartan 150 mg/HCTZ 25 mg	649	21	31	81	.6
Losartan 150 mg/HCTZ 25 mg	691	22	28	99	.5
Losartan 150 mg/HCTZ 25 mg	748	243	186	98	.9
Losartan 150 mg/HCTZ 25 mg	776	244	167	128	.9

Elevations in total bilirubin alone occurred but the majority of patients had baseline elevations. In a few patients with normal baseline total bilirubin, increases were observed without increases other liver function tests. In most of these cases, the total bilirubin did not exceed 3.0 mg/dl. There are several cases where minor increases in total bilirubin were associated with minor increases in other tests of liver function. None of these cases appear to be associated with symptoms. Thus, their clinical relevance is questioned. None of the cases of isolated total bilirubin increase was associated with decreasing hemoglobin (R/O hemolytic anemia).

Hepatitis

Patient 0548 in study 011 had hepatitis A. Patient 7411 in study 049 did not have abnormal liver function tests so it is unclear why this patient was listed with hepatitis as an adverse event.

Hyperkalemia

Thirty-two patients had hyperkalemia (no limit defined) as an adverse event. Twenty-five of these patients received losartan. Four patients received losartan/HCTZ. The majority (22) of the losartan patients with hyperkalemia were from study 58 (renal insufficiency patients).

One-hundred and twenty-seven patients had serum potassium ≥ 5.5 mEq/L on at least one occasion. For the majority of patients, the increased potassium was an isolated event.

Hypernatremia

Five patients had hypernatremia as an adverse event. For the most part, if patients had increases in sodium while on losartan, the sodium returned to normal with continued therapy.

Hypokalemia

One hundred and eight patients had hypokalemia. The lowest potassium for all except two patients were between 3.0 and 3.4 mEq/L. The majority of patients with hypokalemia were receiving losartan/HCTZ. Two patients had potassiums less than 3.0 mEq/L. Both were enrolled in study 47 (CHF) and were receiving losartan and presumably a diuretic.

Creatinine and BUN Increased

Forty-eight patients had "creatinine increased" as an adverse event. Seven cases appeared to have clinically relevant changes in creatinine. Four of these received losartan/HCTZ. The creatinine improved in two of these patients when HCTZ was discontinued. Of the remaining three patients, one had CHF. Overall, the effect of losartan on renal function probably does not differ much from ACEI.

Partial Thromboplastin (PTT) or Prothrombin Time (PT) Increased

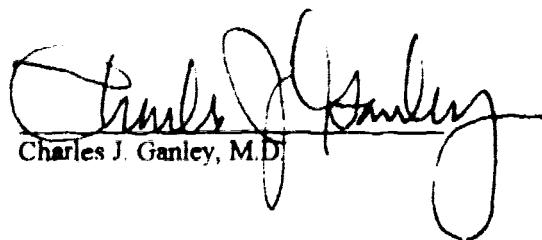
Four patients had increased PT or PTT. Lab results are not provided.

Study 58 Baseline and Last Value Creatinine and Potassium

The mean baseline and last values for creatinine and potassium does not include 12 patients and eliminates much of the data. This is the data the FDA requested and in retrospect, it is probably insufficient to make conclusion about creatinine and potassium in this population (renal insufficiency).

Conclusions:

- 1) Although losartan cannot be ruled out entirely as the cause of elevation of transaminases, the incidence of events is low and clinical hepatitis does not appear to be a problem.
- 2) Hypokalemia can still occur in patients on losartan/HCTZ.
- 3) There is nothing new to add to previous comments in the NDA review regarding increases in creatinine. Isolated instances of increased creatinine (reversible) occurred.
- 4) Creatinine and potassium data from study 58 is insufficient to make conclusions regarding changes in these parameters with losartan therapy.
- 5) No data is provided for patients with increased PT or PTT.


Charles J. Ganley, M.D.

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Medical Officer Review - Addendum to NDA Review

Safety Summary of Losartan and Renal Cell Carcinoma

NDA #: 20-386
 Drug Name: Losartan (DuP 753, MK-954)
 Sponsor: MSDRL
 Date Completed:
 Medical Reviewer: Charles J. Ganley, M.D.

The purpose of this addendum to the Medical Review of the NDA is to summarize the issue of losartan and renal cell cancer. It was not included in the primary Medical Officer review of the NDA because the original NDA database does not contain all of the clinical and pre-clinical data pertinent to the discussion. Over the course of 1994, pre-clinical trial data and information pertaining to renal cell cancer in losartan treated patients has been submitted to the NDA. These have been summarized in a separate review by Dr. Proakis (Review Date 1/18/95) and consultation by Dr. Burkhart (Division of Epidemiology Consultation Dated 11/14/94).

Background

In July of 1992, Merck submitted to the IND the results of an animal study from independent Italian investigators lead by Andrea Remuzzi. Forty-eight male Sprague-Dawley rats were treated with one of three treatments: 1) control, no treatments; 2) single dose of streptozotocin [STZ] (60 mg/kg i.v.), insulin as needed for blood sugar control; 3) single dose of streptozotocin (60 mg/kg i.v.), insulin as needed for blood sugar control, and losartan 30 - 35 mg/kg in drinking water. Table 1 outlines the treatments of this study.

Table 1.

SHORT- AND LONG-TERM EFFECT OF ANGIOTENSIN II RECEPTOR BLOCKADE IN RATS WITH EXPERIMENTAL DIABETES

Treatment Groups	Dose mg/kg	Males/Group
Untreated Control	0/0	16
STZ*⊙	60/0	16
STZ*⊙/Losartan†	60/30	15

* Intravenous streptozotocin administration on Day 1
 ⊙ Insulin administration to STZ-treated animals from Day 3
 † Losartan administration from Day 5

The purpose of the study was evaluate glomerular injury in diabetic rats (streptozotocin induced) treated with losartan. Eight rats of each treatment group would be sacrificed at 1 month and at one year to evaluate glomerular histology. When necropsy was performed after one year, the investigators observed gross tumors in losartan treated rats but not in control animals. Table 2 outlines the results. Five of eight losartan treated rats had gross tumors identified as cancers (3 renal cell, 1 sarcoma, 1 unidentified).

Table 2.

SHORT- AND LONG-TERM EFFECT OF ANGIOTENSIN II RECEPTOR BLOCKADE IN RATS WITH EXPERIMENTAL DIABETES

TREATMENT GROUPS MG/KG	REPORTED INCIDENCE	GROSS FINDINGS	HISTOLOGICAL DIAGNOSIS
Untreated Control 0/0	0/8	—	—
STZ 60/0	0/8	—	—
STZ/Losartan 60/30	5/8	4/5, 0.3 to 0.9 cm, round, nodular, pale-yellow, soft, well-delimited, anterior polar (3) or multifocal (1), left kidney 1/5, 6.0 cm, multinodular, multicystic, pale yellow to dark red-brown, soft, with significant renal parenchymal destruction, right kidney	3/4*, renal epithelial tumors (reported as renal cell carcinoma) renal mesenchymal tumor (reported as sarcomatous carcinoma)

*One tumor not evaluated histologically

The observation from the Remuzzi study raised a concern within the Cardio-Renal Division (DCRDP) that losartan may be acting as a promoter of renal tumors. This possibility was apparently also raised by Dr. Remuzzi who speculated that tumor promotion may be linked to increased levels of angiotensin II caused by losartan. In July/August 1992, Merck was encouraged by DCRDP to repeat the Remuzzi protocol to determine if this is a reproducible finding. Merck initiated two studies after discussions with DCRDP.

In February of 1994, Merck submitted information on six cases of renal cell cancer in patients enrolled in clinical trials. Five of the patients received losartan or losartan/HCTZ and one patient received placebo. The number of renal cancers in the NDA appeared to be high compared to anecdotal experience of past NDA submissions for hypertensive drugs. Since the patient exposure in the losartan and losartan/HCTZ NDAs is large relative to previous experience, it was important to determine whether the renal cancer incidence rate deviated from the expected rate. The Division of Epidemiology was consulted to address this issue.

Table 3 lists submissions to the NDA after February 1994 by Merck pertaining to renal cell cancer in animals or humans.

Table 3. NDA Submissions Pertaining to Renal Cell Carcinoma

Date Received	Submission (Volume)	Information Included in Submission
4/15/94	20-386/BM (4.1 - 4.2)	1) Case Report Forms for six patients diagnosed with renal cell carcinoma 2) Report on Pro-Renin as a marker for renal cell carcinoma 3) Reference/Report outlining increased risk for renal cell carcinoma in hypertensive patients. 4) MedWatch report of a possible seventh case of renal cell cancer in the losartan database.
7/22/94	20-386/BM (6.1)	1) Preliminary report on the results of the Merck STZ trials. 2) Report of 28 days genotoxicity/cytotoxicity study in STZ rats. 3) Summaries of eight patients with renal cell cancer. 4) Renal cell cancer epidemiology report. 5) Reports of expert consultants.
7/28/94	20-386/NC (7.1)	1) References from the medical literature pertaining to the risk factors associated with renal cancer.
8/19/94	20-386/BM (7.1)	1) Methodology used in the calculation of person years in the losartan and enalapril/lisinopril data.
8/30/94	20-386/BM (7.1)	1) References pertaining to the incidence of renal tumors in STZ treated animals. 2) Incidence of renal tumors in 2 year rat carcinogenicity studies (Merck Database Control Animals)
9/13/94	20-386/NC (7.1)	1) Incidence of Renal Cell Cancer in the SOLVD Study.
10/7/94	20-386/AP (9.1 -9.3)	1) Merck study report of their STZ trials.
10/25/94	20-386/BM (10.1)	1) Report on Incidence of All Cancers in Losartan, Enalapril and Lisinopril database.

Summary of Pre-Clinical Data Exclusive of the Remuzzi Study

There are three relevant sources of pre-clinical data that address the observations presented by the Remuzzi study. These include: 1) Losartan 2-year carcinogenicity study in Sprague-Dawley rat, 2) a Merck sponsored 28 day in vivo genotoxicity study in Sprague-Dawley rats, and 3) Merck sponsored replication of the Remuzzi protocol

In the 105 week carcinogenicity study in Sprague-Dawley rats, 150 rats (75 males, 75 females) per treatment group received losartan in daily oral doses of 15 mg/kg, 45 mg/kg or 135/270 mg/kg. There was one control group of 260 rats (130 males, 130 females). There were no malignant renal tumors observed in any group. Benign tumors were observed in one (.4%) control animal, in two (1.3%) 15 mg/kg animals, in two (1.3%) 45 mg/kg animals and in three (2.0%) 135/270 mg/kg animals. The following conclusions could be inferred from this study. Losartan did not significantly increase the incidence of benign tumors with increasing doses of losartan. Conclusions about malignant renal tumors requires more caution. The expected underlying incidence of any malignant renal tumors in Sprague-Dawley rats on no therapy is .5%. [Reviewer's Note: This is based on information provided by Merck in the 8/30/94 submission. The incidence of transitional cell or tubular adenocarcinoma is about .1%.] Thus, in a study of 150 animals with a drug that is not a carcinogen, one malignant renal tumor might be expected to be seen. The likelihood of observing a tubular or transitional cell carcinoma is less. Since no malignant renal tumors were observed, it suggests that losartan is not a tumor promoter. On the other hand, it might also suggest that the size of the study is insufficient to detect promoter activity because of the low incidence of renal malignancy in control populations. But by definition, tumor promoters should increase the incidence of benign, not just malignant tumors, and that is not seen in this study.

Merck performed an in vivo 28 day genotoxicity study (in vivo alkaline elution assay on kidney tissue) in rats treated with STZ with or without losartan. This study has been summarized by Dr. Proakis. Losartan showed no effect on the STZ damage in the kidney. Losartan alone showed no evidence of a genotoxic effect in rat kidney.

The two animal studies conducted by Merck which attempted to reproduce the results of the Remuzzi study were summarized in detail by Dr. Proakis (date review 1/18/95). The protocol followed by Merck was similar to Remuzzi with the following exceptions: 1) Merck treated 50 rats per treatment group as opposed to 8 in the Remuzzi study; 2) the purpose of the Merck study was to identify gross and microscopic tumors whereas the Remuzzi study attempted to identify glomerular changes; 3) Merck studied multiple doses of losartan (5, 30, 90 mg/kg) whereas the Remuzzi study included one dose (30 mg/kg); and 4) one of the Merck treatment groups included the combination of losartan and lisinopril in STZ treated animals whereas Remuzzi did not (The purpose of the combination was to prevent the elevations of angiotensin II seen with losartan alone.). The Merck studies produced the following results:

- 1) There were no tumors in the placebo control group (gross or histologically diagnosed).
- 2) The percentage of animals with gross tumors (benign or malignant) in STZ +/- losartan treated animals ranged from 37% - 42%. There was no significant difference between treatments groups
- 3) The treatment group, STZ plus losartan plus lisinopril, had a significant increase in the number of rats with gross tumors (benign or malignant). Seventy percent of the animals had gross tumors. However, the percentage of animals with histologically detected malignant renal tumors was 18% compared to 14% in the STZ control group
- 4) The percentage of animals with malignant tumors (histologically detected) was not significantly different between treatment groups.

Conclusion from Pre-Clinical Data

- 1) The Merck studies that followed the Remuzzi protocol did not reproduce the results observed in the Remuzzi trial. The incidence of gross renal tumors was approximately 40% in STZ control and STZ/losartan treated animals. There was no difference in malignant tumors between losartan and control animals. The incidence of tumors in STZ treated animals in the Merck trials is consistent with the published reports.
- 2) Based on the literature references provided (8/30/94 submission), the absence of tumors in the STZ control group of the Remuzzi study appears to be the aberration. The appearance of tumors in the STZ/losartan animals would be expected.
- 3) Losartan is not genotoxic to renal tissue.
- 4) The rat carcinogenicity studies do not suggest that losartan is a promoter of renal tumors.

Summary of Clinical Information

As of August 1994, Merck submitted information on eight cases of renal cancer diagnosed in the losartan database. Six of the patients received losartan or losartan/HCTZ therapy, one received placebo and one received captopril/HCTZ. The duration of treatment prior to diagnosis ranged from 158 to 929 days in the losartan +/- HCTZ patients, 42 days in the placebo patient and 51 days in the captopril/HCTZ patient (NOTE: this patient had symptoms, flank pain, referable to tumor starting on day 1 of therapy). A table listing pertinent information on these eight patients and narrative summaries for these patients are provided in the appendix. As of February 1995, there have been no additional cases of renal cancer diagnosed (personal communication with Dr. Bell, MSDRL).

A formal consultation was made to the FDA Division of Epidemiology to determine whether the rate of renal cell tumors in the losartan NDA was elevated. In order to sort out the incidence rate of renal cell cancer in the losartan database, comparative information was obtained from several sources. This information included the following

- 1) information on patient exposure and renal cell carcinoma in the enalapril and lisinopril NDA databases (Merck);
- 2) the DCRDP requested that several pharmaceutical companies provide information on all cancers and patient exposure in NDAs from other anti-hypertensive agents;
- 3) the incidence of renal cell cancer in the SOLVD Trial [Reviewer's Note: This database in CHF patients could be compared to enalapril hypertensive database.]
- 4) the FDA Division of Epidemiology obtained cancer incidence rates from the SHEP trial;
- 5) the National Institute of Health's Surveillance, Epidemiology and End Results (SEER) project data which provided renal cell cancer rates based on age and gender for the general population;
- 6) a review of the medical literature for the relative risk of developing renal cell cancer in hypertensives.

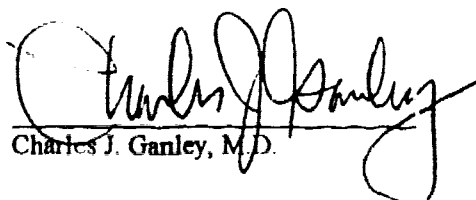
Dr. Burkhart has summarized the pertinent information in his consultation. Please refer to Dr. Burkhart's consultation for details. There was no difference in the renal cell cancer incidence rates between the losartan database and enalapril/lisinopril database. Compared to the SEER data, patients in both the losartan and enalapril/lisinopril database had increased relative risk ratios for renal cancer. There are at least two possible explanations for this observation. Either losartan and the ACE inhibitors increased the risk for renal cancer or hypertension is a risk factor for renal cell cancer. The latter explanation appears to be the more plausible based on the following reasoning. In the SOLVD Trial, enalapril did not increase the incidence of renal cancer compared to placebo. If a pharmacologic class of drugs increases the risk of developing a tumor, this should occur in all patients regardless of underlying diagnosis. Thus, failing to increase tumors in all patients supports the conclusion that the underlying disease may be the risk factor. This is supported by the cohort studies in the literature (see submission dated 7/28/94) which suggest that hypertension is a risk factor for renal cell cancer. Since enalapril is not perceived to be a promoter of renal tumors, the increased risk in the losartan and enalapril/lisinopril hypertension database could be attributed to underlying disease.

The cancer incidence rates and patient exposure databases obtained from other sponsors were not helpful for two reasons. First, most of the databases contained a limited amount of patient exposure greater than one year. Second, there was doubt that the surveillance mechanisms in these databases were as rigorous as those utilized by Merck since the expected overall cancer incidences reported was less than expected from the SEER data.

Overall Summary

When the pre-clinical data is viewed in its entirety, there is no convincing evidence that leads one to believe that losartan acts as a promoter of kidney tumors. The Remuzzi study observations are not supported by studies performed by Merck or by data from the medical literature.

Although the number of renal cancers reported in the losartan database seems high, the incidence is comparable to that observed in the enalapril/lisinopril database. The pre-clinical and clinical database do not suggest that losartan is a promoter of renal tumors.



Charles J. Ganley, M.D.

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Plus 11 appendix pages

The appendix contains narrative summaries for the patients diagnosed with renal cell cancer in the NDA. There are some corrections. For patient #8111, there is no data to support a 20 year history of hematuria. For Patient #575, Dr. Sealey did not contact the investigator prior to randomization and inform him of the patient's high pro-renin level. All of the urine tests collected in the double-blind and open label period showed no urine blood or at most 1-3 RBC/HPF until gross hematuria developed. Patient 7411 is a lawyer and it is unlikely that a renal cystic mass diagnosed in 1984 was thought to be cancerous. Although not stated, there must have been a change in the scans performed 12/92 compared to previous.

Table

**EIGHT CASES OF RENAL CELL CARCINOMA
REPORTED TO DATE IN LOSARTAN CLINICAL TRIALS**

WAES #	Protocol/ Study #	AN	Age/ Sex	Treatment (mg Daily Dose)	Treatment Duration* (Days)	Date of Diagnosis	History/Pre-Study Evaluations	Symptoms/ Rei Day of SX Onset***	Diagnoses/Pathology	Drug Relationship
93110403	011/028	0575	75/M	Losartan 50	929	10/25/93	Essential hypertension Elevated pre-study prorenin (163 ng A ₁ /ml/hr)	Gross hematuria/ Day 689	7x7x3.7 cm right renal cell carcinoma, clear cell type Tumor positive for prorenin Post nephrectomy plasma prorenin activity 33 ng A ₁ /ml/hr	Not Drug Related
92080592	047/008	1071	74/F	Losartan 50	158	8/15/92	Essential hypertension NYHA Class II heart failure Microscopic hematuria (20-29 ; 30-39 RBC/HPF)	Asymptomatic - Discovered during follow-up of renal insufficiency	6x5x3.5 cm right renal cell carcinoma, tubulopapillary pattern	Not Drug Related
92121500	049/023	7411	62/M	Losartan 50/ HCTZ 12.5	292	12/9/92	Essential hypertension Tobacco use 8 cm left renal mass - 1984 Microscopic hematuria (3-5 RBC/HPF)	Asymptomatic - Discovered during follow-up of pre- existing left renal mass	7x7x8 cm left renal cell carcinoma, multifocal papillary renal cell carcinoma	Not Drug Related
93120150	054/011	8255	43/M	Losartan 50/ HCTZ 6.25	484	10/7/93	Essential hypertension Tobacco use Chronic low back pain - 1991	Gross hematuria, Dysuria, Right flank pain/Day 348	10x10x10 cm right renal cell carcinoma, predominantly clear cell type	Not Drug Related
93101058	054/019	8876	63/F	Losartan 50/ HCTZ 12.5/ Felodipine 5	452	10/4/93	Essential hypertension	Gross hematuria Left flank pain Urinary retention with clots/Day 448	8.2x8.2x8.0 cm left renal cell carcinoma, predominantly clear cell type	Not Drug Related
**93110771	076/001	102	59/M	Placebo	42	11/11/93	Essential Hypertension	Urinary frequency Nocturia	7 cm left renal cell carcinoma	Not Drug Related
4040801	084/008	0081	67/F	Captopril 50/ HCTZ 25	51	4/11/94	Hypertension	Umbilic pain/ Day 3	8x5x5 cm left renal cell carcinoma, nuclear grade II	Not Drug Related
4040165	054/005	8111	56/M	Losartan 50/ HCTZ 6.25	651	3/14/94	Essential Hypertension Unexplained mild microscopic hematuria - past 20 years	Gross hematuria/ Day 633	5x 5x4.3 cm left renal cell carcinoma, clear cell type.	Not Drug Related

* Treatment duration is based on calendar days post initiation of losartan therapy up to and including date of diagnosis.

** This patient was found to have a renal cell carcinoma at the time of his participation in the felodipine-nalapril interaction study subsequent to his participation in the RAAS II study during which he received placebo therapy.

*** Day symptoms were first noted (approximately) relative to the start date of losartan or comparative agent therapy.

Study #011-028 AN 0575
WAES # 93110403

Patient AN 0575 is a 75 year-old Caucasian male with a past medical history of essential hypertension. The patient was enrolled into the placebo baseline phase of A Double-Blind, Randomized, Parallel, Placebo-Controlled Study to Investigate the Antihypertensive Efficacy and Safety of Different Doses of DuP 753 (MK-954) on 2/10/91. The patient was randomized to double-blind treatment with losartan 50 mg once-daily on 3/10/91. The patient completed the 8 week double-blind treatment phase of the study and began open-label maintenance therapy with losartan 50 mg once-daily on 5/13/91. At the time of the diagnosis of renal cell carcinoma, the patient had been receiving losartan 50 mg therapy for 929 days.

The patient's clinical and laboratory safety profiles during the double-blind phase of the study were unremarkable with the exception of microscopic hematuria (10-15 RBC/HPF) noted in a routine urinalysis performed on 3/23/91. During open-label maintenance, the patient developed intermittent gross hematuria, the episodes of hematuria becoming more frequent. The hematuria was first noted in a clinic visit on September 3, 1993. When questioned about the first occurrence of the hematuria, the patient stated that it had been intermittently occurring since February, 1993, but had not been reported by the patient to the study physician. Periodic urinalyses performed as a part of study procedures during this time period were totally devoid of blood.

During follow-up of the gross hematuria on 10/1/93, an IVP was performed, which indicated the presence of a right renal mass. Subsequent CT scan located the solid mass coming off the lower pole of the right kidney. Cystoscopic examination did not reveal any abnormalities to account for the hematuria. Based on these findings, right renal exploratory surgery was performed on 10/26/93 which resulted in a right radical nephrectomy. The kidney with attached perirenal adipose tissue was subjected to pathological examination. The mass was diagnosed as a 7x7x3.7 cm renal cell carcinoma, clear cell type, extending through the renal capsule into perirenal fat. Metastasis was not noted. The patient recovered and was discharged from the hospital. The patient was discontinued from the study due to the development of the renal cell carcinoma. The investigator felt the development of renal carcinoma was not related to study drug therapy.

Plasma renin (PRA) and plasma prorenin activity were measured prior to the start of double-blind treatment and periodically thereafter during the course of double-blind and open-label therapy for all patients participating in the clinical trial. These measurements were performed by Dr. Jean Sealey at Cornell University. Prior to the patient's randomization to losartan therapy in 1991, Dr. Sealey contacted the study investigator to alert him to this patient's high prorenin activity (163 ng A1/ml/hr on 3/9/91), displayed in Table below. It was Dr. Sealey's opinion that the elevated pre-study prorenin value could have been indicative of the presence of a renal tumor. A plasma sample obtained from the patient post-nephrectomy revealed that the prorenin activity normalized to 33 ng A1/ml/hr (normal range : 28-44 ng A1/ml/hr). Analysis of

the tumor revealed staining for prorenin. The surrounding normal tissue stained positive for renin.

Table

Plasma Renin and Prorenin Activity Levels
Patient AN #0575

Study Phase	Sample Date	Plasma Renin Activity ng A ₁ /ml/hr	Prorenin Activity * ng A ₁ /ml/hr
Pre-Study	3/9/91	4.4	163
Double-Blind	5/4/91	19.0	111
	5/5/91	5.5	123
	5/12/91	3.2	163
Post-Nephrectomy	1/15/94	1.6	33

*Normal Levels Prorenin Activity = 28-40 ng A₁/ml/hr

Study #047-008 AN 1071

WAES # 92080592

Patient AN #1071 is a 73 year-old black female with a past medical history of hypertension, atrial fibrillation, coronary artery disease, NYHA Class II heart failure, hyperthyroidism and hematuria. This patient was enrolled into the Multicenter, Double-Blind, Randomized, Parallel, Multiple-Dose, Placebo-Controlled Study of the Hemodynamic and Clinical Effects of Losartan in Patients with Heart Failure on 2/24/92. Baseline urinalysis performed prior to the initiation of double-blind therapy indicated the presence of microscopic hematuria (20-29 RBC/HPF on 2/24/92, 30-39 RBC/HPF on 3/9/92). The patient began double-blind therapy with losartan 2.5 mg once-daily on 3/10/92. She entered open-label maintenance on 6/10/92 with losartan 2.5 mg once-daily and was gradually titrated to a final maximal dose of losartan 50 mg once-daily on 7/16/92 which was maintained for the duration of her open-label participation. At the time of diagnosis of the renal cell carcinoma, the patient had been receiving losartan therapy for 158 days. Concomitant medication included quinidine gluconate, quinine sulfate, sodium warfarin, furosemide, digoxin, potassium chloride, and acetaminophen-codeine.

On 8/15/92, the patient was admitted to the hospital complaining of nausea, vomiting and general malaise. Laboratory tests performed on 8/14/92 indicated elevated BUN, serum creatinine and digoxin levels. Losartan therapy was discontinued on 8/14/92; therapy with all other previous concomitant therapies was discontinued on 8/15/92. An initial diagnosis of renal insufficiency was made. The patient was discontinued from the study due to the development of renal insufficiency; early termination procedures required by the study protocol were completed on 8/28/92. Further work-up of the patient's renal insufficiency included a sonogram followed by a CAT scan of her abdomen and pelvis, which revealed a large right renal mass believed to be a neoplasm. A left renal calculus was also observed. A CAT scan of her chest and a bone scan revealed no other evidence of disease. On 9/9/92, the patient underwent a right nephrectomy. Pathological examination of the tumor revealed a single nodular mass measuring 6x5x3.5 cm. The microscopic diagnosis was renal cell carcinoma, predominantly tubulopapillary pattern, Stage I. The patient was discharged from the hospital on 9/19/92 and subsequently recovered. The investigator felt the renal insufficiency and renal carcinoma were not related to study drug therapy.

Study #049-023 AN 7411
WAES #92121500

Patient AN 7411 is a 62 year-old Caucasian male patient with a medical history of hypertension and tobacco use. The patient also had a documented history of an asymptomatic 8 cm left upper pole renal cyst first discovered in a CT scan of the abdomen performed in 1984. The impression of the consulting physician at the time of the initial discovery of the mass was that the calcifications and general appearance of the mass suggested the possibility of a renal cell carcinoma. The physician suggested further evaluation of the mass by skinny needle biopsy and/cr arteriography. These tests were not performed. Status of the mass was evaluated periodically over the course of the next 8 years, prior to the patient's entry into the losartan clinical trial. The last prior examination of the cyst had occurred in 1988, via IVP analysis. The impression from this examination was that the asymptomatic left renal cyst was unchanged in appearance and therefore was believed to be benign. The patient was enrolled into A Randomized, Double-Blind, Parallel Study of the Safety and Antihypertensive Efficacy of Hydrochlorothiazide in Combination with Losartan on 1/30/92. On 2/13/92, the patient began single blind therapy with 25 mg hydrochlorothiazide once daily. On 3/5/92, the patient was randomized to double-blind therapy with 100 mg losartan once-daily in addition to the 25 mg hydrochlorothiazide. At the time of diagnosis of the renal cell carcinoma, the patient had been receiving losartan therapy for 292 days.

Clinical and laboratory safety data from this period were unremarkable with the exception of mild microscopic hematuria (3-5 RBC/HPF) noted on a routine urinalysis performed on 3/4/92, prior to initiation of the losartan therapy. The patient completed the double-blind phase of the study and entered the open-label study extension on 5/28/92. Therapy was initiated with 50 mg losartan once-daily. Hydrochlorothiazide 6.25 mg therapy was added after 2 weeks and eventually titrated to 25 mg once-daily. Combination therapy with losartan 50 mg/hydrochlorothiazide 25 mg once-daily was maintained until 12/15/92. During the patient's participation in the study extension, the patient initiated further follow-up of the renal mass at the Baylor VA hospital. The evaluation consisted of a renal ultrasound and CT scan. A bone scan for metastatic workup was also performed. The metastatic workup was negative. The ultrasound and CT scan revealed two calcified cystic densities in the left kidney. There was also a questionable calcification on the right kidney. The patient was admitted to the hospital on 12/9/92 for a radical nephrectomy of the left kidney. Pathological examination of the kidney revealed a large 7x7x8 cm necrotic tumor in the upper pole extending through the capsule into adjacent fat. An additional multifocal papillary renal cell carcinoma in the lower pole and remainder of the kidney parenchyma was discovered. The patient recovered from the surgery and was discharged on 1/8/93. Follow-up of this patient was planned to evaluate the lesion seen on the patient's right kidney. The patient was discontinued from the clinical trial on 12/22/92 due to the left renal carcinoma. The investigator did not feel this adverse experience was study drug related.

Study #054-011 AN 8255
WAES # 93120150

Patient AN 8255 is a 43 year-old Caucasian male patient with a medical history of essential hypertension, chronic low back pain (from 1991) and tobacco use. The patient entered A Randomized, Placebo-Controlled, Double-Blind Parallel Study of the Safety and Antihypertensive Efficacy of Losartan Monotherapy as Compared to HCTZ Monotherapy and to the Combination of Losartan and HCTZ in Patients with Mild to Moderate Hypertension on 5/13/92. He was randomized to double-blind therapy with losartan 50mg once-daily on 6/11/92. The patient's clinical and laboratory safety profiles during the double-blind phase of the study were unremarkable. The patient entered open-label maintenance therapy with losartan 50mg/ HCTZ 6.25mg once-daily on 9/3/92. At the time of diagnosis of the renal cell carcinoma, the patient had been receiving losartan therapy for 484 days.

On 5/21/93, the patient experienced dysuria, gross hematuria and right flank pain. He was treated for a urinary tract infection with antibiotics; the condition resolved. Follow-up of the gross hematuria was performed. An IVP revealed a distorted right renal collecting system. Subsequent renal ultrasound identified a right renal mass. The patient was admitted to the hospital on 10/4/93 for additional work-up of the mass by computerized tomography and magnetic resonance imaging. A chest X-ray performed upon admission showed no evidence of metastatic disease. Based on the tomography and MRI results, exploratory surgery of the renal mass was performed on 10/7/93, which led to a right radical nephrectomy. The patient recovered from the surgery and was discharged from the hospital on 10/15/93. The patient continued with study medication during hospitalization and post-nephrectomy.

Pathological examination of the kidney revealed a 10x10x10 cm mass expanding the renal capsule without identified gross penetration. Gross renal vein involvement was apparent. Microscopic analysis identified the mass as a renal cell carcinoma, predominantly clear cell type but with some granular cells. The patient is continuing with the clinical trial. The investigator felt the renal carcinoma was not related to study drug therapy.

Study # 054-019 AN 8876
WAES # 93101058

Patient AN 8876 is a 63 year-old Caucasian female patient with a medical history of essential hypertension. The patient entered A Randomized, Placebo-Controlled, Double-Blind, Parallel Study of the Safety and Antihypertensive Efficacy of Losartan Monotherapy as Compared to HCTZ Monotherapy and to the Combination of Losartan and HCTZ in Patients with Mild to Moderate Hypertension on 6/10/92. She was randomized to double-blind therapy with losartan 50mg once-daily on 7/9/92. The patient's clinical and laboratory safety profiles during the double-blind phase of the study were unremarkable. The patient entered open-label maintenance therapy with losartan 50mg/ HCTZ 6.25mg once-daily on 10/1/92. Her treatment was eventually titrated to losartan 50mg/ HCTZ 12.5mg/ felodipine 5mg once-daily on 9/29/93, and was maintained as such for the duration of her participation in the study. At the time of diagnosis of the renal cell carcinoma, the patient had been receiving losartan therapy for 452 days.

On 9/30/93, the patient experienced an episode of gross hematuria and was placed on antibiotics for treatment of a suspected urinary tract infection. The hematuria reoccurred on 10/1/93 and was accompanied by left flank pain and urinary retention with clots. An IVP revealed a large left renal mass. A CT scan indicated that the mass had an appearance fairly typical for that of renal cell carcinoma. No signs of metastases were observed on the CT scan. Subsequent chest X-ray and bone scan also failed to show any evidence of metastases. The patient was admitted to the hospital on 10/4/93. A left radical nephrectomy, extended lymphadenectomy and unilateral salpingo-oophorectomy were performed. Pathological examination of tissue samples indicated that the lesion was confined to the kidney. Gross examination of the kidney revealed a mass encompassing the entire lower pole which measured 8.2x8.2x8.0 cm. No tumor encroached into the renal pelvis, calyces or renal vein. Microscopic examination confirmed the diagnosis of stage I renal cell carcinoma, predominantly clear cell type, with focal sarcomatoid features. Metastases to hilar lymph nodes were not found. The patient recovered from the surgery and was discharged on 10/15/93. Her study medication was continued during hospitalization. The patient was discontinued from the clinical trial upon discharge from the hospital. The study investigator felt the renal cell carcinoma was not related to study drug therapy.

Study # 076-001 (017-001) AN 102 (0003)*
WAES #93110771

Patient AN 102 is a 59 year-old Caucasian male patient with a medical history of essential hypertension. The patient entered an Open, Randomized, Three-Period Crossover Study to Investigate the Pharmacokinetic Interaction Between Felodipine ER and Enalapril in Hypertensive Patients on 9/9/93. On 9/28/93 he was randomized to enalapril maleate 5 mg once-daily. On 10/12/93 he was placed on therapy with felodipine ER 5 mg/enalapril maleate 5 mg once-daily. On 10/18/93 felodipine ER 5 mg/enalapril maleate 5 mg was discontinued as per protocol and on 10/26/93 he resumed therapy with felodipine ER 5 mg once-daily through 11/1/93. The patient's clinical and laboratory safety profiles during the double-blind phase of the study were unremarkable. Prior to entry into this study, the patient had been a participant in the RAAS II study during which he received placebo therapy (the patient had never received losartan therapy).

In 1993 (exact date unknown), the patient experienced urinary frequency, nocturia, and slowing of his stream. Ultrasound revealed a 7 cm solid mass in the upper pole of the left kidney. A CT scan revealed a solid tumor without evidence of perirenal lymphadenopathy or renal vein involvement. On 11/15/93 the patient was hospitalized for a left radical nephrectomy. On 11/21/93 the patient was voiding well, his wound was clean and he was discharged; however, the patient was considered not recovered.

Pathological examination of the kidney revealed renal cell carcinoma. The vascular margins, renal capsular margins, and ureteral margins were free of tumor. In addition, there were no positive lymph nodes. The investigator felt the renal cell carcinoma was not related to study drug therapy.

*This patient was found to have a renal cell carcinoma at the time of his participation in the felodipine/enalapril interaction study subsequent to his participation in the RAAS II study during which he received placebo therapy only.

Study # 084-008 AN 0081
WAES # 93110771

Patient AN 0081 is a 67 year-old Latin American female with a past medical history of hypertension. The patient entered the double-blind treatment phase of A Randomized, Double-Blind, Multicenter Study of the Safety and Antihypertensive Efficacy of the Losartan 50 mg/Hydrochlorothiazide (HCTZ) 12.5 mg Combination Compared to the Captopril 50 mg/HCTZ 25 mg Combination in Elderly and Younger Patients With Mild to Moderate Essential Hypertension on 2/20/94 and was randomized to Captopril 50 mg/HCTZ 25 mg once-daily. At the time of diagnosis of the renal cell carcinoma, the patient had been receiving Captopril/HCTZ therapy for 51 days and had never received losartan therapy.

On 2/23/94, the patient began to experience lumbar pain. On 4/4/94, an abdominal examination revealed mild pain in the left kidney. A sonogram performed on 4/11/94 revealed a renal mass. The presence of the mass was confirmed by a CT scan performed on 4/13/94. Surgery to explore the mass was performed on 4/18/94.

The final pathological report on specimens obtained during the exploratory surgery confirmed that the 8x5x5 cm tumor found in the upper lobe of the left kidney was a renal cell adenocarcinoma (hypernephroma), nuclear grade II, with microscopic involvement of the perirenal fat. There was no evidence of metastases. The patient recovered from the surgery and continued to participate in the study. The investigator felt the renal cell carcinoma was not related to study drug therapy.

Study # 054-005 AN 8111
WAES # 94040165

Patient AN 8111 is a 56 year-old Caucasian male patient who had been treated with "cholesterol medication" with a medical history of essential hypertension and unspecified orthopedic surgery. He had unexplained mild microscopic hematuria present for the past twenty years, which could not be attributed to any type of chronic infection, as well as borderline/mildly increased BUN and serum creatinine levels. The patient entered A Randomized, Placebo-Controlled, Double-Blind Parallel Study of the Safety and Antihypertensive Efficacy of Losartan Monotherapy as Compared to HCTZ in Patients with Mild to Moderate Hypertension on 5/22/92. He was randomized to double-blind therapy with losartan 50 mg/HCTZ 6.25 mg once-daily on 6/19/92. The patient's clinical safety profile during the double-blind phase of the study was unremarkable. The patient's baseline laboratory revealed microscopic hematuria (RBC 8-18/HPF) which remained relatively constant throughout the study until the patient developed gross hematuria. The patient started open-label maintenance therapy with losartan 50 mg/HCTZ 6.25 mg once-daily on 9/11/92. At the time of diagnosis of the renal cell carcinoma, the patient had been receiving Losartan therapy for 633 days.

On 3/14/94, the patient developed gross painless hematuria. A subsequent MRI revealed a left kidney mass. An intravenous urogram was abnormal and a CT scan showed a large mass in the left kidney. Cystoscopic examination revealed a clear bladder and some "mild" prostatitis. Based on the MRI, urogram and CT scan results, the patient was hospitalized for a left radical nephrectomy performed on 4/1/94. There was no evidence of metastases discovered during the surgery. The patient recovered from the operation and continued with study drug therapy.

Histopathological examination of the mass and surrounding tissue was conducted post-nephrectomy. The report indicated that the left kidney weighed 260 gm and measured 11x6.5x6 cm. The adrenal gland was not seen and no hilar lymph nodes were noted. A "canary yellow, fairly circumscribed neoplasm" measuring 5x5x4.3 cm was noted extending from the mid portion of the kidney near the hilum. The tumor extended into the capsule and bulged above the surrounding parenchyma to a height of 2.5 cm with areas of central scarring and focal cyst formation. The nephric capsule was not penetrated. The renal vein contained an approximately 1.8 cm tumor from the renal vein line of surgical resection. The renal vein margin was free of tumor and the capsule was intact. In addition, no adenopathy was noted during surgery. A diagnosis of a renal cell carcinoma, clear cell variant with invasion of the renal vein was made. It was considered to be a T3bNXMX lesion under the American Joint Committee on cancer staging. The patient is continuing with the clinical trial. The investigator felt the renal cell carcinoma was not related to study drug therapy.

Medical Officer Review

FEB 27 1995

NDA #: 20-386/BM
Drug Name: Losartan
Sponsor: MSDRL
Date of Receipt: 2/10/94
Review Start Date: 2/27/95
Medical Reviewer: Charles J. Ganley, M.D.

Merck has proposed losartan labeling that states there is no drug interaction of clinical significance between losartan and warfarin. The support for this statement is based on the results of study 70. In study 70, ten healthy male subjects received a 30 mg dose of warfarin on the seventh day of a 12 day course of losartan and placebo. The pharmacokinetic parameters did not differ for warfarin enantiomers. The AUC for the prothrombin time was not different between treatments. In addition, the sponsor notes that 25% of the patients in study 47 (CHF study) received warfarin and an increased prothrombin time was only noted in patient 1031 (associated with bleeding gums). This submission contains the prothrombin times from patients in study 68 (CHF study).

Study 70 appears to show that there is not a pharmacokinetic and pharmacodynamic interaction between losartan and warfarin. However, similar trial designs performed in the past have not predicted an interaction when one may be present. The most compelling example is the interaction between norfloxacin and warfarin. Bjornsson et al. (the primary investigator in study 70) published a trial (J Clin Pharmacol 1990;30: 728-732) in which subjects received warfarin 30 mg on the fourth day of a nine day treatment period of norfloxacin and placebo. Unlike study 70, total warfarin concentration was measured as opposed to the individual enantiomers. The study suggested that warfarin pharmacokinetics did not change with norfloxacin. Pharmacodynamics as measured by AUC for prothrombin time did not change. Thus, the conclusion by the investigator was that a clinically important interaction of norfloxacin and warfarin is unlikely to occur. Why then does the Physicians Desk Reference and the American Hospital Formulary Service (AHFS) Drug Information book suggest otherwise? The PDR labeling (1994 edition) for norfloxacin states, "Quinolones, including norfloxacin, may enhance the effects of the oral anticoagulant warfarin or its derivatives". The AHFS (1993) states the following:

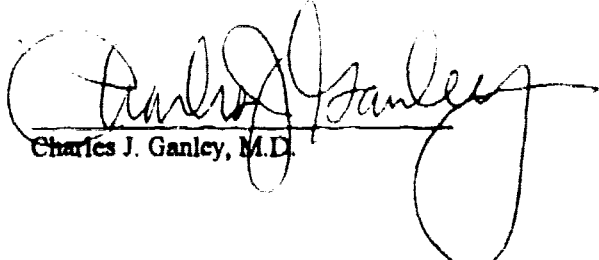
Initiation of oral norfloxacin therapy in patients stabilized on warfarin has resulted in prolongation of the prothrombin time in several patients and, in at least one patient, concomitant use of the drugs resulted in an increased prothrombin time and fatal pontine hemorrhage. Concomitant use of some other quinolones (e.g., ciprofloxacin, nalidixic acid) in patients receiving coumarin anticoagulants has also resulted in increased prothrombin times. The mechanism of this interaction has not been determined to date, but norfloxacin, like nalidixic acid, may displace the anticoagulants from serum albumin binding sites. Norfloxacin should be administered with caution in patients receiving a coumarin anticoagulant and prothrombin time or another appropriate coagulation test should be closely monitored.

Conclusion:

Prothrombin times included in this submission are not helpful in providing proof that there is no interaction. Additional information for patient #1031 from study 47 has not been provided.

Losartan is a > 99% bound to plasma protein, primarily albumin. If losartan displaces warfarin from albumin binding sites, the acute increase in free warfarin concentration may be sufficient to be clinically significant. Although study 70 suggests that there is not a pharmacokinetic interaction, it does not rule out a clinically significant pharmacodynamic interaction acutely.

It would be worthwhile to have FDA Division of Biopharm comment on the discrepancy between the results of the norfloxacin study and the labeling for norfloxacin and what should be done with the labeling for losartan. The proposed labeling should not be permitted.


Charles J. Ganley, M.D.

cc: orig
HFD-110
HFD-110/cso/ganley/chen/lipicky
HFD-426/e.fadiran; HFD-100/robert temple

Medical Officer Review

JAN 31 1995

NDA #: 20-386
Drug Name: Losartan
Sponsor: MSDRL
Date of Receipt: 10/7/94
Review Start Date: 1/26/95
Medical Reviewer: Charles J. Ganley, M.D.

This submission contains responses to following request for information:

1) Further clarification of the circumstances surrounding the withdrawal of patients from clinical trials for the reasons --> Patient Withdrew or Lost to follow-up. In the long term extension studies, 16 patients withdrew due to Lost to Follow-up and 27 for Patient Withdrew. In the acute double blind period, 30 patients were lost to follow-up and 48 are listed as Patient Withdrew.

For patients lost to follow-up, I am interested in knowing what attempts were made by the investigator to contact the patients and if there are other circumstances that may have contributed to the patients not returning for additional visits (i.e. adverse events or lack of therapeutic benefit).

For patients listed as Patient Withdrew, this is really not an acceptable explanation for withdrawing a patient. Lists of patients Lost to Follow-up and Patient Withdrew are attached.

2) I am interested in looking at all of the coagulation profile (i.e. PT, INR) information on all patients who received an anticoagulant while on losartan therapy. I have attached a list of patients in the CANDA who have been on anticoagulants and losartan. Most are from studies 016 and 047 although 4 patients are not. These labs are not in the CANDA. Where can I find them in the paper copy? If the data for patients in 016 and 047 is not together, can a spreadsheet be generated from your database that makes this information available on a floppy disk for Excel on the Canda?

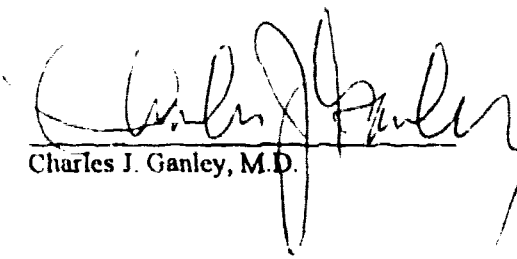
In the extension studies, WMA database:

3) In the CANDA, patients #648 and #2248, are listed as withdrawing due to clinical AE in the extension periods. They are not included in the summary table 87a of the sponsor's CSR. Please explain?

4) In table 87a, the ae responsible for discontinuation of patient 0322 is decreased libido. Is this correct?

If additional clarification for any of these requests is needed, please contact me?

The responses to these questions have been incorporated into the NDA review


Charles J. Ganley, M.D.

cc: orig
HFD-110
HFD-110/cso/ganley/chen

JUL 19 1994

Medical Officer Review

107

IND # 20-386/BM

Drug Name: Losartan

Sponsor: MSDRI

Date of Receipt: 7/15/94

Date of Completion: 7/19/94

Medical Reviewer: Charles J. Ganley, M.D.

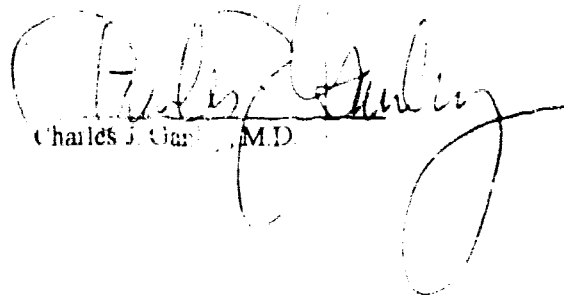
In a 4/15/94 submission describing cases of renal cell cancer in patients on losartan, a MedWatch report describing a case of a patient with a newly diagnosed renal mass (see attachment). This submission provides the pathology report of the kidney post resection.

This is a 56 year old male who entered an open label study of losartan on 7/16/92. The patient received losartan 50 mg/HCTZ 6.25 mg. Apparently, he had a 20 year history of unexplained mild hematuria as well as borderline increased BUN and creatinine (values not provided). In March of 1994, the patient developed painless, gross hematuria. A left kidney mass was diagnosed by MRI scan. The patient had a nephrectomy performed on 4/1/94. The pathology report indicates the mass is a renal cell (clear cell) carcinoma.

This is the sixth case of renal cell cancer in a patient receiving losartan.

Regulatory Action:

The sponsor needs to provide a complete case report form (copies of the original ---not computerized copy of information), including lab reports, for this patient. The sponsor should also obtain from the investigator any information on this patient pertaining to past work-ups for the 20 year history of painless hematuria prior to entering this trial.



Charles J. Ganley, M.D.

cc: orig
HFD-110
HFD-110/cao/ganley/chen
greg burkhart (Room 655 in Woodmont II Bldg.)

K5

MERCK Human Health Division

Merck Form 104 of FDA Form 302DA
Approved by FDA (10/21/1988)

For use by user-facilities,
distributors and manufacturers for
MANDATORY reporting

MedWatch

FDA MEDICAL PRODUCTS REPORTING PROGRAM

MR report #	WARS 94040165
UF/DA report #	
FDA Use Only	

A. Patient information

1. Patient identifier in codepage	2. Age at time of event or Date of birth: 56 YRS	3. Sex ☐ female ☒ male	4. Weight 155 LBS

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g. defects/malfunctions)	
2. Causes attributed to adverse event (check all that apply)	
☐ death (m/day/yr)	☐ disability
☐ life-threatening	☐ congenital anomaly
☒ hospitalization - initial or prolonged	☐ required intervention to prevent permanent impairment/damage
☐ other: _____	
3. Date of event (m/day/yr) 03/14/94	4. Date of this report (m/day/yr)

5. Describe event or problem
A 56-year-old male entered a study comparing the safety and antihypertensive efficacy of losartan monotherapy, hydrochlorothiazide monotherapy and the combination of losartan and hydrochlorothiazide in patients with mild to moderate essential hypertension. He had unexplained "mild" microscopic hematuria present for the past twenty years, which could not be attributed to any type of chronic infection, as well as "borderline/mildly" increased BUN and serum creatinine levels. The patient entered the open-label extension phase of the study and was placed on therapy with losartan 50 mg daily and hydrochlorothiazide 6.25 mg daily on 16JUL92 for the treatment of hypertension. On 14MAR94, the patient
(CONTINUED ON ATTACHED PAGE)

6. Relevant laboratory data, including dates	
DIAGNOSTIC TEST	DATE
MRI	
COMMENT: LEFT KIDNEY TUMOR	

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy smoking and alcohol use, hepatic/renal dysfunction, etc.)
CONCURRENT CONDITIONS: Hematuria, microscopic; Bun increased; Serum creatinine increased

C. Suspect medication(s)

1. Name (give labeled strength & salt/base, if known)	
#1 Tab Losartan 50 mg	
#2 Tab HydroDIURIL® 6.25 mg	
2. Dose, frequency & route used	3. Therapy dates (month/year) of admission, give duration
#1 50 mg/DAILY/PO	#1 07/16/92-CONT
#2 6.25 mg/DAILY/PO	#2 07/16/92-CONT
4. Diagnosis for use (indication)	
#1 Hypertension	
#2 Hypertension	
5. Lot # (if known)	7. Exp. date (if known)
#1	#1
#2	#2
8. NDC # - for product problems only (if known)	
#1	#1
#2	#2
9. Event started after use stopped or after resuse	
#1	yes no N/A unk
#2	☐ ☐ ☒ ☐
10. Event happened after reinitiation	
#1	yes no N/A unk
#2	☐ ☐ ☒ ☐
10. Concomitant medical problems and therapy dates (include treatment of event)	
UNKNOWN	

G. All manufacturers

1. Contact office - name/address	2. Phone number
Merck Human Health Division Merck & Co., Inc. P.O. Box 4 West Point, PA 19486-0004	(215)397-2416
3. Report source (check all that apply)	
☐ family	
☒ study	
☐ the store	
☐ advertiser	
☒ health professional	
☐ user facility	
☐ company representative	
☐ distributor	
☐ other:	
4. Date received by manufacturer (m/day/yr) 04/01/94	5. AND, protocol #
	GENSTUDY 054005
6. Type of report	7. MR. report number
☐ 1-day ☐ 10-day	WARS 94040165
☐ 10-day ☐ periodic	
☒ initial ☐ follow-up	
8. Adverse event (terms)	
MASS, KIDNEY	

E. Initial reporter

1. Name, address & phone #		
UNKNOWN PHONE #		
2. Health professional?	3. Occupation	4. Initial reporter sent report to FDA
☒ yes ☐ no	H.D.	☐ yes ☐ no ☒ unk

FDA

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEXICO HUMAN HEALTH DIVISION

Page 2

MFR REPORT #: WAES 94040165 (CONT.)

B. ADVERSE EVENT OR PRODUCT PROBLEM**5. DESCRIBE EVENT OR PROBLEM**

developed gross hematuria. A subsequent MRI revealed a left kidney mass. The patient was hospitalized for a left radical nephrectomy on 01APR94. A biopsy was not performed prior to surgery but histopathological examination of the mass and surrounding tissue was to be done post-nephrectomy. At the time of the report, the patient had not recovered. Study drug continued and the investigator felt that the patient's experience was not related to study drug therapy.

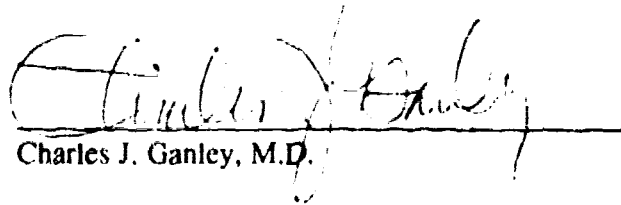
Bongiorno

MEDICAL OFFICER REVIEW

SEP 23 1994

IND #: 20/386/BM
IND Volume: 7.1
DRUG NAME: losartan
SPONSOR: Merck
TYPE OF DOCUMENT: information amendment
DATE RECEIVED: 9/20/94
DATE REVIEW COMPLETED: 9/23/94
MEDICAL OFFICER: Charles J. Ganley, M.D.

This submission contains information on the incidence of renal cell ca in the felodipine database.


Charles J. Ganley, M.D.

cc: orig.
HFD-110
HFD-110 / CSO / C. GANLEY ~~SECRET~~

NDA 020386

FIRM:

MERCK

2 OF 10

TRADE NAME:

COZAAR (LOSARTAN POTASSIUM) 25/50 MG TAB

GENERIC NAME:

LOSARTAN POTASSIUM

FEB 21 1995

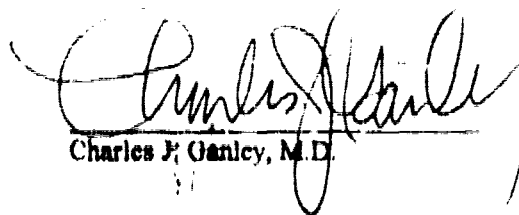
NDA #: 20-386/SU
Volume: 11.1
Drug Name: Losartan (DulP 753, MK-954)
Sponsor: MSDRI
Date Received: 2/1/95
Review Completed: 2/21/95
Medical Reviewer: Charles J. Ganley, M.D.

This Safety Update includes case report forms submitted to Merck by the cut-off date of 6/30/94 or 7/14/94, depending on the study. Additional information was provided for 1,114 patients previously exposed to losartan and 695 patients newly exposed.

Seventy-seven patients discontinued losartan +/- HCTZ therapy due to adverse experiences. A complete listing of patients withdrawn due to adverse events is provided in the appendix.

Adverse events incidence rates (clinical or laboratory) for losartan alone therapy appeared to be similar to previous safety updates. There is a distinction between laboratory adverse events in the losartan/HCTZ patients and losartan alone patients. Increases in creatinine and BUN and decreases in potassium occurred more frequently in the losartan/HCTZ patients. In the losartan alone patients, neither of these adverse lab experiences occurred with greater than 1% frequency. In the losartan/HCTZ group, creatinine increased in approximately 1.2%, BUN increased in approximately 2.0 - 2.7% and potassium decreased in approximately 2.7 - 3.2%. The decreases in potassium are not unexpected with HCTZ. However, the changes in creatinine and BUN are suggestive of renal insufficiency. This could possibly be explained by a diuretic induced volume depleted state combined with a drug that inhibits the RAAS system. In this regard, it would not be much different than an ACEI.

There were three deaths in hypertensive patients. Two were related to cardiac disease and one from Hodgkin's Disease. Four patients with renal insufficiency died (one aortic aneurysm, one hepatitis unrelated to losartan therapy, one myocardial infarction, one DIC). Seven patients in CHF trials died (five cardiac, one trauma, one sudden death of unknown cause). One patient died in a non-Merck Research Labs trial due to complications of pneumonia.



Charles J. Ganley, M.D.

cc: orig.
HFD-110 file
HFD-110/c ganley/r.lipicky/cso

7 appendix pages attached

Losartan and Losartan/HCTZ
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Table 10 Discontinuations Due to Adverse Experiences in Losartan-Treated Hypertensive Patients in Open-Label Trials (Based upon case report form information received Oct. 5, 1993 to July 14, 1994)

Protocol No./ Study	AN	Sex/Age	Treatment	Daily Dose (mg)	Relative Day of Onset	Adverse Experience	Serious	Drug Relationship	Outcome
011/005	0088	M/88	Los/HCTZ	100/12.5	1046	Dizziness	No	Possibly	Recovered
011/005	0094	M/57	Los	50	862	Cramp, Muscic	No	Possibly	Present
				100	874	Headache	No	Possibly	Recovered
				100	894	Flushing	No	Possibly	Recovered
				100	895	Atrial Fibrillation	No	Possibly	Recovered
011/005	0177	F/60	Los/HCTZ	100/12.5	1127	Rt. Bundle Branch Block	No	Probably Not	Not Reported
011/019	0381	M/50	Los	50	607	Myocardial Infarction	Yes	Definitely Not	Recovered
011/037	0763	F/42	Los/HCTZ	150/25	769	Urticaria	No	Possibly	Recovered
011/038	0781	F/56	Los/HCTZ	100/25	823	Nephrotic Syndrome	No	Probably Not	Present
011/038	0783	M/61	Los/HCTZ	100/12.5	232	Neoplasm, Anal/Rectal, Malignant	Yes	Probably Not	Recovered
044/008	3143	M/49	Los/HCTZ	50/12.50	225	Headache	No	Probably Not	Present
044/011	3180	M/56	Los/HCTZ	50/6.25	352	Myocardial Infarction	Yes	Definitely Not	Present
045/003	4101	M/52	Los	50	120	Proteinuria	No	Probably	Not Reported
			Off-Drug	-	211	Creatinine Clearance Decreased	No	Probably	Not Reported
			Off-Drug	-	211	Renal Insufficiency	No	Possibly	Recovered
045/009	4132	F/71	Los	50	104	Pain, Abdominal	No	Possibly	Present
045/012	4138	M/56	Los	50	281	Headache	No	Possibly	Present
045/012	4203	M/58	Off-Drug+	-	182	Myocardial Infarction	Yes	Possibly	Recovered

+On Los 50 mg through Study Day 181.

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Table 10 (Cont.)

Discontinuations Due to Adverse Experiences in Losartan-Treated Hypertensive Patients in Open-Label Trials (Based upon case report form information received Oct. 5, 1993 to July 14, 1994)

Protocol No./ Study No.	AN	Sex/Age	Treatment	Daily Dose (mg)	Relative Day of Onset	Adverse Experience	Serious	Drug Relationship	Outcome
048/004	6381	M/58	Los/HCTZ/ Felodipine	50/12.5/5	155	Headache	No	Probably	Recovered
048/006	6019	F/42	Los/HCTZ Los/HCTZ	50/12.5 50/12.5	208 208	Glycemia Hyperglycemia	No No	Probably Not Probably Not	No. Reported Not Reported
048/029	6209	M/54	Lo.	50	183	Urticaria	No	Definitely	Recovered
048/029	6223	M/43	Los/HCTZ/ Diltiazem	50/12.5/240	573	Hyperglycemia	No	Probably	Not Reported
049/005	7114	F/59	Off-Drug*	-	156	Edema/Swelling	No	Probably	Present
049/013	7214	F/47	Los/HCTZ	50/6.25	354	Myocardial Infarction	Yes	Definitely Not	Recovered
050/001	2006	M/57	Los/HCTZ Lo/HCTZ Los/HCTZ	50/6.25 50/6.25 50/6.25	674 674 674	Headache Tinnitus Asthenia/Fatigue	No No No	Possibly Possibly Possibly	Present Present Present
050/002	2032	M/73	Los	50	105	Weight Gain	No	Definitely Not	Recovered
050/008	2131	F/66	Los	50	584	Pain, Chest	No	Definitely Not	Present
050/013	2225	F/49	Los	50	715	Myocardial Infarction	Yes	Definitely Not	Present
050/013	2421	F/63	Los	50	726	Myeloma, Multiple	Yes	Probably Not	Present
054/001	8009	M/67	Los/HCTZ/ Felodipine	50/12.5/5	428	Heart Disorder, Ischemic	Yes	Probably Not	Present
054/004	8085	M/51	HCTZ** HCTZ**	6.25 6.25	497 497	AST Increased ALT Increased	No No	Possibly Possibly	Not Reported Not Reported

*On Los/HCTZ/50/12.5 prior to discontinuation
 **Last dose of Los/HCTZ (50/6.25) was 18 days prior to discontinuation.

Appendix 2

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Table 10 (Cont.) Discontinuations Due to Adverse Experiences in Losartan-Treated Hypertensive Patients in Open-Label Trials (Based upon case report form information received Oct. 5, 1993 to July 14, 1994)

Protocol No./ Study No.	AN	Sex/Age	Treatment	Daily Dose (mg)	Relative Day of Onset	Adverse Experience	Serious	Drug Relationship	Outcome
054/004	8090	M/50	Los/Felodipine	50/10	462	Dizziness	No	Possibly	Recovered
054/004	8095	M/48	Los/HCTZ	50/12.5	392	Libido Decreased	No	Possibly	Present
054/025	8522	M/74	Los/HCTZ	50/12.5	208	Edema/Swelling	No	Probably Not	Present
054/025	8529	M/59	Los/HCTZ/ Felodipine	50/12.5/10	373	Edema/Swelling	No	Definitely	Present
054/034	8716	M/44	Los/HCTZ	50/12.5	193	Headache	No	Probably Not	Recovered
054/036	8749	F/64	Los/HCTZ	50/12.5	341	Dizziness	No	Possibly	Present
054/037	8774	M/55	Los/HCTZ	50/12.5	100	Headache	No	Possibly	Present
054/038	8800	F/41	Los/HCTZ	50/12.5	141	Serum Creatinine Increased	No	Probably Not	Not Reported
			Los/HCTZ	50/12.5	141	Hyperuricemia	No	Probably Not	Not Reported
054/039	8818	F/73	Los/HCTZ/ Felodipine	50/12.5/5	602	Atrial Fibrillation	No	Probably Not	Recovered
			Los/HCTZ/ Felodipine	50/12.5/5	602	Sinus Tachycardia	No	Probably Not	Recovered
054/040	8176	M/31	Los/HCTZ	50/12.5	113	Urinary Frequency	No	Probably	Present
055/010	5171	F/66	Los	50	122	CVA	Yes	Probably Not	Recovered
056/001	3506	M/67	Los	100	352	Neoplasm, Prostate, Malignant	Yes	Definitely Not	Present
056/002	3509	F/54	Los	50	75	Heart Failure	No	Probably Not	Present
056/004	3521	F/42	Los	50	231	Swelling, Joint	No	Definitely Not	Present
			Los	50	231	Pain, Ankle	No	Definitely Not	Present
056/008	3543	F/39	Los	50	53	Cough	No	Definitely	Recovered
056/008	3547	M/51	Los	50	65	Cough	No	Probably	Recovered
056/009	3561	F/53	Los	50	97	Cough	No	Possibly	Present

Appendix 3

Losartan and Losartan/HCTZ
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Table 10 (Cont.)

Discontinuations Due to Adverse Experiences in Losartan-Treated Hypertensive Patients in Open-Label Trials (Based upon case report form information received Oct. 5, 1993 to July 14, 1994)

Protocol No./ Study No.	AN	Sex/Age	Treatment	Daily Dose (mg)	Relative Day of Onset	Adverse Experience	Serious	Drug Relationship	Outcome
056/009	3564	M/50	Los	50	98	Cough	No	Possibly	Recovered
			Los	50	98	Diarrhea	No	Possibly	Present
			Los	50	98	Asthenia/Fatigue	No	Possibly	Present
			Los	50	98	Headache	No	Possibly	Present
			Los	50	98	Impotence	No	Possibly	Recovered
056/015	3683	M/63	Los/Felodipine	100/10	284	Angina Pectoris	Yes	Probably Not	Present
059/005	5550	M/47	Los/HCTZ/ Felodipine	100/25/10	6	Headache	No	Possibly	Present
			Los/HCTZ/ Felodipine	100/25/10	65	Edema/Swelling	No	Possibly	Present
			Los/HCTZ/ Felodipine	100/25/10	109	Pain, Back	No	Definitely Not	Present
			Los/HCTZ/ Felodipine	100/25/10	119	Nausea	No	Possibly	Present
			Los/HCTZ/ Felodipine	100/25/10	119	Vomiting	No	Possibly	Present
			Los/HCTZ/ Felodipine	100/25/10	126	Tremor	No	Possibly	Present

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Table 10 (Cont.) Discontinuations Due to Adverse Experiences in Losartan-Treated Hypertensive Patients in Open-Label Trials (Based upon case report form information received Oct. 5, 1993 to July 14, 1994)

Protocol No./ Study No.	AN	Sex/Age	Treatment	Daily Dose (mg)	Relative Day of Onset	Adverse Experience	Serious	Drug Relationship	Outcome
059/012	5614	F/45	Los/HCTZ/ Amlodipine	100/25/5	108	Hemoglobin Decreased	No	Possibly	Recovered
			Los/HCTZ/ Amlodipine	100/25/5	108	Hematocrit Decreased	No	Possibly	Recovered
059/015	5648	F/45	Los	100	38	Pain, Back	No	Probably Not	Present
064/010	4546	M/60	Los/HCTZ/ Atenolol/ Felodipine	100/50/100/10	448	Angina Pectoris	No	Possibly	Recovered
065/001	1434	F/66	Los	50	321	CVA	Yes	Probably Not	Recovered
065/007	1761	M/43	Los	50	98	Hypokalemia	No	Possibly	Not Reported
065/010	1240	M/37	Los	100	187	Impotence	No	Possibly	Present
065/012	1459	M/45	Los	100	180	Pain, Chest	No	Probably Not	Present
065/014	1473	M/39	Los/Atenolol	100/50	334	Atrial Fibrillation	Yes	Possibly	Recovered
065/014	1480	M/52	Los/HCTZ/ Felodipine	100/25/10	335	Myocardial Infarction, Non Q wave	Yes	Possibly	Present
065/014	1483	M/62	Los/Felodipine	100/10	336	Impotence	No	Possibly	Present
065/015	1269	F/35	Los	50	527	Asthenia/Fatigue	No	Possibly	Present

Appendix 5

Losartan and Losartan/HCTZ
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Table 10 (Cont.) Discontinuations Due to Adverse Experiences in Losartan-Treated Hypertensive Patients in Open-Label Trials (Based upon case report form information received Oct. 5, 1993 to July 14, 1994)

Protocol No./ Study No.	AN	Sex/Age	Treatment	Daily Dose (mg)	Relative Day of Onset	Adverse Experience	Serious	Drug Relationship	Outcome
065/017	1336	M/60	Los/Atenolol	100/50	196	Pain, Chest	Yes	Probably Not	Present
065/017	1338	M/66	Off-Drug++	--	108	Pain, Chest	Yes	Probably Not	Recovered
065/019	1506	F/51	Los	50	172	Pain, Chest	No	Possibly	Present
065/029	1183	M/58	Los/Felodipine	100/10	513	Irritability	No	Probably Not	Recovered
			Los/Felodipine	100/10	513	Pain, Chest	No	Probably Not	Recovered
			Los/Felodipine	100/10	526	Spasm	No	Possibly	Recovered
065/034	1304	F/55	Los	50	345	Dizziness	No	Possibly	Recovered
			Los	50	345	Nausea	No	Possibly	Recovered
			Los	50	345	Vomiting	No	Possibly	Recovered
			Los	50	345	Pain, Abdominal	No	Possibly	Recovered
065/037	1645	M/63	Los/Felodipine	100/5	258	Polymyositis	No	Probably Not	Present
065/037	1646	M/67	Los	50	90	Pain, Abdominal	No	Probably	Recovered
065/037	1649	M/55	Los	50	104	Lipids Decreased	No	Possibly	Recovered
065/038	1151	M/61	Los/Atenolol	100/50	351	Angina Pectoris	No	Definitely Not	Present
065/041	1440	M/39	Off-Drug++	--	146	ALT Increased	No	Possibly	Not Reported
065/041	1443	M/65	Los	100	210	Angina Pectoris	No	Definitely Not	Recovered
065/041	1446	F/36	Los	50	116	Dizziness	No	Probably	Recovered
			Los	50	116	Hypesthesia	No	Probably	Recovered
065/042	1678	M/45	Los	50	100	Tachycardia	No	Probably Not	Present
			Los	50	100	Atrial Fibrillation	No	Probably Not	Not Reported
			Los	50	100	Ventricular Arrhythmia	No	Probably Not	Not Reported
085/005	3047	M/51	Los/HCTZ	100/25	75	Serum Creatinine Increased	No	Possibly	Not Reported

++On los 50 prior to discontinuation.

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Table 10 (Cont.) Discontinuations Due to Adverse Experiences in Losartan-Treated Hypertensive Patients in Open-Label Trials (Based upon case report form information received Oct. 5, 1993 to July 14, 1994)

Protocol No./ Study No.	AN	Sex/Age	Treatment	Daily Dose (mg)	Relative Day of Onset	Adverse Experience	Serious	Drug Relationship	Outcome
085/007	3065	M/51	Los/HCTZ	50/12.5	3	Dizziness	No	Possibly	Present
			Los/HCTZ	50/12.5	3	Pain, Chest	No	Possibly	Present
			Los/HCTZ	50/12.5	3	Palpitation	No	Possibly	Present
			Los/HCTZ	50/12.5	3	Tremor	No	Possibly	Present
			Los/HCTZ	50/12.5	6	Diarrhea	No	Possibly	Present
			Los/HCTZ	50/12.5	6	Pain, Elbow	No	Possibly	Present
			Los/HCTZ	50/12.5	6	Pain, Wrist	No	Possibly	Present
			Los/HCTZ	100/25	12	Asthenia/Fatigue	No	Possibly	Recovered
			Los/HCTZ	100/25	12	Somnolence	No	Possibly	Recovered
			Los/HCTZ/ Felodipine	100/25/10	35	Nausea	No	Possibly	Recovered
			Los/HCTZ/ Felodipine	100/25/10	35	Depression	No	Possibly	Recovered
			085/008	3077	M/62	Los/HCTZ	50/12.5	2	Pain, Chest
085/011	3103	M/66	Los/HCTZ	50/12.5	2	Nervousness	No	Possibly	Recovered
			Los/HCTZ	50/12.5	6	Hypersonmia	No	Possibly	Recovered
085/014	3137	M/69	Los/HCTZ	100/25	57	Atrial Fibrillation	No	Probably Not	Recovered
085/014	3139	M/34	Los/HCTZ/ Felodipine	100/25/5	29	Nausea	No	Possibly	Present
			Los/HCTZ/ Felodipine	100/25/5	29	Headache	No	Possibly	Present
095/001	0012	M/67	Los/HCTZ	50/12.5	4	Hypotension, Orthostatic	Yes	Probably	Recovered
			Los/HCTZ	50/12.5	5	Syncope	Yes	Probably	Recovered

Los=Losartan
 HCTZ=Hydrochlorothiazide

FEB 13 1995

NDA #: 20-3P6/SU
 Drug Name: Losartan (DuP 753, MK-954)
 Sponsor: MSDRL
 Date Received: 4/5/94
 Review Start Date: 2/3/95
 Review Completed: 2/10/95
 Medical Reviewer: Charles J. Ganley, M.D.

The CANDA cannot be easily reviewed for safety data due to limitations in the Query function. Thus, the tables in the Safety Update cannot be validated. The safety update does not include a complete report for study 58 (Reviewer's Note: This study was not complete in the NDA). Within the Safety Update summary, the sponsor has reported the adverse events for several populations. The populations are all hypertensive patients in open label studies (most double-blind data was included in the WMA submission), as hypertensive patients with ≥ 1 year of losartan exposure, as hypertensive patients with ≥ 1 year of losartan/HCTZ exposure, as hypertensive patients with renal impairment and as patients with heart failure.

Table SU.1 lists the patient exposure to losartan in the WMA (original NDA) database and in the SUR (safety update) database. Of the 1712 patients included in the SUR database, 1282 had information included in the WMA database and 430 were newly exposed patients. The cut-off of case report forms for the safety update was 10/4/93. Serious adverse events were reported up until 12/31/93 (WAES Data).

Table SU.1. Number of Patients Exposed to Losartan as a Treatment Regimen

Indication For Losartan Therapy	Time Frame	Treatment Regimen		Total* (Losartan With or Without Other Antihypertensives)
		Losartan Alone	Losartan/HCTZ Alone	
Uncomplicated Essential Hypertension	WMA	2551	1386	3008
	SUR	791	989	1593
	CUM†	2823	1872	3384
Renally-Impaired Hypertensives	WMA	115	—†	115
	SUR	33	—	33
	CUM	148	—	148
Heart Failure	WMA	180	—	180
	SUR	84	—	84
	CUM	199	—	199
Clinical Pharmacology	WMA	263	63	325
	SUR	2	0	2
	CUM	265	63	327
All Indications	WMA	3109	1449	3628
	SUR	910	989	1712
	CUM	3435	1935	4058

* Patients who received losartan alone and later received losartan/HCTZ are counted in both treatment groups. However, the Total column only counts a given patient once and therefore does not reflect the addition of the Losartan Alone column plus the Losartan/HCTZ Alone column.

† The CUM column is not simply the addition of the WMA and SUR columns because a patient who was treated in the WMA time frame and continued to be treated in the SUR time frame is counted in both time frames. However, this patient is only counted once in the CUM time frame.

‡ No data. (These studies were not designed to evaluate the safety profile of losartan/HCTZ alone.)

The patients whose data were received during the SUR time frame were in the vast majority, those who participated in the open-label extension phases of 13 trials (protocols 011, 021, 044, 045, 048, 049, 050, 054, 055, 056, 059, 064, 065). Incidence tables for the open-label trials show cumulative values (i.e., adverse events on case report forms received as of October 4, 1993).

As of October 4, 1993, 2056 patients were treated with losartan alone or as part of a treatment regimen in open-label hypertension trials. The duration of treatment with losartan ranged from 2 days to approximately 2.2 years and the mean duration of drug exposure was approximately 8.2 months. Tables SU.2 - SU.2b. show the length of exposure to losartan therapy in hypertensive patients in open-label trials, hypertensives with renal insufficiency and heart failure.

Table SU.2. Number of Hypertensive Patients Treated With Respect to Duration of Therapy—Cumulative Time Frame (Based on Case Report Forms Received Through October 4, 1993)

Duration of Therapy (Days)	Losartan Alone	Losartan/HCTZ Alone	Losartan/HCTZ Plus Other Agents	Losartan Plus Other Agents Excluding HCTZ	Total (Losartan With or Without Other Agents)
1-30	533	279	87	40	87
31-91	429	318	125	42	284
92-183	149	263	166	18	411
184-365	255	438	20	16	1005
366-548	43	49	0	0	101
549-730	59	64	0	0	130
731-913	4	1	0	0	18
>913	0	0	0	0	0
Total Number of Patients	1472	1412	547	116	2056
Total Patient Days on Drug	184913	234953	79458	8632	507956
Range of Duration on Drug	1 to 789	1 to 768	1 to 485	1 to 277	2 to 804
Mean Duration on Drug	125.6	166.4	145.3	74.4	247.1

Table SU.2a. Number of Hypertensive Patients with Renal Impairment Treated By Duration of Therapy and Total Daily Dose

Days of Therapy	Losartan 50 mg		Losartan 100 mg		Losartan 150 mg	
	WMA	CUM	WMA	CUM	WMA	CUM
1-7	12	16	28	29	1	1
8-30	48	64	12	13	0	0
31-91	26	36	53	71	0	0
92-183	5	7	2	2	0	0
>183	0	0	0	0	0	0
Total Number of Patients			WMA	CUM		
			115	148		
Total Patient Days on Drug			6982	9547		
Range of Duration on Drug (days)			2 to 124	2 to 124		
Mean Duration on Drug (days)			60.7	64.5		

Table SU.2b. Duration of Chronic Therapy by Total Daily Dose in Patients with Heart Failure

Days of Therapy	Losartan Dose*							
	2.5 mg	5 mg	10 mg	25 mg	50 mg	75 mg	150 mg	>150 mg
1-7	33	2	34	24	1	0	1	0
8-30	32	1	14	7	0	0	0	0
31-91	9	0	7	11	7	0	0	0
92-183	11	1	13	14	6	0	0	0
184-274	0	0	4	5	29	0	0	0
275-365	2	0	1	2	9	0	0	0
>365	0	0	0	1	0	0	0	0
* Three patients are not included in this table as they received doses not specified by the protocols.								
Total Number of Patients			78					
Total Patient Days on Drug			22899					
Range of Duration on Drug (Days)			89 to 718					
Mean Duration on Drug (Days)			293.6					

The distribution of the open-label hypertensive study population with respect to gender, age, race, and duration of disease is displayed in Table SU.3. The majority of patients who participated in the open-label trials were male (60%), Caucasian (78%) with a mean age of 53 years and a mean duration of hypertension of 10 years.

Table SU.3. Demographics of Hypertensive Patients in Open-Label Trials - Cumulative Time Frame (Based on Case Report Forms Received Through October 4, 1993)

		Losartan Alone		Losartan/HCTz Alone		Total (Losartan With or Without Other Agents)	
Total Patients		1472		1412		2056	
Gender	Male	891	(61%)	853	(60%)	1230	(60%)
	Female	581	(39%)	559	(40%)	826	(40%)
Age (yrs)	<36	82	(6%)	92	(7%)	125	(6%)
	36-45	277	(19%)	278	(20%)	391	(19%)
	46-55	475	(32%)	450	(32%)	652	(32%)
	56-64	387	(26%)	372	(26%)	533	(26%)
	65-74	229	(16%)	206	(15%)	329	(16%)
	≥75	22	(1%)	14	(1%)	26	(1%)
	Mean	53.4		52.8		53.3	
Range	23.0-88.0		21.0-88.0		21.0-88.0		
Race	Caucasian	1151	(78%)	1095	(78%)	1606	(78%)
	Black	179	(12%)	191	(14%)	251	(12%)
	Hispanic	96	(7%)	77	(5%)	120	(6%)
	Other*	46	(3%)	49	(3%)	79	(4%)
Duration Of Disease (yrs)	<1	68	(5%)	57	(4%)	97	(5%)
	1.00-5.00	470	(32%)	448	(32%)	668	(32%)
	5.01-10.00	340	(23%)	336	(24%)	475	(23%)
	>10	559	(38%)	545	(39%)	777	(38%)
	Unknown	35	(2%)	26	(2%)	39	(2%)
	Mean	9.97		10.26		10.05	
Range	0.00-52.00		0.00-56.00		0.00-56.00		

* Other includes: Oriental, Latin American, Asian, Hawaiian, Indian, Spanish, Mestizo, Mulatto, Vietnamese, Cape Verdean, Maori.

Deaths

One hypertensive patient died while receiving losartan or within 14 days after discontinuation of therapy during the reporting period July 1, 1993 through December 31, 1993. Data for this patient are summarized in Table SU.4. A narrative providing more detail is presented following the table.

Table SU.4. Serious Fatal Adverse Experiences From All Sources -- Hypertensive Patients; Report Time Frame: July 1, 1993 through December 31, 1993

Protocol/ Study #	Patient #	Age/Sex	Treatment	Daily Dose (mg)	Day of Onset	Adverse Experience
065-042	1684	61/M	Losartan	100	340	Myocardial Infarction
					340	Cardiac Arrest
					340	Death

Patient #1684 was 61-year-old hypertensive male with a history of arthritis started therapy with losartan 50 mg on January 12, 1993, and his dose was increased to 100 mg on September 7, 1993. He was transported to a hospital on November 11, 1993, in full cardiac arrest. He subsequently died after unsuccessful re-suscitation. The cause of death was reported as probable myocardial infarction and cardiopulmonary arrest. At the time of the event, the patient had been receiving losartan 100 mg and allopurinol 150 mg.

In patients with CHF, death has been reported for a total of 8 patients from July 1, 1993 through December 31, 1993. All deaths resulted from cardiovascular events with the exception of Study 017-017, # 1207, who had metastatic cancer leading to cardiopulmonary failure. All serious adverse experiences, reported from July 1, 1993 through December 31, 1993, in patients who died while receiving losartan or within 14 days after discontinuation of therapy are tabulated in Table SU.5. The adverse experiences are categorized by body system.

Table SU.5. Serious Clinical Adverse Experiences From All Sources in Losartan-Treated Patients with Heart Failure Who Died--Report Time Frame: July 1, 1993 through December 31, 1993

Study #/ Protocol #	Patient #	Age/Sex	Treatment	Daily Dose (mg)	Study Day of Onset	Adverse Experience
047-017 047-21	1207	60/Male	Losartan	20 20 20 20	285 396 Unknown 515	Metastatic Neoplasm Worsening Heart Failure Intestinal Obstruction Respiratory Failure, Malignant Neoplasm, Death
047-001 047-20	1002	52/Male	Losartan	50	590	Myocardial Infarction, Death
047-001 047-20	1010	71/Male	Losartan	25 25	440 466	Myocardial Infarction Cardiac Arrest, Death
047-015 047-21	1167	55/Male	Losartan	50 50	Unknown 512	Coronary Artery Disease, Chronic Obstructive Pulmonary Disease Death
047-021 047-21	1135	75/Male	Losartan	50 50	637 641	Myocardial Infarction Cardiac Arrest Death
071-001 071-10	135	60/Male	Losartan	2.5	285	Sudden Death
071-003 071-10	106	69/Male	Losartan	50	189	Sudden Death
071-019 071-10	80	72/Male	Losartan	50 50 50	166 167 202	Anemia Ventricular Tachycardia Worsening Heart Failure, Sudden Death

This 60-year-old male (# 1207 - Protocol #047-21, Study #047-017) with heart failure, multiple bony metastases and a history of herpes zoster, diverticulitis, cancer of the larynx and partial laryngectomy received a single daily dose of losartan 2.5 mg for 12 weeks. Concomitant medication included isosorbide dinitrate, furosemide, acetylsalicylic acid, diclofenac, lormetazepam dextropropoxyphene HCl, augmentin, morphine sulfate, fluoxetine, paraffin and lactitolium monohydratum. He entered open-label extension on a single daily dose of losartan 5 mg and was titrated to 20 mg. On Day 285 the patient was hospitalized with sciatic pain and a diagnosis of lytic pelvic lesion was made. He was released from the hospital and treated with radiotherapy. On Day 396 he experienced worsening heart failure and was hospitalized. The patient was hospitalized again on Day 512 due to stenosis of the colon. On Day 515 the patient died of cardiopulmonary failure and terminal stage of cancer.

This 52-year-old male (# 1002 - Protocol #047-20, Study #047-001) with heart failure and a history of silent myocardial infarctions and mitral and tricuspid valve replacements received placebo for 12 weeks. Concomitant medication included furosemide and potassium chloride. He entered open-label extension on a single daily dose of losartan 2.5 mg and was titrated to 50 mg. On Day 590 (day 500 of losartan therapy) the patient was at home working on his roof when he collapsed. He was found dead by his wife. An autopsy was performed which revealed myocardial infarction as the cause of death.

This 71-year-old male (# 1010 - Protocol #047-20, Study #047-001) with heart failure, hypertriglyceridemia, coronary artery disease and a history of myocardial infarction and PVCs received placebo for 12 weeks. Concomitant medication included furosemide, triamterene, digoxin, potassium chloride and cholestyramine. He entered open-label extension on a single daily dose of losartan 2.5 mg and was titrated to 25 mg. On Day 440 (day 348 of losartan therapy) the patient developed chest pain and was hospitalized with a diagnosis of myocardial infarction. The patient recovered and was released from the hospital. On Day 466 (day 374 of losartan therapy) he suffered cardiac arrest while golfing. He was hospitalized, treated with dopamine and subsequently died.

This 55-year-old male (# 1167 - Protocol #047-21, Study #047-015) with heart failure, gout, angina pectoris, chronic obstructive pulmonary disease, coronary artery disease, and a history of myocardial infarction received placebo for 12 weeks. Concomitant medication included furosemide, potassium chloride, allopurinol, salbutamol and beclomethasone. He entered open-label extension on a single daily dose of losartan 2.5 mg and was titrated to 50 mg. On Day 512 (Day 427 of losartan therapy) the patient experienced myocardial infarction, ventricular fibrillation and died later that day. Probable causes of death were identified as acute myocardial infarction, ventricular fibrillation, coronary artery disease, congestive heart failure and chronic obstructive airways disease.

This 75-year-old male (# 1135 - Protocol #047-21, Study #047-021) with heart failure, atrial fibrillation, angina pectoris, ventricular tachyarrhythmia and a history of myocardial infarction, renal cancer and nephrectomy received placebo for

12 weeks. Concomitant medication included furosemide, amiodarone, digitoxin, allopurinol, thyroxine, warfarin, trichlormethazine and spironolactone. He entered open-label extension on a single daily dose of losartan 2.5 mg and was titrated to 50 mg. On Day 637 (Day 486 of losartan therapy) the patient was admitted to the hospital due to a myocardial infarction and cardiac arrest. The patient was resuscitated after 25 minutes but never regained consciousness. On Day 641 (Day 490 of losartan therapy) he died at the hospital.

This 60-year-old male (# 135 - Protocol #071-10, Study #071-001) with heart failure and a history of diabetes, hypercholesterolemia, myocardial infarction and transient ischemic attack was titrated from a single daily dose of losartan 12.5 to 50 mg for 8 weeks. Concomitant medication included warfarin, furosemide, and lovastatin. The patient entered open-label extension and received a single daily dose of losartan 25 mg. On Day 285, the patient died suddenly. No autopsy results are available.

This 69-year-old male (# 106 - Protocol #071-10, Study #071-003) with heart failure and a history of myocardial infarction, hernia surgery, mitral regurgitation, and nephrolithiasis was titrated from a single daily dose of losartan 12.5 to 50 mg for 8 weeks. Concomitant medication included isosorbide mononitrate, digoxin, furosemide, warfarin and amiodarone. The patient entered open-label extension and received a single daily dose of losartan 50 mg. On Day 189, the patient died suddenly. No autopsy results are available.

This 72-year-old male (# 80 - Protocol #071-10, Study #071-019) with heart failure and a history of myocardial infarction, stroke, abdominal aortic aneurysm, pacemaker, angina pectoris, hyperuricemia, hypokalemia, and ulcer was titrated from a single daily dose of losartan 12.5 to 50 mg for 8 weeks. Concomitant medication included digitoxin, furosemide, isosorbide dinitrate, allopurinol, ranitidine, and potassium. The patient entered open-label extension and received a single daily dose of losartan 50 mg. On Day 166 the patient was hospitalized due to anemia. Ventricular tachycardia was observed the next day. Metoprolol therapy was initiated to treat the ventricular arrhythmias. Iron sulphate therapy was initiated approximately 1 month later to treat the anemia. On Day 202 the patient died suddenly. Autopsy revealed signs of heart failure.

Adverse Events - Clinical

The reporting of adverse event incidence rates is made difficult by the fact that many patients received multiple therapies during the open label period. In the tables that follow, if an adverse event occurred while the patient received losartan alone and again while on combination therapy, it was counted as occurring with each therapy. If a adverse event started while a patient was on one therapy and continued after they added an additional therapy, it was counted only for the therapy that the patient was receiving at the start of the adverse event. Adverse events which occurred in the double-blind period are not included in these counts.

Table SU.6 presents the most frequently reported clinical adverse experiences that occurred in uncomplicated essential hypertensive patients. Specifically, Table SU.4 shows adverse events that occurred in $\geq 1\%$ and 2 or more patients exposed to a given losartan treatment group. The most frequently reported adverse experiences in the cumulative losartan monotherapy group were headache (11.8%), upper respiratory infection (9.6%), dizziness (3.8%), asthma/fatigue (3.3%), and cough (3.1%). The most frequently reported adverse experiences in the cumulative losartan/HCTZ group were upper respiratory infection (10.3%), headache (9.1%), dizziness (4.7%) and back pain (4.0%). With few exceptions, the safety profile of losartan/HCTZ plus other antihypertensives was similar to losartan/HCTZ alone in the cumulative time frame. The exceptions included higher incidence values for edema/swelling (1.9% and 7.7%), joint swelling (0.2% and 1.3%) and flushing (0.3% and 3.1%) in the losartan/HCTZ plus other antihypertensives category, which is most likely due to the adverse experience profile of the antihypertensives that were administered in addition to the losartan/HCTZ (e.g., calcium channel blockers).

Table SU.6 Percentage of Clinical Adverse Experiences That Occurred in $\geq 1\%$ of Losartan-Treated Hypertensive Patients*
Open-Label Trials

	Losartan Monotherapy		Losartan/HCTZ		Losartan/HCTZ Plus Other Antihypertensives		Losartan Plus Other Antihypertensives Without HCTZ	
	WMA n=851	CUM n=1472	WMA n=601	CUM n=1412	WMA n=212	CUM n=547	WMA n=12	CUM n=116
Body as Whole								
Athensia/fatigue	3.4	3.3	2.8	3.0	1.9	2.2	16.7	3.4
Edema/swelling	1.9	2.3	1.3	1.9	6.6	7.7	0.0	5.2
Fever	0.6	0.5	0.5	1.1	0.5	0.7	0.0	0.9
Flu-like illness	0.4	0.6	1.3	1.0	0.5	0.5	0.0	0.0
Pain, abdominal	2.3	2.4	2.3	2.1	0.5	1.5	0.0	1.7
Pain, chest	2.0	1.6	3.0	2.5	0.9	2.6	0.0	0.0
Syncope	0.1	0.2	0.2	0.3	0.5	0.5	8.3	1.7
Cardiovascular System								
Palpitation	0.6	0.7	0.3	0.8	0.5	0.7	8.3	2.6
Digestive System								
Diarrhea	3.1	2.3	2.0	2.8	1.4	2.4	0.0	2.6
Dyspepsia	1.1	1.0	1.3	1.6	1.4	0.9	0.0	0.9
Nausea	1.9	1.8	1.3	1.3	0.5	1.6	0.0	0.0
Pain, dental	0.6	0.5	0.5	1.1	0.0	0.9	0.0	0.9
Vomiting	0.2	0.3	0.3	1.0	0.0	0.4	0.0	0.9
Musculoskeletal System								
Cramp, muscle	0.4	0.7	1.3	1.3	1.4	0.5	0.0	0.0
Myalgia	1.2	1.0	0.5	0.9	0.5	1.3	0.0	0.0
Pain, knee	0.7	1.0	0.8	0.8	0.9	0.5	0.0	0.9
Pain, back	2.2	1.7	2.7	4.0	1.4	2.0	0.0	0.9
Pain, leg	1.0	0.9	0.3	0.5	0.0	0.2	0.0	0.0
Pain, neck	0.4	0.5	0.7	1.0	0.0	0.2	0.0	0.0
Pain, shoulder	0.6	0.5	1.5	1.5	0.5	0.4	0.0	0.0
Swelling, joint	0.6	0.4	0.0	0.2	0.0	1.3	0.0	0.0
Nervous System and Psychiatric								
Anxiety	0.8	1.0	0.8	1.3	1.9	2.0	0.0	0.9
Depression	1.2	0.7	0.2	0.7	0.7	1.3	0.0	0.0
Dizziness	3.7	3.8	5.8	4.7	4.2	6.6	8.3	4.3
Headache	12.5	11.8	8.5	9.1	7.5	10.8	0.0	12.1
Insomnia	1.3	1.2	1.0	1.1	0.0	0.7	0.0	0.9
Libido decreased	0.4	0.3	0.2	0.3	0.0	0.0	0.0	1.7
Paresthesia	0.7	0.7	1.3	1.6	0.0	0.5	8.3	1.7
Somnolence	0.4	0.4	0.2	0.9	0.5	1.1	0.0	2.6
Respiratory System								
Bronchitis	0.7	1.6	1.5	3.1	0.5	1.5	0.0	0.9
Congestion, Nasal	1.1	1.2	2.0	1.3	0.9	0.5	0.0	0.0
Cough	2.5	3.1	2.7	3.3	1.9	2.4	0.0	4.3
Dyspnea	0.7	0.4	0.8	0.6	0.5	0.2	0.0	1.7
URI	9.1	9.6	6.7	10.3	6.6	9.3	16.7	10.3
Influenza	0.5	1.3	1.0	2.0	0.9	2.6	0.0	1.7
Pharyngitis	2.5	2.2	2.0	2.3	1.4	3.1	0.0	2.6
Sinus disorder	1.3	1.4	0.8	1.2	0.0	0.5	0.0	3.4
Sinusitis	1.8	1.8	0.7	2.1	0.5	1.6	8.3	2.6
Skin and Skin Appendage								
Flushing	0.2	0.2	0.5	0.3	2.8	3.1	0.0	1.7
Rash	2.0	1.8	1.5	1.8	0.9	1.3	8.3	0.9
Special Senses								
Fullness in ears	0.2	0.1	0.3	0.2	0.0	0.0	0.0	1.7
Urogenital System								
Impotence	0.6	0.5	1.2	1.1	1.4	1.6	0.0	0.9
Infection, Urinary Tract	1.7	1.5	1.5	1.2	0.9	1.3	0.0	0.9

* Occurring in $\geq 1\%$ and 2 or more hypertensive patients in at least one of the losartan treatment groups.

Table SU.6a list the incidence of adverse events occurring in hypertensives with renal impairment. Headache, dizziness, URI, edema, chest pain, and nausea were the most commonly reported adverse events.

Table SU.6a. Percentage of Clinical Adverse Experiences that Occurred in More Than One Losartan-Treated Hypertensive Patient with Renal Impairment

Body System	WMA Losartan (n = 115)	Cumulative Losartan (n=148)	Body System	WMA Losartan (n = 115)	Cumulative Losartan (n=148)
Body as a Whole			Nervous System and Psychiatric		
Asthenia/Fatigue	3.5	4.1	Dizziness	9.6	9.5
Distention, Abdominal	0.9	1.4	Headache	16.5	18.9
Edema/Swelling	5.2	5.4	Hyposthesia	1.7	1.4
Fever	1.7	2.0	Insomnia	1.7	2.0
Orthostatic Effects	1.7	2.0	Neuropathy, Peripheral	1.7	1.4
Pain, Abdominal	4.3	4.1	Sleep Disorder	1.7	1.4
Pain, Chest	4.3	6.1	Somnolence	1.7	1.4
Pain, Flank	1.7	2.0	Tremor	0.9	1.4
Syncope	0.9	2.0	Vertigo	0.9	1.4
Cardiovascular System			Respiratory System		
Blood Pressure Increased	0	1.4	Congestion, Nasal	1.7	1.4
Hypotension	3.5	4.1	Cough	2.6	3.4
Occlusion, Vasular Graft	0.9	1.4	Dyspnea	4.3	4.1
Tachycardia	1.7	2.0	Epistaxis	2.6	2.0
Digestive System			Infection, Respiratory, Upper	12.2	13.5
Constipation	1.7	1.4	Influenza	2.6	2.0
Diarrhea	1.7	2.0	Pharyngitis	2.6	2.0
Flatulence	2.6	3.0	Pneumonia	0.9	1.4
Nausea	7.0	6.8	Skin and Skin Appendage		
Vomiting	6.1	5.4	Infection, Skin	0	2.0
Metabolic/Nutritional System/Immune			Pruritus	0	1.4
Allergy	0.9	1.4	Rash	1.7	1.4
Fluid Overload	1.7	1.4	Special Senses		
Gout	1.7	1.4	Blurred Vision	2.6	2.0
Weight Gain	0	1.4	Urogenital System		
Musculoskeletal System			Dysuria	0.9	1.4
Cramp, Muscle	2.6	2.7	Impotence	2.6	2.0
Osteoarthritis	1.7	1.4			
Pain, Arm	0.9	1.4			
Pain, Back	4.3	4.7			
Pain, Hip	0.9	1.4			
Pain, Leg	1.7	1.4			
Pain, Neck	1.7	1.4			
Pain, Shoulder	1.7	2.0			
Stiffness	1.7	1.4			
Weakness, Muscle	0.9	1.4			

Table SU.6b list adverse event incidences for CHF patients. The profile is similar to the patient populations just described except that dyspnea is a more common complaint.

Table SU.6b. Number of Clinical Adverse Experiences in >1 Patient with Heart Failure Receiving Chronic Therapy With Losartan

Body System	Losartan (n=78) # Pts. (%)	Body System	Losartan (n=78) # Pts. (%)
Any Adverse Experience	59 (75.6)	Nervous System and Psychiatric	23 (29.5)
Body as a Whole	33 (42.3)	Headache	10 (12.8)
Asthenia/Fatigue	14 (17.9)	Dizziness	9 (11.3)
Edema/Swelling	6 (7.7)	Respiratory System	31 (39.7)
Chest Pain	5 (6.4)	Dyspnea	15 (19.2)
Fever	5 (6.4)	Cough	7 (9.0)
Death [†]	4 (5.1)	URI	5 (6.4)
Sudden Death [†]	3 (3.8)	Pneumonia	3 (3.8)
Syncope	3 (3.8)	Exertional Dyspnea	2 (2.6)
Orthostatic Effects	2 (2.6)	Nasal Congestion	2 (2.6)
Unknown Cause of Death ^{††}	2 (2.6)	Pulmonary Congestion	2 (2.6)
Cardiovascular System	21 (26.9)	Rhinorrhea	2 (2.6)
Heart Failure (worsening)	14 (17.9)	Sinus Disorder	2 (2.6)
Palpitation	3 (3.8)	Skin and Skin Appendage	11 (14.1)
Angina Pectoris	2 (2.6)	Rash	4 (5.1)
Hypertension Increased	2 (2.6)	Laceration	2 (2.6)
Myocardial Infarction	2 (2.6)	Skin Infection	2 (2.6)
Orthostatic Hypotension	2 (2.6)	Special Senses	6 (7.7)
Digestive System	17 (21.8)	Blurred Vision	2 (2.6)
Nausea	7 (9.0)	Cataract	2 (2.6)
Diarrhea	5 (6.4)		
Constipation	4 (5.1)		
Endocrine System	2 (2.6)		
Diabetes Mellitus	2 (2.6)		
Metabolic/Nutritional/Immune	3 (3.8)		
Weight Gain	3 (3.8)		
Musculoskeletal System	16 (20.5)		
Shoulder Pain	4 (5.1)		
Back Pain	3 (3.8)		
Arm Pain	2 (2.6)		
Jaw Pain	2 (2.6)		
Leg Pain	2 (2.6)		
Muscle Cramp	2 (2.6)		

[†] WAES report information on deaths of these 7 patients were presented in the losartan WMA.

^{††} Unknown cause of death was reported for 2 of the 7 patients.

Adverse Events - Laboratory

Laboratory adverse events were treated the same as was described for clinical adverse events. The major difference between the clinical data and laboratory data is that not all patients had labs obtained by 10/4/93. As a consequence, it is difficult to interpret the percentages of patients with losartan adverse events. The safety update is deficient in that actual laboratory values for these patients are not provided.

Table SU.7 summarizes the most frequently reported (i.e., in $\geq 1\%$ and in a parameter tested in at least 100 patients) laboratory adverse experiences. The incidences of laboratory adverse experiences in the cumulative time frame are similar to those presented in the WMA. In the losartan monotherapy group for the cumulative time frame, the most frequently reported laboratory adverse events were urine blood increased (3.8%), urine hemoglobin increased (3.6%), ALT increased (3.0%), urine RBCs increased (2.5%), and urine WBC increased (2.5%). In the losartan/HCTZ alone group, the most common adverse events were urine blood increased (3.5%), ALT increased (3.3%), serum potassium decreased (2.5%), fasting serum glucose increased (2.5%), and AST increased (2.4%).

Table SU.7. Laboratory Adverse Experiences Occurring in ≥1% of Hypertensive Patients Treated With Losartan®--Open-Label Trials (Reviewer's Note: The denominator for each lab is the number of patients who had that lab obtained)

Laboratory Parameter	Losartan Monotherapy				Losartan/HCTZ				Losartan/HCTZ Plus Other Antihypertensives				Losartan Plus Other Antihypertensives Without HCTZ			
	WMA (n=831)		CUM (n=1472)		WMA (n=601)		CUM (n=1412)		WMA (n=212)		CUM (n=547)		WMA (n=12)		CUM (n=116)	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Hematology																
Hemoglobin decreased	5/504	1.0	7/825	0.8	4/479	0.8	7/1066	0.7	2/197	1.0	4/487	0.8	1/8	12.5	1/79	1.3
WBC Count increased	2/504	0.4	2/825	0.2	5/479	1.0	7/1065	0.7	1/197	0.5	1/487	0.2	0/8	0.0	0/79	0.0
WBC Count decreased	0/504	0.0	0/825	0.0	1/479	0.2	4/1065	0.4	2/197	1.0	3/487	0.6	0/8	0.0	0/79	0.0
Eosinophils increased	1/503	0.2	3/824	0.4	0/479	0.0	3/1065	0.3	2/198	1.0	5/487	1.0	0/8	0.0	0/79	0.0
Blood Chemistry																
Blood Urea increased	1/64	1.6	1/162	0.6	1/47	2.1	2/185	1.1	1/24	4.2	1/102	1.0	0/1	0.0	0/4	0.0
Serum Creatinine increased	2/508	0.4	3/842	0.4	6/489	1.2	8/1086	0.7	1/198	0.5	5/489	1.0	0/8	0.0	1/79	1.3
Total Serum Bilirubin increased	1/508	0.2	3/817	0.4	5/489	1.0	7/1046	0.7	1/198	0.5	5/473	1.1	0/8	0.0	0/80	0.0
AST increased	5/509	1.0	8/839	1.0	14/489	2.9	26/1078	2.4	2/198	1.0	8/488	1.6	0/8	0.0	0/81	0.0
ALT increased	14/507	2.8	25/839	3.0	19/486	3.9	36/1081	3.3	5/198	2.5	15/487	3.1	0/8	0.0	3/81	3.7
Serum Alkaline Phosphatase increased	5/507	1.0	6/836	0.7	6/489	1.2	10/1083	0.9	0/198	0.0	1/488	0.2	0/8	0.0	0/80	0.0
Serum Glucose increased	3/327	0.9	8/628	1.3	12/344	3.5	19/921	2.1	4/117	3.4	11/401	2.7	0/5	0.0	1/73	1.4
Fasting Serum Glucose increased	1/181	0.6	1/211	0.5	3/146	2.1	4/163	2.5	3/80	3.8	4/91	4.4	0/3	0.0	0/6	0.0
Triglycerides increased	0/91	0.0	2/252	0.8	1/110	0.9	5/489	1.0	0/20	0.0	0/160	0.0	0/0	0.0	0/53	0.0
Serum Uric Acid increased	3/496	0.6	5/826	0.6	8/478	1.7	15/1072	1.4	3/198	1.5	7/489	1.4	0/8	0.0	0/79	0.0
Serum Potassium decreased	3/508	0.6	4/843	0.5	18/490	3.7	27/1088	2.5	4/198	2.0	10/489	2.0	0/8	0.0	0/79	0.0
Serum Phosphorus decreased	1/496	0.2	1/826	0.1	2/488	0.4	2/1075	0.2	5/197	2.5	4/488	0.8	0/8	0.0	0/79	0.0
Urinalysis																
Urine Protein increased	4/498	0.8	5/819	0.6	7/477	1.5	8/1055	0.8	0/193	0.0	3/480	0.6	0/7	0.0	0/77	0.0
Urine WBCs increased	7/359	1.9	11/436	2.5	8/337	2.4	9/780	1.2	4/114	3.5	5/275	1.8	0/4	0.0	0/10	0.0
Urine RBCs increased	7/359	1.9	11/436	2.5	9/337	2.7	12/780	1.5	4/114	3.5	7/275	2.5	0/4	0.0	0/10	0.0
Bacteria	1/359	0.3	2/436	0.5	1/337	0.3	1/780	0.1	2/114	1.8	2/275	0.7	0/4	0.0	0/10	0.0
Urine Blood increased	4/126	3.2	7/185	3.8	3/110	2.7	5/141	3.5	2/59	3.4	1/89	1.1	0/3	0.0	0/18	0.0
Urine Hemoglobin increased	-----	-----	5/140	3.6	-----	-----	0/6	0.0	-----	-----	1/40	2.5	-----	-----	2/49	4.1
Any Laboratory Adverse Experience	59/539	11	106/894	12	88/494	18	143/1095	13	33/198	17	70/490	14	1/8	12.5	8/82	9.8

†The dashes denote that no tests were performed on this parameter

Table SU.7a lists the number of hypertensive patients with renal impairment who experienced laboratory adverse events. Compared to hypertensives without renal impairment (table SU.7), more patients with renal impairment had increases in potassium and creatinine. These cases will require additional data from the sponsor. It is not clear that this increase is due to losartan or underlying disease.

Table SU.7a. Laboratory Adverse Experiences Occurring in More Than One Losartan-Treated Hypertensive Patient with Renal Impairment

	Losartan No. (%) WMA	Losartan No. (%) CUM
Any Laboratory Adverse Experiences	21/114 (18.4)	36/145 (24.8)
Hematology		
Increased Eosinophils	3/113 (2.7)	3/143 (2.1)
Blood Chemistry		
Increased BUN	0/101 (0.0)	4/132 (3.0)
Increased Serum Creatinine	4/114 (3.5)	6/145 (4.1)
Increased AST	1/112 (0.9)	2/142 (1.4)
Increased ALT	3/112 (2.7)	4/142 (2.8)
Increased Serum Alkaline Phosphatase	2/114 (1.8)	3/145 (2.1)
Increased Serum Glucose	1/75 (1.3)	2/105 (1.9)
Increased Serum Potassium	7/114 (6.1)	16/145 (11.0)
Decreased Serum Calcium	3/112 (2.7)	3/142 (2.1)
Urinalysis		
Increased Urine WBCs	1/93 (1.1)	2/118 (1.7)
Decreased Urine Chloride	0/59 (0.0)	2/82 (2.4)
Decreased Creatinine Clearance	1/89 (1.1)	2/112 (1.8)

Table SU.7b lists the incidence of lab adverse events.

Table SU.7b. Laboratory Adverse Experiences In >1 Patient with Heart Failure Receiving Chronic Therapy With Losartan

	Losartan No. + (%)
Any Laboratory Adverse Experiences	13/77 (19.5)
Blood Chemistry	
Increased Serum Glucose	5/77 (6.5)
Increased Blood Urea Nitrogen	4/77 (5.2)
Increased Serum Creatinine	3/77 (3.9)
Decreased Serum Potassium	2/77 (2.6)
Hematology	
Decreased Hemoglobin	2/77 (2.6)
Urinalysis	
Increased Urine Glucose	3/76 (3.9)
Increased Urine White Blood Cells	3/76 (3.9) [†]

[†] One patient died prior to any laboratory evaluations; therefore, laboratory values are reported for only 77 patients.

Adverse Event - Serious

All nonfatal serious adverse experiences that occurred in patients while receiving losartan or within 14 days after discontinuation of therapy during the reporting period July 1, 1993, through December 31, 1993, are presented in Table SU.8. Serious nonfatal adverse experiences have been reported for a total of 77 patients. At the time of the adverse event, 21 were on losartan monotherapy, 31 on losartan/HCTZ, 21 on losartan/HCTZ plus other antihypertensives and 4 on losartan plus other antihypertensives. Nonfatal serious adverse experiences attributed to the cardiovascular system were observed in 20 of the patients and 17 patients had serious adverse experiences attributed to the urogenital system. One patient with renal impairment experienced a serious adverse event (table SU.8b.)

Table SU. 8. Serious Nonfatal Adverse Experiences From All Sources – Hypertensive Patients; Report Time Frame: July 1, 1993 through December 31, 1993

Protocol/ Study #	Patient #	Age/Sex	Treatment	Daily Dose (mg)	Study Day of Onset	Adverse Experience	Outcome
011-028	0583	80/M	Los	50	871	Pain, Chest	Recovered
055-015	5318	88/M	Los	100	237#	Hernia	NR
065-010	1232	50/F	Los/HCTZ/Aten	100/12.5/100	482	Pain, Chest	Recovered
085-008	3077	62/M	Los/HCTZ	50/12.5	9	Pain, Chest**	Still Present
011-003	0025	65/M	Los	100	NR	Obstruction, Carotid Artery	Recovered
011-040	0830	40/F	Los	150	488	Myalgia**	Recovered
			Los	150	500	Angina Pectoris	Recovered
			Los	150	500	Occlusion, Coronary Artery	Still Present
011-040	0836	55/F	Los/HCTZ	100/12.5	647#	Occlusion, Arterial	Recovered
044-006	3101	65/M	Los	50	173	Palpitation	Recovered
044-011	3180	57/M	Los/HCTZ	50/6.25	382#	Myocardial Infarction**	Recovered
045-001	4024	68/M	Los	50	206#	Claudication, Intermittent	Recovered
048-007	0590	42/F	Los	50	10	Supraventricular Tachycardia**	Recovered
054-001	8009	69/M	Los/HCTZ	50/12.5	426	Atherosclerosis, Coronary**	Still Present
			Los/HCTZ	50/12.5	419	Fibrosis, Pulmonary	Still Present
054-005	8105	62/F	Los/HCTZ	50/12.5	411#	Atherosclerosis, Coronary	Still Present
054-008	8184	72/M	Los/HCTZ	50/6.25	389#	Heart Failure**	Still Present
			Los/HCTZ	50/6.25	389#	Pneumonia	Still Present
054-021	8454	71/M	Los/HCTZ	50/6.25	337	Premature Ventricular Contrac.	Still Present
054-016	8348	69/M	Los/HCTZ/Fel	50/25/5	159#	Atherosclerosis, Coronary	Recovered
054-019	8879	64/M	Los/HCTZ/Fel	50/12.5/10	190#	Aneurysm, Aortic	Recovered
054-027	8568	67/M	Los/HCTZ	50/12.5	377#	Pain, Chest	Recovered
			Los/HCTZ	50/12.5	377#	Atherosclerosis, Coronary	Recovered
054-029	8608	59/F	Los/HCTZ/Fel	50/12.5/5	306#	Angina, Unstable**	Recovered
056-015	3683	64/M	Los	100	207#	Angina Pectoris**	NR
059-011	5604	34/M	Los/HCTZ/Aten/Nif	100/25/100/40	142	Hypertension	Recovered
065-011	1584	70/M	Los/HCTZ/Aten	100/25/100	230#	Angina Pectoris	Recovered
065-014	1477	39/M	Los/Aten	100/50	333	Atrial Fibrillation**	Recovered
065-028	1387	51/F	Los	50	159	Syncope**	Recovered
			Los	50	159	Dizziness	Recovered
			Los	50	159	Blurred Vision	Recovered
			Los	50	159	Headache	Recovered
			Los	50	159	Pain, Abdominal	Recovered
			Los	50	159	Cholelithiasis	Still Present
011-013	0255	-/M	Los	NR	NR	Inflammatory Bowel Disease	Recovered
045-003	4095	57/M	Los	50	67#	Ulcer, Duodenal w/ Hemorrhage	Recovered
			Los	50	67#	Melena	Recovered
048-016	6295	43/F	Off-drug	--	213	Pancreatitis**	Recovered
054-004	8092	40/M	Los/HCTZ/Fel	50/12.5/10	281#	Cholelithiasis	Recovered
054-011	8247	63/M	Los/HCTZ	50/6.25	337#	Cholelithiasis	Recovered
054-015	8334	44/F	Los/HCTZ	50/6.25	415#	Cholecystitis	Still Present
054-026	8557	69/F	Los/HCTZ/Fel	50/6.25/5	489#	Vomiting	Recovered
			Los/HCTZ/Fel	50/6.25/5	489#	Diarrhea	Recovered
			Los/HCTZ/Fel	50/6.25/5	489#	Dehydration	Recovered
059-007	5567	67/M	Los	100	319	Neoplasm, Intestinal, Malignant**	Still Present
065-019	1505	54/M	Los/Aten/HCTZ	100/100/25	283#	Ileus	Still Present
065-038	1159	43/F	Los/Fel/HCTZ	100/10/25	416	Cholecystitis	Still Present
065-042	1683	58/M	Los/Fel/HCTZ	100/5/12.5	379	Cholecystitis	Recovered
054-009	8206	56/F	Los/HCTZ/Fel	50/12.5/5	381#	Neoplasm, Thyroid, Malignant	Still Present
055-010	5166	76/F	Los/Fel	100/15	369	Hypoglycemia	Recovered
			Los/Fel	100/15	369	Confusion	Recovered
055-010	5166	76/F	Los/Fel	100/15	379	Hypoglycemia	Recovered
			Los/Fel	100/15	379	Confusion	Recovered
044-009	3005	35/M	Los/HCTZ	50/6.25	290	Pain, Back	Recovered
050-018	2318	52/M	Los/HCTZ/Fel	50/12.5/10	385#	Pain, Neck	Recovered
054-003	8047	45/M	Off drug	--	295	Fracture, Leg, Multiple	Recovered

Table SU. 8. Serious Nonfatal Adverse Experiences From All Sources -- Hypertensive Patients; Report Time Frame: July 1, 1993 through December 31, 1993 (cont)

Protocol/ Study #	Patient #	Age/Sex	Treatment	Daily Dose (mg)	Study Day of Onset	Adverse Experience	Outcome
059-010	5593	51/M	Los/HCTZ	100/12.5	229#	Fracture, Femur	Still Present
			Los/HCTZ	100/12.5	229#	Fracture, Foot	Still Present
059-021	5728	56/F	Los/HCTZ/Aten	100/25/100	296	Fracture, Ankle	Still Present
065-038	1150	65/M	Los/Fel	50/5	225	Pain, Knee	Still Present
			Off-drug	--	232	Hematoma	Recovered
011-040	0828	65/M	Los	100	607	Dizziness	Recovered
045-010	4175	69/M	Los/HCTZ	50/12.5	217	Stiffness	Recovered
			Los/HCTZ	50/12.5	217	Akinesia/Iradykinesia	Recovered
			Los/HCTZ	50/12.5	240	Confusion	Recovered
045-015	4250	45/F	Off-drug	--	162	Sclerosis, Multiple**	Still Present
050-023	2403	53/M	Los	50	506#	Hypoesthesia	Still Present
			Los	50	506#	Pain, Chest	NR
011-002	0027	60/M	Los/HCTZ	100/25	230#	Neoplasm, Lung, Metastatic	Still Present
011-030	0611	66/F	Los/HCTZ	100/50	824#	Neoplasm, Lung, Malignant	Recovered
044-006	3082	69/M	Los	50	177	Neoplasm, Lung, Malignant**	Still Present
045-001	4019	67/M	Los/HCTZ	50/6.25	365#	Neoplasm, Lung, Malignant	Still Present
			Los/HCTZ	50/6.25	341#	Dyspnea	Still Present
054-011	8257	63/M	Los/HCTZ/Fel	50/12.5/5	308#	COPD	Still Present
055-010	5169	82/M	Los	100	128	Neoplasm, Pharyngeal, Malignant**	Still Present
048-007	6014	43/M	Los/HCTZ/Nif	50/12.5/40	169	Neoplasm, Skin, Malignant	Recovered
050-008	2133	70/F	Los	50	119	Neoplasm, Skin, Malignant	Recovered
050-015	2254	46/F	Los/HCTZ	50/50	518	Neoplasm, Skin Malignant	Recovered
054-019	8409	61/M	Los/HCTZ	50/12.5	505#	Neoplasm, Skin, Malignant	Still Present
064-014	4597	68/M	Los/HCTZ	100/25	312#	Neoplasm, Skin, Malignant	Recovered
054-026	8549	66/M	Los/HCTZ	50/6.25	331	Visual Loss**	Still Present
			Los/HCTZ	50/6.25	356	Glaucoma	Still Present
011-028	0575	75/M	Los	50	929	Neoplasm, Kidney, Malignant**	Still Present
011-034	0697	79/F	Los/HCTZ	100/25	810#	Septicemia (Urosepsis)	Recovered
011-038	0781	58/F	Los/HCTZ	100/25	727	Nephrotic Syndrome	Still Present
011-038	0784	54/F	Los/HCTZ	100/12.5	794	Implant, Breast, Complication	Recovered
044-006	3101	66/M	Los	50	354#	Neoplasm, Prostate, Malignant	Recovered
044-011	3170	58/M	Los	50	105	Neoplasm, Prostate, Malignant**	Recovered
045-001	4022	43/M	Los	50	327#	Benign Prostatic Hypertrophy	Recovered
048-004	6109	44/M	Los/HCTZ	50/12.5	15#	Obstruction, Urinary Tract	Recovered
050-013	2423	51/F	Los/HCTZ/Fel	50/12.5/10	491#	Neoplasm, Breast, Malignant	Still Present
054-005	8132	55/M	Los/HCTZ	50/12.5	329#	Neoplasm, Prostate, Malignant	Still Present
			Los/HCTZ	50/12.5	346#	Diverticulitis, Intestinal	Still Present
			Los/HCTZ	50/12.5	377#	Neoplasm, Urethral, Malignant	Still Present
054-011	8244	71/M	Los/HCTZ/Fel	50/12.5/5	4#	Neoplasm, Prostate, Malignant	Still Present
054-011	8255	43/M	Los/HCTZ	50/6.25	484#	Neoplasm, Kidney, Malignant	Recovered
054-016	8342	34/F	Los/HCTZ	50/12.5	391#	Pyelonephritis	Recovered
			Los/HCTZ	50/12.5	392#	Anemia	Recovered
054-019	8876	63/F	Los/HCTZ/Fel	50/12.5/5	452	Neoplasm, Kidney, Malignant	Still Present
056-001	3558	--/M	Los/HCTZ/Fel	100/12.5/10	230#	Neoplasm, Bladder, Malignant	Still Present
056-009	3550	48/F	Los/HCTZ	100/6.25	274#	Neoplasm, Uterine, Malignant	Still Present
085-016	3152	70/M	Los/HCTZ	100/25	31	Neoplasm, Prostate, Malignant	Still Present

*Case Report Form data in-house during the SUR time frame take precedence over the WAES report; ** = DISCONTINUED

#Study day of onset calculated from start of open-label extension; Aten=Atenolol; Fel= Felodipine; HCTZ=Hydrochlorothiazide; Los=Losartan; Nif=Nifedipine

Table SU.8a. Serious Clinical Adverse Experiences During the Safety Update Report Time Frame in Hypertensive Patients With Renal Impairment Who Did Not Die

Protocol- Study	Patient #	Age/ Sex	Treatment	Dose (mg)	Day of Onset	Adverse Experience	Outcome
058-003	131	61 M	Losartan	100	58	Pain, chest	Recovered

Serious nonfatal adverse experiences have been reported for a total of 30 CHF patients who are listed in table SU.6b.

Table SU.8b. Nonfatal Serious Clinical Adverse Experiences From All Sources in Losartan-Treated Patients with Heart Failure—Report Time Frame: July 1, 1993 through December 31, 1993 [All patients received losartan]

Study # Protocol #	Patient #	Age/Sex	Losartan Daily Dose (mg)	Day of Onset	Adverse Experience	Discontinued	Outcome
047-006 047-20	1051	70/Male	10	480	Syncope	No	Recovered
047-007 047-20	1061	68/Male	25	490	Dizziness	No	Recovered
047-008 047-20	1077	62/Male	50	448	Syncope	No	Still Present
047-011 047-20	1103	57/Male	10 12.5	420 476	Syncope Worsening Heart Failure	No Yes	Recovered Recovered
047-015 047-20	1180	53/Male	50	373	Abdominal Pain	No	Recovered
068-014 068-00	169	54/Male	25	428	Syncope	No	Recovered
071-006 071-10	185++	68/Male	12.5	63	Abdominal Pain	No	Recovered
071-014 071-00	176	53/Male	50	20	Trauma	No	Recovered
047-003 047-20	1025	63/Male	50 50 12.5	514 548 567	Ventricular Tachycardia Worsening Heart Failure, Acute Renal Failure, Coagulopathy, Hypotension Orthopnea, Exertional Dyspnea, Nausea, Vomiting	No No No No No No No	Recovered Recovered Recovered Recovered Recovered Recovered Recovered
047-004 047-20	1035	47/Male	50	541	Worsening Heart Failure	No	Unknown
047-012 047-20	1120*	53/Male	50	573	Worsening Heart Failure	No	Recovered
047-015 047-21	1177	66/Male	50	432	Cerebral Vascular Accident	No	Still Present
068-003 068-00	90	49/Male	50 50	145 147	Sweating, Dizziness, Chest Pain Atrial Fibrillation, Atrial Flutter	No No No No	Still Present Still Present Still Present Still Present
068-006 068-00	65	81/Male	12.5 12.5	247 251	Worsening Heart Failure Atrial Fibrillation	No No	Recovered Unknown
068-008 068-00	85	61/Male	50	362	Angina	No	Recovered
068-008 068-00	88	43/Male	50	235	Palpitations, Syncope	No No	Recovered Recovered
071-003 071-10	102	47/Male	50	142 168	Atrial Fibrillation Worsening Heart Failure	No No	Still Present Recovered
071-003 071-10	104	67/Male	50 50 50	194 196 207	Worsening Heart Failure Atrial Fibrillation Worsening Heart Failure, Ventricular Fibrillation	No No No No	Still Present Recovered Still Present Recovered
071-004 071-10	146	72/Male	50	214	Worsening Heart Failure	No	Recovered
071-007 071-10	246	74/Male	50	131	Worsening Heart Failure	Yes	Recovered
071-009 071-10	223	57/Female	50	174	Worsening Heart Failure	Yes	Still Present
071-018 071-00	67	55/Male	25	29	Pulmonary Edema, Worsening Heart Failure	No No	Recovered Unknown
047-012 047-20	1115	66/Male	50	661	Gastrointestinal Bleed	No	Recovered
068-010 068-00	110	38/Male	50	163	Cholelithiasis	No	Recovered

Table SU.8b. Nonfatal Serious Clinical Adverse Experiences From All Sources in Losartan-Treated Patients with Heart Failure—Report Time Frame: July 1, 1993 through December 31, 1993 [All patients received losartan] (cont.)

Study # Protocol #	Patient #	Age/Sex	Losartan Daily Dose (mg)	Day of Onset	Adverse Experience	Discontinued	Outcome
071-006 071-10	185++	68/Male	50	243	Duodenal Ulcer	No	Recovered
047-012 047-20	1120*	53/Male	50	329	Vertebral Fracture	No	Unknown
047-015 047-21	1162	61/Male	50	558	Musculoskeletal Pain	No	Recovered
047-015 047-21	1169	44/Male	50	639	Dizziness	No	Unknown
071-012 071-00	12	60/ Unknown	12.5	12	Orthopnea, Dyspnea	Yes Yes	Recovered Unknown
071-020 071-00	128	71/Male	25	51	Pulmonary Edema, Hypotension	No No	Recovered Recovered
071-014 071-10	179	64/Male	50	204	Psoriasis	No	Recovered
047-015 047-21	1147	76/Male	50	515	Prostate Disorder	No	Still Present

Discontinuations Due to Adverse Events

Case report forms were received in-house for 27 double-blind patients during the SUR time frame. Of these, 1 patient (AN 0590, Study 048-007) had an adverse experience that resulted in discontinuation. This patient was a 45-year-old male who was treated with losartan 50 mg and developed severely increased blood pressure accompanied by dizziness, headache, and palpitations on the fourth day of double-blind therapy.

Fifty-four of patients in open label hypertension trials had adverse experiences that resulted in discontinuation. Three patients (not included in the WMA) were discontinued due to laboratory adverse experiences during the SUR time frame. A table listing the patients discontinued for adverse events and the reason for discontinuation has been requested.

Four patients with renal impairment discontinued due to adverse events during the SUR time frame. Table SU.9 list the patients and the reason for withdrawal.

Table SU.9. Hypertensive Patients With Renal Impairment Discontinued Due to Clinical Adverse Experiences During the Safety Update Report Time Frame [Reviewer's Note: Study 58 is an open label study.]

Protocol-Study	Patient #	Age/ Sex	Treatment	Dose (mg)	Day of Onset	Day Stopped	Adverse Experience
058-003	134	59 M	Losartan	50	9	9	Allergy
058-008	316	58 M	Off drug	-	29	28	Hypotension
058-008	315	78 M	Losartan	100	45	72	Hyperkalemia
058-020	671	36 M	Losartan Losartan	100 100	83 83	85	AST Increased ALT Increased

Patient #316 received losartan 50 mg on day 28. The time of onset of hypotension is not provided in the CANDAs. It is unclear that drug can be excluded as responsible for this adverse event. Patient #315 had baseline potassium between 4.7 mEq/L and 5.6 mEq/L. During treatment with losartan, potassium were between 5.6 and 6.5 mEq/L. Serum creatinine and BUN increased slightly from baseline also. (baseline creatinine = 2.6 mg/dl, day 61 creatinine = 3.0 mg/dl; baseline BUN = 45 mg/dl, day 61 BUN = 76 mg/dl).

Ten patients with CHF withdrew from CHF trials due to adverse events. A table listing the patients discontinued for adverse events and the reason for discontinuation has been requested.

Cancers

The SUR database lists 27 patients with the diagnosis of a malignant neoplasm (Table SU.10.). Three patients had multiple cancers listed. Two of these patients had skin and intestinal cancer. The third had lung cancer with metastatic disease to liver and bone. There were ten skin cancers, five prostate cancers and six intestinal cancers.

Table SU. 10. Cancers in the Safety Update Database

Study	Patient #	AE Drug Dose	Age	Sex	Race	Neoplasm	Day
11	27	150mg losartan/25mg HCTZ	37	M	Caucasian	INTESTINAL	577
						SKIN, MALIGNANT	403
11	70	50mg losartan	53	M	Caucasian	INTESTINAL	484
11	71	50mg losartan	49	M	Caucasian	SKIN, MALIGNANT	237
11	508	150mg losartan/12.5mg HCTZ	66	M	Caucasian	INTESTINAL, MALIGNANT	645
						SKIN, MALIGNANT	498
11	577	50mg losartan	44	F	Caucasian	BREAST, MALIGNANT	459
11	656	150mg losartan	51	M	Caucasian	INTESTINAL	630
11	666	100mg losartan	58	F	Caucasian	SKIN, MALIGNANT	66
11	828	OFF-DRUG	65	M	Caucasian	SKIN, MALIGNANT	133
11	832	100mg losartan/12.5mg HCTZ	59	F	Caucasian	BLADDER, MALIGNANT	589
11	833	150mg losartan/25mg HCTZ	68	M	Caucasian	PROSTATE, MALIGNANT	769
44	3170	50mg losartan	58	M	Caucasian	PROSTATE, MALIGNANT	105
47	1071	50mg losartan	73	F	Negro	KIDNEY, MALIGNANT	156
48	6014	40mg NIFEDIPINE/12.5mg HCTZ/50mg losartan	43	M	Mulatto	SKIN, MALIGNANT	169
49	7145	50mg losartan	47	M	Caucasian	SKIN, MALIGNANT	366
49	7279	50mg losartan	52	M	Caucasian	TONGUE, MALIGNANT	267
49	7280	25mg losartan/25mg HCTZ	62	M	Black	LUNG, MALIGNANT	46
49	7411	50 mg losartan/25 mg HCTZ	61	M	Caucasian	KIDNEY, MALIGNANT	293
49	7418	100mg losartan/25mg HCTZ	64	M	Caucasian	INTESTINAL, MALIGNANT	42
49	7447	50mg losartan/12.5mg HCTZ	48	M	Caucasian	BONE, METASTATIC	310
						LIVER, METASTATIC	310
						LUNG, MALIGNANT	309
50	2022	50mg losartan/12.5mg HCTZ/5mg FELODIPINE	66	M	Caucasian	PROSTATE, MALIGNANT	336
50	2133	50mg losartan	70	F	Caucasian	SKIN, MALIGNANT	119
50	2254	50mg losartan/50mg HCTZ	46	F	Caucasian	SKIN, MALIGNANT	518
54	8254	50mg losartan/6.25mg HCTZ	71	M	Caucasian	PROSTATE, MALIGNANT	288
54	8433	OFF-DRUG	69	M	Black	PROSTATE, MALIGNANT	98
54	8871	50mg losartan/6.25mg HCTZ	70	F	Caucasian	SKIN, MALIGNANT	208
59	5567	100mg losartan	67	M	Black	INTESTINAL, MALIGNANT	319
65	1194	50mg losartan	64	M	Caucasian	MALIGNANT	15
65	1421	2TABLETS PLACEBO	66	M	Caucasian	INTESTINAL, METASTATIC	43

Of special interest is the incidence of kidney cancer. During the development of losartan, an independent Italian investigator (Remuzzi) performed a study in diabetic (streptozocin induced) Sprague-Dawley rats. Diabetic rats (n = 8 per group) whose blood sugars were controlled by insulin, were treated with oral losartan or placebo for a period of one year for the purpose of evaluating glomerular morphology. A non-diabetic control group treated with nothing was also included. After one year, five of eight losartan treated rats had gross kidney tumors evident on necropsy. All were cancerous. Neither the diabetic or non-diabetic control groups had any gross tumors. A systematic histologic evaluation of the tissue was not performed to search for microscopic tumors. Two patients in the SUR data were diagnosed with kidney cancer. Four additional cases, three in patients treated with losartan and one placebo, are included in the Safety Update summary report. All of the cases of renal cancer as of February 28, 1994 are summarized in table SU.11.

Table SU.11. Renal Cancers

Protocol/ Study #	Patient #	Age/ Sex	Treatment (mg Daily Dose)	Treatment Duration* (Days)	Date of Diagnosis	History/Prestudy Evaluations	Symptoms	Diagnoses/Pathology
011/028	0575	73/M	Losartan 50	962	10/26/93	Essential hypertension Elevated pre-study prorenin (163 ng A ₁ /mL/hr)	Gross hematuria	7 x 7 x 3.7 cm right renal cell carcinoma, clear cell type Tumor positive for prorenin Post nephrectomy plasma prorenin activity 33 ng A ₁ /mL/hr
047/008	1071+	73/F	Losartan 50	159	8/15/92	Essential hypertension NYHA Class II heart failure Microscopic hematuria (20-29 ; 30-39 RBC/HPF)	Asymptomatic - Discovered during follow-up of renal insufficiency	6 x 5 x 3.5 cm right renal cell carcinoma, tubulopapillary pattern
049/023	7411+	62/M	Losartan 50/ HCTZ 25	280	12/9/92	Essential hypertension Tobacco use 8 cm left renal mass - 1984 Microscopic hematuria (3-5 RBC/HPF)	Asymptomatic - Discovered during follow-up of pre- existing left renal mass	7 x 7 x 8 cm left renal upper pole necrotic tumor, lower pole multifocal papillary renal cell carcinoma
054/011	8255	43/M	Losartan 50/ HCTZ 6.25	484	10/7/93	Essential hypertension Tobacco use Chronic low back pain - 1991	Gross hematuria Lynuria Right flank pain	10 x 10 x 10 cm right renal cell carcinoma, predominantly clear cell type
054/019	8876	63/F	Losartan 50/ HCTZ 12.5/ Felodipine 5	453	10/4/93	Essential hypertension	Gross hematuria Left flank pain Urinary retention with clots	8.2 x 8.2 x 8.0 cm left renal cell carcinoma, predominantly clear cell type
076/001	102	59/M	Placebo	42	11/11/93	Essential Hypertension	Urinary frequency Nocturia Slowing of urinary stream	7 cm left renal cell carcinoma

* Treatment duration is based on calendar days post initiation of losartan therapy up to and including date of diagnosis.

** This patient was found to have a renal cell carcinoma at the time of his participation in the felodipine/enalapril interaction study subsequent to his participation in the losartan RAAS II study during which he received placebo therapy.

+ Case presented in WMA

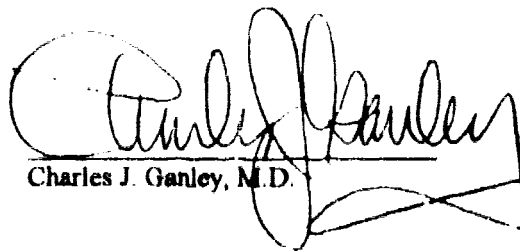
Summary:

There are no major differences in the incidence of clinical adverse events with losartan during the open label period compared to the WMA database. Laboratory adverse events incidence rates are difficult to interpret for the reasons stated in the review. CANDA failures limit the ability to review the laboratory data in the SUR database. For this reason, multiple requests for additional laboratory information has been made to the sponsor.

The data from the Remuzzi streptozocin study raised the issue of losartan being a promoter of kidney tumors. The concern was enhanced by the observation that renal cancer has been reported in five losartan or losartan/HCTZ patients as of February 28, 1994. Additional data, both clinical and pre-clinical, is summarized in separate reviews by Dr. Proakis and Dr. Burkhardt. This information provides a compelling argument that there is insufficient evidence to conclude that losartan is a promoter of kidney tumors. A complete summary of the information is provided in a separate review document. However, before this issue can be laid to rest, the sponsor needs to supply additional information on patients with hematuria, reported either as an adverse event or as an abnormal laboratory value.

Requests for Information:

- 1) Provide a table listing the patients withdrawn and the reason for withdrawal (plus other pertinent information) during the SUR time period for clinical or laboratory adverse events from the CHF population and hypertensive population.
- 2) A complete report for study 58 (Open study of losartan in hypertensive patients with renal impairment) has not been submitted. Although this not a controlled study, it would be interesting to determine the mean changes in laboratory parameters with time.
- 3) Queries of the Safety Update database for liver function tests, creatinine/BUN, potassium abnormalities and urine blood have been sent to Merck.



Charles J. Ganley, M.D.

cc: orig.
HFD-110 file
HFD-110/c.ganley/r.lipicky/cso/k.knudson/a.proakis

FEB - 1 1995

Medical Officer Review

NDA #: 20-386
 Drug Name: Losartan (DuP 753, MK-954)
 Sponsor: MSDRL
 Date of Application: 12/3/93
 Date of Receipt: 12/6/94
 Review Start Date: 3/30/94
 Review Completed: 2/1/95
 Medical Reviewer: Charles J. Ganley, M.D.

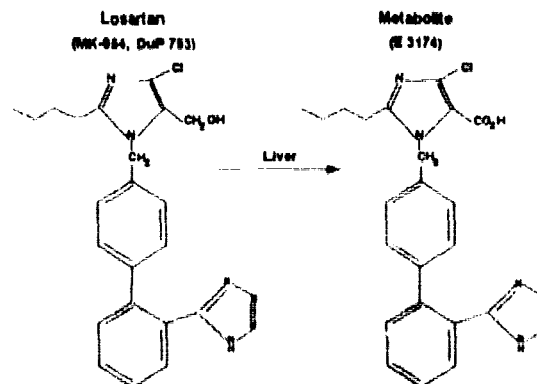
General Information

Name of Drug

Generic: losartan potassium

Trade: COZAAR

Chemical: 2-n-butyl-4-chloro-5-hydroxy-methyl-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole potassium salt



M.W. = 461.0

Pharmacologic Category: Angiotensin II Receptor AntagonistProposed Indication: Treatment of Essential HypertensionDosage Form: 25 mg, 50 mg and 100 mg film coated tabletsRoute of Administration: OralRelated Drugs: None ApprovedApproved for this Indication in: Not Approved in Other Countries; Applications Pending**Resume**

Losartan is an angiotensin II receptor antagonist. It has an absolute bioavailability in humans of approximately 23% with an elimination half-life of approximately 2 hours. Losartan is metabolized by a cytochrome P450 enzyme to an active metabolite, E-3174. E-3174 has an elimination half-life of approximately 9 hours and may be responsible for the blood pressure lowering effect 24 hours post-dosing with losartan.

There are three randomized, double-blind, placebo controlled, parallel dose trials of 8 to 12 weeks duration. Losartan 50 and 100 mg once a day significantly lowered diastolic blood pressure. Black patients have minimal, if any response, to losartan and as such, losartan should not be recommended as monotherapy in black patients.

There are no significant safety issues apparent. Cough may occur less frequently than with ACEI. There are instances of reversible elevation of creatinine with losartan and losartan/HCTZ. Facial and eyelid edema has been reported with losartan.

Losartan is an effective anti-hypertensive agent with a reasonable safety profile. The NDA is approvable pending review of the safety update and the review of the Division of Epidemiology of the cancer rates. [Medical Reviewer's Note: It is not apparent from the data in the NDA but there is a concern about the risk of developing renal cell cancer with losartan therapy based on animal and human data. This subject will be addressed in separate reviews by Dr. Knudson, Dr. Greg Burkhart, Dr. Proakis and Dr. Ganley.]

Introduction

Losartan is an angiotensin II receptor antagonist. It selectively binds to angiotensin II receptor subtype 1 (AT₁). The location of angiotensin II receptors, the effect of angiotensin on the receptor and the potential response to blockade of the receptor are shown in table 1. In the NDA, the effect of losartan on the urinary excretion of electrolytes, GFR and plasma neurohormones are explored in numerous clinical pharmacology trials. The clinical efficacy (ability to decrease DBP) is explored in several placebo controlled trials of 8 weeks or greater duration. Active control trials and open label trials provide additional information regarding the safety of losartan.

Table 1. Angiotensin II Receptors

Location	Action	Effect	Blockade	
			Initial	Long-Term
Vessels				
Afferent	↑R*	↓RBF, ↓ΔP, ↑GFR	↑GFR, ↑UNa	↑RBF, ↑ΔP, ↓GFR
Efferent	↑R	↓RBF, ↑ΔP, ↑GFR		↑RBF, ↓P, GFR (+/NC)
Vasa Recta	↑R	↑Medullary Osmolality	↓GFR, ↑UNa ↓OSM (↓UOSM)	
Mesangium				
	Contraction	↓Kf, ↓GFR	↑Kf, ↑GFR	↓Uprot
		↑Uprot	↓Uprot	↑GFR
Tubules				
Proximal	↑NA/H	↓UNa, ↓UHCO ₂	↑UNa, ↓UNH ₄	?
	Exchange	↓UpH, ↑NH ₃	↑UHCO ₃ , ↑UpH ↑V, ↑UCl, ↑UPO ₄	
		↑UNH ₄	↑Uurate	
			↑ULi	
Distal	↑Aldo	↓UNa	↑UNa	
		↑K secretion	↓UK, ↑SK	
JG Cells	↓Renin	Negative Feedback	↑Reactive Renin ↑A II (Blunt Blockade)	

*R - Resistance

✓ The original NDA or Worldwide Marketing Application (as designated by Merck; abbreviated WMA) was submitted 12/6/93. The cut-off date for inclusion of data from case report forms in the WMA was data received by Merck on or prior to 3/31/93. The 4 month Safety Update Report (SUR) was submitted on 4/4/94. The sponsor states that the Safety Update Report (SUR) provides incidence calculations based upon case report form information received by Merck through October 4, 1993. As of 10/4/93, 4058 patients/subjects have been exposed to losartan as monotherapy or as part of a treatment regimen. This may seem straight forward but it is not. For example, patient 1002 in study 047 died in September of 1993. A MedWatch report for this event was submitted to the NDA by the sponsor on 9/23/93. Although this patient died prior to the cut-off date for the SUR and the information was in the sponsor's database, this patient's event is not included in the CANADA safety update database. The explanation for this is that the sponsor did not have a completed case report form as of 10/4/93. To confuse things further, even though the death is not included in the CANADA database, the death is included in the sponsor's integrated summary of the safety update. This patient is included in the integrated summary because the WAES data (serious adverse events) covers data up until 12/31/93. Thus, I cannot validate all of the information included in the Safety Update Summary report. Table 2 indicates what data is included in the databases

Table 2. Final Dates for Data Included in the CANADA Databases

CANDA Database	Case Report Information at Merck	WAES Data
World Marketing Application	3/31/93	6/30/93
Safety Update	10/4/93	12/31/93

In the WMA, the safety profile was presented for 3628* losartan-treated patients. The Safety Update Report (SUR) contained additional safety data on 1282 losartan-treated patients who were first presented in the WMA and continued in the studies post-WMA as well as information on 430 patients/subjects who were newly exposed to losartan therapy and were not included in the original WMA. Most of these 430 patients were on control agents during the acute phases in WMA studies and then switched to losartan subsequent to the completion of the acute phase. Of the 4058 patients/subjects treated with losartan therapy to date, 3384 were treated in studies for uncomplicated essential hypertension, 148 were treated in studies for hypertension involving renal impairment, 199 were treated in studies for heart failure, and 327 were subjects in clinical pharmacology studies.

dates are wrong

This review document will only review the Monotherapy CANDA. Clinical trials that include HCTZ will be reviewed by Dr. Knudson. The Safety Update data will not be included in this review but will be summarized in a separate review document.

Safety data is included in the CANDA for all trials. Efficacy measurements and laboratory data are included for selected studies. Case report forms were not included in the CANDA at the request of the medical reviewer. Computer generated reproductions of case report forms are included in the paper submission. Copies of actual case report forms are not included in the NDA. Information regarding the number of subjects enrolled at the screening visit is not provided for any study.

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* = designated pivotal by the sponsor

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Study Location (con't)**Open Label - Hypertensives**

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Efficacy Summary

Placebo Controlled Multi-Dose Trials

Trough Diastolic Blood Pressure

The monotherapy NDA included six randomized, double blind, placebo controlled trials ranging in duration of treatment from 5 days to 12 weeks. Losartan monotherapy was also included in study 54 which was reviewed in the losartan/HCTZ NDA. Data from study 54 was not included in this review. Table E.1 lists the study characteristics of the six multi-dose placebo controlled trials. Protocols 005, 021 and 043 did not permit the inclusion of black patients. Protocols 011, 050 and 065 limited the enrollment of black patients as a percentage of those randomized. All of the trials had a primary endpoint involving changes in DBP except for study 043. The primary endpoint in study 043 evaluated the change in plasma renin and angiotensin II levels with losartan treatment. Blood pressure change was a secondary endpoint in study 043.

Table E.1. Placebo Controlled Trials

Protocol #	Design	Primary Measure of Efficacy	Treatment Groups	N
005	- randomized, double-blind, placebo controlled and active control, multi-center - 5 day treatment period - non-black hypertensives	Trough suDBP	- placebo - losartan 50 mg - losartan 100 mg - losartan 150 mg - enalapril 10 mg	23 20 18 20 19
011	- randomized, double blind, placebo controlled, multi-center parallel dose - hypertensives (limit 25% black) - 8 week treatment period	Trough suDBP at week 8	- placebo - losartan 10 mg od. - losartan 25 mg od. - losartan 50 mg od. - losartan 100 mg od. - losartan 150 mg od. - enalapril 20 mg od.	78 80 82 79 90 84 83
050	- randomized, double-blind, placebo controlled, parallel, multi-center, dose titration - 12 week treatment period - hypertensives (limited to ≤ 30% black) - open label extension optional	Trough suDBP at week 12	- placebo - losartan 50/100 mg - losartan 50/P	116 123 127
065	- randomized, double blind, placebo controlled - 12 week treatment period - hypertensive, no more than 30% black, 30% with moderate hypertension - open label extension optional	Trough suDBP at week 12	- placebo - losartan 25 mg daily - losartan 25 mg bid - losartan 50 mg daily	108 108 106 106
021	- randomized, double blind, placebo controlled, parallel - 6 week treatment period - non-black hypertensives - Ambulatory Blood Pressure Monitoring (ABPM) - open label extension	Change in ABPM blood pressure at 4 weeks	- placebo - losartan 50 mg - losartan 100 mg - losartan 50 mg bid	32 29 30 31
043	- randomized, double-blind, placebo controlled and active control - 6 week treatment period - non-black hypertensives	Plasma renin Plasma angiotensin II	- losartan 25 mg od - losartan 100 mg od - placebo - enalapril 20 mg od	11 14 12 14

N = Number of Patients Randomized per Treatment Group

Table E.2 summarizes the placebo subtracted mean change in DBP in the placebo controlled studies. Doses of losartan greater than or equal to 25 mg daily significantly lowered diastolic blood pressure (supine or sitting) compared to placebo. Twice a day dosing was studied in protocols 065 (losartan 25 mg bid) and protocol 021 (losartan 50 mg bid). In both cases, the decrease in diastolic blood pressure was numerically but not significantly greater than the comparable total daily dose provided as a single once a day dose. The maximum dose studied was losartan 150 mg once a day in study 005. Patients were treated for 5 days in this trial. The blood pressure response for 150 mg was similar to 50 mg and 100 mg. Losartan 100 mg was slightly better numerically than losartan 50 mg in studies 005, 050 (titration to 100 mg) and 021. In study 011, there was no difference between losartan 100 mg and 50 mg treatment effect.

Table E.2. Placebo Subtracted Mean Change in Diastolic Blood Pressure (mmHg) in Multi-Dose Placebo Controlled Trials (All Patients Treated Data)

Dose	Study 005* (day 5)	Study 011* (week 8)	Study 050** (week 12)	Study 065** (week 12)	Study 021 (week 4)
enalapril 10 mg od	-5.9				
enalapril 20 mg od		-5.6			
losartan 10 mg od		-2.3			
losartan 25 mg od		-1.2		-3.8	
losartan 25 mg bid				-6.0	
losartan 50 mg od	-6.7	-4.5	-3.6	-4.3	-4.8
losartan 50/100 mg ¹			-4.3		
losartan 50 mg bid					-8.2
losartan 100 mg od	-8.1	-4.3			-6.3
losartan 150 mg od	-7.0				

different from p 61

¹ = once a day dosing; dose titration permuted at four weeks; * change in suDBP; ** change in siDBP; bid = twice a day dosing

Diastolic Blood Pressure Response in Subgroups

Diastolic blood pressure response in several subgroups based on sex, race and age are listed in tables E.3 - E.5. The placebo subtracted change in diastolic blood pressure suggests that losartan lowered diastolic blood pressure regardless of sex or age < 65 and ≥ 65 years. The change in DBP in black patients was unimpressive.

Table E.3. Diastolic Blood Pressure by Sex (All Patients Treated Data)

Dose	Study 011* (week 8)				Study 050** (week 12)				Study 065** (week 12)			
	Male		Female		Male		Female		Male		Female	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
enalapril 20 mg od	55	-5.3	27	-6.5								
losartan 10 mg od	51	-3.6	29	-.3								
losartan 25 mg od	55	-1.0	27	-3.0					65	-5.9	40	-3.6
losartan 25 mg bid									67	-6.6	34	-4.9
losartan 50 mg od	53	-4.4	25	-5.0	81	-3.5	44	-4.0	68	-4.6	33	-3.8
losartan 50/100 mg ¹					77	-6.1	41	-1.0				
losartan 50 mg bid												
losartan 100 mg od	58	-5.4	31	-2.4								
losartan 150 mg od	62	-4.8	22	-2.9								

¹ = once a day dosing; dose titration permuted at four weeks; * change in suDBP; ** change in siDBP; bid = twice a day dosing

Table E.4. Diastolic Blood Pressure by Racial Subgroup (All Patients Treated Data)

Dose	Study 011* (week 8)				Study 050** (week 12)				Study 065** (week 12)			
	Black		non-Black		Black		Non-Black		Black		Non-Black	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
enalapril 20 mg od	7	.8	75	-6.2								
losartan 10 mg od	10	.5	70	-2.8								
losartan 25 mg od	14	2.5	68	-2.0					21	-1.5	84	-4.4
losartan 25 mg bid									10	-.3	91	-6.7
losartan 50 mg od	10	-3.2	66	-4.7	14	.3	111	-4.1	16	-1.0	85	-5.3
losartan 50/100 mg ¹					16	-1.6	102	-4.7				
losartan 50 mg bid												
losartan 100 mg od	17	-2.8	72	-4.7								
losartan 150 mg od	11	-2.3	73	-4.5								

¹ = once a day dosing; dose titration permuted at four weeks; * change in suDBP; ** change in siDBP; bid = twice a day dosing

Table E.5. Diastolic Blood Pressure by Age (All Patients Treated Data)

Dose	Study 011* (week 8)				Study 050** (week 12)				Study 065** (week 12)			
	< 65		> 65		< 65		> 65		< 65		> 65	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
enalapril 20 mg od	71	-6.1	11	-3.5								
losartan 10 mg od	68	-3.3	12	2.6								
losartan 25 mg od	64	-1.3	18	0					89	-3.6	16	-4.0
losartan 25 mg bid									90	-5.5	11	-8.3
losartan 50 mg od	66	-5.4	12	.3	106	-3.1	19	-6.3	85	-4.0	16	-5.0
losartan 50/100 mg ¹					90	-4.2	28	-5.1				
losartan 50 mg bid												
losartan 100 mg od	72	-4.6	17	-2.7								
losartan 150 mg od	71	-5.1	13	.7								

¹ = once a day dosing; dose titration permitted at four weeks; * change in suDBP; ** change in siDBP; bid = twice a day dosing

Only study 011 suggests that black patients had a minimal response (approximately 50% of the decrease of non-black patients). During the process of validating this data, it becomes apparent that the response of black patients in study 011 is influenced by the small number of patients in the placebo group. Table E.6 lists the change in DBP (placebo subtracted) when only the week 8 data is included in the analysis. The placebo subtracted decrease in DBP is less than 1 mm for losartan 50 - 150 mg. Both analysis are greatly influenced by the size of the placebo group and the effect of the single dropout on the mean blood pressure change.

Table E.6. Change in supine DBP in black patients at week 8

Treatment	N	Change in suDBP (S.D.) [mm Hg] (non-carry forward analysis)*	Placebo Subtracted Change in suDBP [mm Hg] (non-carry forward analysis)	N	Change in suDBP (S.D.) [mm Hg] (carry forward analysis)**	Placebo Subtracted Change in suDBP [mm Hg] (carry forward analysis)
placebo	4	-7.5 (4.5)	-	5	-5.2	-
enalapril	7	-4.4 (8.3)	3.1	7	-4.4	.8
losartan 10 mg	9	-4.3 (7.8)	3.2	10	-4.7	.5
losartan 25 mg	12	-3.7 (7.2)	3.8	14	-2.7	2.5
losartan 50 mg	10	-8.4 (6.0)	-0.9	10	-8.4	-3.2
losartan 100 mg	13	-8.0 (6.6)	-0.5	17	-8.0	-2.8
losartan 150 mg	9	-8.3 (9.8)	-0.8	11	-7.5	-2.3

* obtained from the CANADA database by eliminating carry-forward data

** obtained from the sponsor's clinical summary report page 48, table 13

The failure of losartan to convincing lower DBP in black patients is supported by categorical response Diastolic Blood Pressure (6 hours Post-Dosing)

Protocols 005, 011, 050 and 065 measured diastolic blood pressures at approximately 6 hours post dose. Table E.7 lists the mean change in peak diastolic blood pressure (placebo subtracted). Trough to peak ratios can be found in the summaries of the individual studies. Losartan 100 mg did not appear to provide a greater response compared to 50 mg of losartan based on the results of study 011 and 050.

Table E.7. Placebo Subtracted Mean Change in DBP at Peak (6 hours post dose).

Dose	Study 005* (day 5)		Study 011* (week 8)		Study 050** (week 12)		Study 065** (week 12)	
	N	Mean	N	Mean	N	Mean	N	Mean
enalapril 10 mg od	18	-11.0						
enalapril 20 mg od			82	-11.0				
losartan 10 mg od			75	-2.6				
losartan 25 mg od			80	-5.2			95	-4.7
losartan 25 mg bid							94	-4.9
losartan 50 mg od	20	-9.7	77	-7.2	108	-5.6	94	-5.7
losartan 50/100 mg ¹					111	-4.8		
losartan 50 mg bid								
losartan 100 mg od	18	-6.3	87	-5.7				
losartan 150 mg od	19	-12.0	81	-8.4				

¹ = once a day dosing; dose titration permitted at four weeks; * change in suDBP; ** change in siDBP; bid = twice a day dosing (All-Patients-Treated Approach)

Diastolic Blood pressure (Multiple Measurements During the 24 Hours Post Dosing)

Protocol 021 measured ambulatory blood pressure for 24 hours. Protocol 005 measured DBP at 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 23, 23.5 and 24 hours post-dosing by Dinamap. Protocol 043 measured supine diastolic blood pressure during the final visit (week 6) at 30 min, 1 hour, 1.5, 2, 3, 4, 6, 8, 12, 24, 28, 32, 36, 48 and 72 hours after dosing. Refer to the individual study summaries for the results from these measurements.

Rebound Hypertension

Studies 011 and 050 evaluated patients for rebound hypertension by measuring DBP after the final double-blind treatment visit while the patients were off of treatment. Study 065 had post-DB visits for only three patients (does not pertain to open label period) and as such does not contribute much information. Table E.8a and E.8b lists the number of patients who had measurements during the post-DB period. In study 011, only 51% of the patients had post-DB treatment visits. Consequently, it would be difficult to conclude anything from this data since half the data was not obtained. In study 050, 87% of patients had post-double-blind treatment visits. The percent of patients with post double-blind siDBP measurements greater than baseline is greatest in the placebo group. When the post-double-blind measurements for each treatment group are compared to baseline or to the last double-blind measurement or the number of patients with post-DB measurement > 110 mmHg are considered, there does not appear to be a significant difference between losartan and placebo. It is not unreasonable to conclude that rebound hypertension is not a problem.

Table E.8a. Patients with Post-DB Visits and BP Measurements in Study 011

Treatment	N ^a	N with post-DB Visit	N with suDBP Change ^c > 0 mmHg	Range of Changes ^c in suDBP during Post-DB Period (mmHg)
Placebo	78	42	6	-21 to 9
Losartan 10 mg	80	41	7	-24 to 6
Losartan 25 mg	82	45	6	-20 to 5
Losartan 50 mg	79	36	0	-29 to 0
Losartan 100 mg	90	43	5	-40 to 12
Losartan 150 mg	84	44	4	-27 to 6
Enalapril 20 mg	83	41	1	-30 to 1
Total	576	297 (51%) ^b	29 (10%) ^d	

a = number of patients randomized; b = percent of patients randomized;

c = Change equals Post-DB suDBP minus baseline suDBP; d = as a percent of patients with post-DB visit.

Table E.8b. Patients with Post-DB Visits and BP Measurements in Study 050

Treatment	N ^a	N with post-DB Visit	N with suDBP Change ^c > 0 mmHg	Range of Changes ^c in siDBP during Post-DB Period (mmHg)	Mean Change ^c from Baseline (mmHg)	Mean Change ^c from Last DB siDBP (mmHg)	N with siDBP Change ^c > 10 mmHg	N with Post-DB siDBP > 110 mmHg
Placebo	116	97	32 (33%) ^d	-20 to 20	-3.4	1.7	5	7
Losartan 50/P	127	115	26 (23%) ^d	-29 to 12	-5.5	2.7	1	4
Losartan 50/100	123	106	23 (22%) ^d	-28 to 18	-5.6	3.0	3	2
Total	366	318 (87%) ^b	81 (22%) ^d					

a = number of patients randomized; b = percent of patients randomized;

c = Change equals Post-DB siDBP minus baseline siDBP (> 0 mmHg indicates that post-DB measurement is greater than baseline);

d = as a percent of patients with post-DB visit; e = Change equals First Post-DB siDBP minus Last DB siDBP

Active Control Studies

Eight studies in hypertensive patients included an active control. Three of the studies (011, 005, 043) included a placebo group and were discussed previously. One study (056) evaluated hypertensive patients with a previous history of ACE inhibitor induced cough for the incidence of cough while receiving losartan. In this study, patients with lisinopril induced cough were randomized to losartan, HCTZ or lisinopril. Losartan had significantly fewer patients complain of cough compared to lisinopril. Four studies (044, 045, 055, 064) compared the anti-hypertensive response of losartan to captopril, atenolol, felodipine and enalapril. All four studies were 12 weeks of double blind therapy. Studies 044, 045 and 055 were performed outside of the United States, did not have efficacy data available from all investigative sites and allowed for doubling of the randomized dose if DBP $\geq$ 90 mmHg after 6 weeks of therapy. Study 064 was performed in the United States in patients with severe hypertension (siDBP 115 - 130 mmHg) and permitted dose titration of randomized medications plus the addition of either HCTZ, atenolol and/or a dihydropyridine calcium channel blocker if blood pressure was not controlled. For the most part, these studies were powered to detect a difference in blood pressure response from baseline after 6 or 12 weeks of treatment and not a difference between treatments. They contribute safety data.

Clinical Pharmacology Summary

Three trials (001, 002, 006) examined the ability of losartan to suppress the pressor response to intermittent infusions of angiotensin I (001) or angiotensin II (002, 006). Losartan (2.5 mg - 120 mg) was administered to healthy male subjects in open label trials. Losartan doses of 10 mg or greater blunted the pressor response. This effect appeared to persist despite non-detectable levels of losartan in plasma. This suggests that the active metabolite of losartan, E-3174, which has a longer terminal elimination half-life than losartan could have a clinically relevant effect on prolonging an anti-hypertensive response. In study 001, pre-angiotensin infusion SBP was increased after losartan dosing which raised a concern that losartan may have agonist properties. In study 006, pre-angiotensin infusion SBP did not increase after losartan therapy.

ACE activity was measured in study 005 at trough and at 5 hours after dosing. Mean ACE inhibitor activity decreased with enalapril therapy. Placebo, losartan 50 mg, 100 mg, and 150 mg had minimal effect on ACE activity. Renin activity and angiotensin II levels increase with losartan (study 004, 007). Aldosterone levels either decreased or remained unchanged within 24 hours after single doses of losartan (study 004, 007, 019).

The metabolism of losartan to the primary metabolite, E-3174 (I-158,641; see page 1 for structure) involves oxidation of an alcohol side chain to form the carboxylic acid derivative, a reaction demonstrated *in vitro* to be carried out by several cytochrome P450 mixed-function oxidases, CYP IIIA4 and CYP IIC. Losartan has an absolute bioavailability of 23% (study 022) and an elimination half-life of approximately 2 hours (studies 003, 004, 007, 013). E-3174 has an elimination half-life of approximately 9 hours (study 007; arithmetic mean). The harmonic mean half-life of E-3174 ranges from 3.9 hours to 6.9 hours (studies 003, 004, 013, 017). Several subjects in the NDA produced minimal or no E-3174 after losartan therapy. Please refer to Dr. Fadiran's biopharm review for details on these patients. In patients who do not metabolize losartan to E-3174, the duration of anti-hypertensive effect is likely to be shortened. Female patients ≥ 65 years of age had an increased losartan AUC, absolute bioavailability and C_{max} compared to male patients ≥ 65 years of age.

Urine sodium and potassium excretion did not change after losartan with or without a depleted sodium diet (study 004, 007, 023, 034). Urine uric acid increased slightly during the first 6 hours after single doses (study 023).

Food decreased the losartan AUC by 19% and the C_{max} by 52% compared to the fasted period (study 015). E-3174 AUC decreased by 13%. Cimetidine (study 24) caused the C_{max} and AUC for losartan to increase by 23% and 36% respectively. However, cimetidine did not affect the AUC for E-3174. There was minimal interaction between a single intravenous or oral dose of digoxin on top of losartan therapy. Losartan increased oral digoxin C_{max} (13%) and AUC (5%) with losartan therapy (study 063). Phenobarbital administration caused the AUC of losartan and E-3174 to decrease by approximately 20% (study 72). An interaction study was performed between warfarin and losartan which suggested that there is not a pharmacokinetic interaction between warfarin and losartan (study 070). However, the study design is inadequate to conclude that there is not a pharmacodynamic interaction. This is discussed further in the summary of study 070 and the safety summary that follows.

Safety Summary

Before summarizing the safety of losartan, it is worthwhile to comment on the quality of the safety data. Due to the size of the database under review, each individual case report form cannot be reviewed by the medical reviewer. The accuracy of the safety database depends on the inclusion of all adverse events, the accurate coding of the adverse event and an accurate summary of adverse events by the sponsor. Information in the clinical summary report for the trials should be consistent with the CANDAs database. For this the medical reviewer is dependent on the sponsor to accurately document and summarize adverse events. The medical reviewer depends on the sponsor to be forthright in the presentation of data. There are occasions that the presentation of the adverse events data is less than satisfactory. For example, patient #783 is listed as withdrawing on relative day 286 secondary to diarrhea. A summary of the adverse event (patient summaries are provided only for serious adverse events in this report) for patient #783 explains that the patient also had hemorrhoidal bleeding and was found to have a large fungating mass in the rectum (? bleeding due to mass). When the CANDAs database is queried for this patient, the only adverse events listed are diarrhea and headache. Hemorrhoidal bleeding and rectal cancer are not listed in the database for this patient.

It is important to note that not all of the laboratory data for each patient is included in the CANDAs. The storage capacity of the system was insufficient to include all of the data. Thus, if there are deficiencies in the review, it is most likely to occur in the evaluation of laboratory data.

Patient Exposure

Tables SS.1 and SS.1b lists the number of patients exposed to losartan monotherapy. Two thousand five-hundred and thirty-three patients received losartan monotherapy. This includes patients from protocols 048, 054, and 073 which are not included in this review (These studies have been reviewed by Dr. Knudson. Patients who received losartan monotherapy at some time during the long term open label periods of protocols 011, 021, 049, 050 and 054 are also included. Patients from 057 are included even though the study was not complete at the time the database was closed. The majority of patients received losartan 50 mg per day

Table SS.1 Losartan Monotherapy Duration of Therapy by Total Daily Dose

Days of Therapy	Number of Patients						
	0-9 mg	10 mg	25 mg	50 mg	100 mg	150 mg	>150 mg
1 - 7	1	0	40	152	99	26	6
8 - 30	0	2	16	674	319	109	1
31 - 91	0	78	186	997	421	95	0
92 - 183	0	0	6	202	21	22	0
184 - 274	0	0	0	42	16	7	0
275 - 365	0	0	0	50	18	2	0
366 - 457	0	0	0	20	1	3	0
458 - 548	0	0	0	17	5	0	0
549 - 639	0	0	0	1	0	0	0
>639	0	0	0	1	1	0	0

Table SS.1a.

Total Number of Patients	2533
Total Patient Days on Drug	218957
Range of Duration on Drug	1 to 677
Mean Duration on Drug	86.4

Deaths

Table SS.1b lists twelve patients who died while enrolled in clinical trials for losartan. Six of the patients were enrolled in heart failure trials and five patients in hypertension trials. Nine of the patients received losartan and two patients received placebo.

Table SS.1b. Deaths in Losartan Trials

Study	Patient #	Treatment	Day of Death	Days in Study	Days on Treatment	Cause of Death
16*	154	Losartan 5 mg	7	7	1	MI / Cardiogenic Shock
16*	512	Losartan 150 mg	12	12	1	Not Reported
47*	1128	Losartan 2.5 mg	85	85	84	Ventricular fibrillation
47*	1133	Losartan 2.5 mg	21	21	21	Ventricular fibrillation
47*	1139	Losartan 10 mg	18	18	10	Ventricular fibrillation
47*	1195	Losartan 10 mg	115	115	85	MI / Cardiac Arrest/ Anoxic Encephalopathy
65	1330	placebo	85	85	85	Accident
65	1373	placebo	39	39	4	MI / CVA
65	1596	Losartan 25 mg BID	68	68	41	Malignant hypertension / CVA
L11	174	Losartan 50 mg	90	27	26	CVA
L50	2414	Losartan 50 mg/ HCTZ 6.25 mg	244	153	153	Cerebral Aneurysm
55	8856	Los 50/H12.5/Fel5	193	193	193	Trauma Death

* Heart Failure Trial. [Study 16 is a single dose trial.]

Patient #154 in study 016 was a 66 year-old Caucasian male with an ejection fraction of 29%, NYHA Class II heart failure and a history of myocardial infarction. He was randomized and received a single oral dose of losartan 5 mg on 4/7/91. On April 11, 1991, he had a myocardial infarction and suffered cardiogenic shock with bradycardia. He was admitted to the hospital and treated with atropine, dopamine, and streptokinase and his heart rate was maintained with a pacemaker. The patient was stable for 48 hours then subsequently had episodes of ventricular tachycardia which were followed by ventricular fibrillation. On April 13, 1991 the patient died. Autopsy demonstrated left ventricular myocardial infarction and extensive sclerosis of the coronary arteries. A thrombus was found in the circumflex artery. The investigator felt the myocardial infarction and ventricular fibrillation were not related to study drug.

Patient #512 in study 016 was a 62 year-old Caucasian male with an ejection fraction of 16% and NYHA Class III heart failure. The etiology of heart failure in this patient was ischemic cardiomyopathy. The patient had a myocardial infarction in 1977. The patient was randomized and received a single oral dose of losartan 150 mg on 6/19/91. On 6/26/91, prestudy therapy of furosemide, quinidine, isosorbide dinitrate, diltiazem, aspirin, and enalapril was reinstated. On 6/30/91, the patient was found dead in bed.

Patient #1128 in study 47 was a 68-year-old Caucasian male with an ejection fraction of 29%, NYHA functional class IIa heart failure, angina, peripheral vascular disease and a history of 2 myocardial infarctions and coronary artery bypass graft was randomized to receive single daily doses of losartan 2.5 mg. The etiology of heart failure in this patient was ischemic heart disease. His last dose of study drug was on Day 84. He was concomitantly treated with dipyridamole. On Day 85, he

experienced a cardiac arrest and was hospitalized. On admission, the patient was found to be in ventricular fibrillation and died that day.

Patient #1133 in study 47 was a 71-year-old Caucasian male with an ejection fraction of 14%, NYHA Class IIb heart failure, atrial fibrillation, diabetes, and a history of 3 myocardial infarctions was randomized to receive single daily doses of losartan 2.5 mg. The etiology of heart failure in this patient was ischemic heart disease. Concomitant medications included digoxin, furosemide, spironolactone, glyburide, and warfarin. On Day 21, the patient died suddenly - attempts at resuscitation failed. The investigator identified the cause of death as ventricular fibrillation.

Patient #1139 in study 47 was a 65-year-old Caucasian male with an ejection fraction of 23%, NYHA Class IIb heart failure, atrial fibrillation and a history of myocardial infarction and coronary artery bypass graft surgery was randomized to receive single daily doses of losartan 10 mg. The etiology of heart failure in this patient was ischemic heart disease. Concomitant medications included digoxin, furosemide, spironolactone, dipyridamole, and aspirin. On Day 10, the patient suffered ventricular fibrillation and cardiac arrest. He was resuscitated and was hospitalized, but remained unconscious. On Day 15, the patient developed pneumonia. On Day 17 life-sustaining measures were withdrawn. On Day 18, the patient died. Autopsy confirmed pneumonia as the cause of death.

Patient #1195 in study 47 was a 67-year-old Caucasian male with an ejection fraction of 22%, NYHA Class IIb heart failure, angina, and a history of myocardial infarction, and ventricular tachycardia was randomized to receive single daily doses of losartan 10 mg. The etiology of heart failure in this patient was ischemic heart disease. The patient completed the study and losartan was discontinued on Day 85. Twelve days following completion of the study, the patient suffered cardiac arrest and was resuscitated. He was hospitalized and was found to have suffered a myocardial infarction. These episodes caused serious cerebral degeneration which led to the patient's death thirty days after completion of the study.

Patient # 1596 (losartan 25 bid) in study 65 was a 78-year-old hypertensive male patient had a blood pressure reading of 211/143 and numbness and tingling of the right leg on Day 41 of treatment with losartan 25 mg b.i.d. He was hospitalized and diagnosed with a cerebral vascular accident secondary to malignant (177/111, 157/110, 170/113, 176/118, 174/105 mmHg readings) hypertension. Therapy was discontinued. Seven days later he had a cardiac arrest and was resuscitated. Eighteen days later he developed an arrhythmia, respiratory failure, and seizures. On Study Day 68 he had a second cardiac arrest and died.

Patient #0174 in study 011 was a 70 year old hypertensive male was hospitalized on 4/30/91 for what appeared to be a stroke. A CT scan of the brain showed a hemorrhagic infarct of the mid-brain. The patient did not recover consciousness and was kept alive via life-support (respirator) until 5/1/91. An EEG done on 5/1/91 showed extremely depressed brain function. It was the opinion of the consulting neurologist that the patient was beyond recovery and advised the family accordingly. The family chose to discontinue life-support at that time. No spontaneous respiratory activity was noted, and the patient died at 7:45 PM on 5/1/91. The patient had been treated for moderately severe hypertension since 1975. He had no other known complications from hypertension; his only abnormal findings were an S4 on physical examination and a LAHB and RBBB on EKG. At the time of the adverse event, the patient was taking losartan 100 mg q.d. and was last seen in the clinic on 22APR91 (Supine BP = 167/100 mmHg, standing BP = 162/110 mmHg). The patient was taking no other concomitant medication.

Patient #2414 in study 050 was a 46-year-old hypertensive male with ankylosing spondylitis, hypercholesterolemia, and back pain, and a history of cigarette smoking, who collapsed at home on 12/7/92. Despite medical intervention, he was pronounced dead. The cause of death was found to be a ruptured cerebral aneurysm. At the time of the event the patient was receiving losartan/HCTZ 50/6.25 mg, and ibuprofen.

Patient #8856 was a 54-year-old hypertensive male who fell asleep "at the wheel" while driving his car at night and subsequently had a motor vehicle accident. The patient died as a result of the impact. At the time of the accident the patient was receiving losartan 50 mg, HCTZ 12.5 mg and felodipine 5 mg.

Adverse Events in Studies 011, 050 and 065.

Adverse events incidence rates are reported for each protocol in the review of each trial. Studies 011, 050 and 065 were the primary randomized, double-blind, parallel, placebo-controlled trials of at least 6 weeks duration. The combined randomization in these trials was 1370, of whom, 1287 were randomized to either placebo or losartan alone. Eighty-seven were randomized to enalapril in study 011. Table SS.2 lists the number of patients by study and treatment with at least one adverse event. Of the patients randomized to placebo and losartan, six-hundred and ninety-three patients experienced at least 1 adverse event during the double blind treatment period. There was no difference between the losartan and placebo incidence rate of patients experiencing at least one adverse event. The incidence of patients with at least one adverse event does not appear to increase with losartan dose.

SS.2. Patients with at Least One Adverse Event during Acute Phase

(% equals percent of total on treatment regimen in study)

	Study 011 (%)	Study 050 (%)	Study 065 (%)	Total Patients (%)
losartan 10 mg	41	0	0	41 (51%)
losartan 25 mg	43	0	60	103 (54%)
losartan 50 mg	36	74	61	171 (54%)
losartan 100 mg	36	0	0	36 (40%)
losartan 150 mg	47	0	0	47 (56%)
losartan 25mg BID	0	0	60	60 (57%)
losartan 50mg/100mg	0	69	0	69 (56%)
losartan TOTAL	203 (49%)	143 (57%)	181 (57%)	527 (54%)
Placebo TOTAL	41 (53%)	59 (51%)	66 (61%)	166 (55%)

Table SS.2a lists the number of patients who experienced adverse events while receiving losartan alone (various doses) or placebo in studies 011, 050 and 065. It includes adverse events that have an incidence > 1% in at least one treatment group, have potential serious clinical implications, are characteristic with ACE Inhibitors or may have clinical relevance based on the mechanism of action of losartan. There are several hundred different adverse event descriptors in the data base. Table SS.2a includes only a fraction of them. The pitfalls associated with multiple comparison testing make it difficult to interpret any statistical analysis comparing treatments. This is compounded by the low incidence rate of individual adverse events. With that being said, the following adverse events warrant additional comment.

The incidence of cough was 3.6 % in losartan treated patients and 3.0 % in placebo patients. Cough may be reported as other adverse events involving the respiratory system. Combining the adverse events cough, bronchitis, respiratory infection, upper respiratory infection and lower respiratory infection may include all patients with cough as a symptom. When this is done, 11.9 % of losartan patients and 10 % of placebo patients had one or more of these adverse events. These results, in conjunction with the results of protocol 056, would be sufficient evidence for excluding from labeling references to cough that are found in ACE inhibitor labeling.

Patient #488 (losartan) from study 011 experienced eyelid and facial edema. This presumably is angioedema.

Patient #1251(losartan) in study 065 experienced anosmia.

Decreased libido was only experienced in patients receiving losartan (6 vs. 0).

Hemoglobinuria was reported in three patients on losartan in study 065 (#1127, #1479, #1582). With this adverse event, the primary concern is to rule out a hemolytic anemia secondary to drug. The sponsor submitted additional information on these patients (document 20-386/BM submitted 12/8/94). All of the patients were reported to have urine rbc's based on a dipstick test. It is not clear that this test can differentiate between red blood cells and hemoglobin in the urine. Patient #1127 had a urinary tract infection and cystoscopy performed. Patients #1479 and #1582 did not have decreases in hemoglobin. It does not appear that these cases are associated with a hemolytic anemia.

Despite evidence that mean uric acid levels of patients receiving losartan decreased in some clinical trials, the incidence of gout and hyperuricemia did not appear to decrease. Thus, there may not be a clinical benefit.

Vertigo occurred in 6 losartan patients and none of the placebo patients.

Table SS.2a. Adverse Event Incidence of Combined Studies 011, 050 and 065. [Includes adverse events that have a incidence > 1% in at least one treatment group, have potential serious clinical implications, are characteristic in ACE Inhibitors or may have clinical relevance based on the mechanism of action of losartan.]

	Losartan	Placebo	Total
Number Randomized	985	302	1287
Adverse Experience			
HEADACHE	14.2%	15.9%	14.6%
URI	7.8%	6.3%	7.5%
ASTHENIA/FATIGUE	3.4%	5.0%	3.7%
COUGH	3.6%	3.0%	3.4%
DIZZINESS	3.2%	2.0%	3.0%
ALT INCREASED	2.8%	1.7%	2.6%
DIARRHEA	2.3%	2.0%	2.3%
NAUSEA	1.7%	3.6%	2.2%
PHARYNGITIS	1.8%	3.0%	2.1%
EDEMA/SWELLING	1.8%	2.0%	1.9%
PAIN, ABDOMINAL	1.5%	2.3%	1.7%
PAIN, BACK	1.8%	1.3%	1.7%
PAIN, CHEST	1.3%	1.7%	1.4%
AST INCREASED	1.5%	0.7%	1.3%
DYSPEPSIA	1.1%	1.0%	1.1%
MYALGIA	0.9%	1.0%	0.9%
PROTEINURIA	0.8%	1.3%	0.9%
CRAMP, MUSCLE	1.0%	0.3%	0.9%
CONGESTION, RESPIRATORY	0.6%	0.7%	0.6%
HEMATURIA	0.7%	0.3%	0.6%
IMPOTENCE	0.7%	0.3%	0.6%
ORTHOSTATIC EFFECTS	0.8%	0.0%	0.6%
EPISTAXIS	0.7%	0.0%	0.5%
GOUT	0.5%	0.3%	0.5%
HYPERURICEMIA	0.5%	0.3%	0.5%
LIBIDO DECREASED	0.6%	0.0%	0.5%
VERTIGO	0.6%	0.0%	0.5%
TINNITUS	0.5%	0.0%	0.4%
URTICARIA	0.2%	0.7%	0.3%
ALOPECIA	0.3%	0.0%	0.2%
ANGINA PECTORIS	0.3%	0.0%	0.2%
ASTHMA	0.3%	0.0%	0.2%
HEMOGLOBINURIA	0.3%	0.0%	0.2%
PAIN, FLANK	0.3%	0.0%	0.2%
TOTAL SERUM BILIRUBIN INCREASE	0.3%	0.0%	0.2%
CONGESTION, PULMONARY	0.2%	0.0%	0.2%
PERVERSION, TASTE	0.1%	0.3%	0.2%
SYNCOPE	0.2%	0.0%	0.2%
ALTERATION, RETINAL PIGMENT	0.1%	0.0%	0.1%
ANOSMIA	0.1%	0.0%	0.1%
ARRHYTHMIA	0.1%	0.0%	0.1%
EDEMA, EYELID	0.1%	0.0%	0.1%
EDEMA, FACIAL	0.1%	0.0%	0.1%
HEARING LOSS	0.1%	0.0%	0.1%
HYPERKALFEMIA	0.1%	0.0%	0.1%

A complete list of adverse event incidence rates for studies 011, 050 and 065 combined is included in the appendix.

The incidence of adverse events within subgroups are reported for each protocol in the review of each clinical trial. Generally, individual studies are under powered to conclude a significant difference between subgroups. In an effort to exam this issue, the adverse event data from the randomized, double-blind, controlled clinical trials in hypertensive patients with a double-blind treatment duration of at least 4 weeks were combined. Trials that enrolled patients with renal insufficiency or congestive heart failure were not included. The following trials were included in this analysis: 011, 021, 043, 044, 045, 050, 055, 064 and 065. The database included only patients receiving losartan alone. Table SS.4 lists the demographics of the patients treated with losartan alone in the nine trials. The nine studies randomized 1,492 patients to losartan alone. Approximately two-thirds were female, one-tenth were black and four-fifths were less than 65 years of age.

Table SS.4. Demographic Characteristics of the Losartan Treated Patients in the Nine Trials. [% = % of total randomized]

Study	Losartan Dose									Total
	10 mg	25 mg	50 mg	100 mg	150 mg	Variable	25 mg BID	50/100 mg	50 mg BID	
011 Outpatient Dose Response	80	82	79	90	84	-	-	-	-	415
021 ABPM (QD vs. BID)	-	-	29	30	-	-	-	-	31	90
043 RAAS Effects	-	11	-	14	-	-	-	-	-	25
044 Captopril Comparison	-	-	-	-	-	109	-	-	-	109
045 Atenolol Comparison	-	-	-	-	-	134	-	-	-	134
050 Mild to Moderate HTN	-	-	127	-	-	-	-	123	-	250
055 Felodipine in Elderly	-	-	-	-	-	89	-	-	-	89
064 Double Blind Severe HTN	-	-	-	-	-	50	-	-	-	50
065 BID vs. QD	-	108	106	-	-	-	106	-	-	320
TOTAL	80 (5%)	201 (14%)	341 (23%)	134 (9%)	84 (6%)	382 (26%)	106 (7%)	123 (8%)	31 (2%)	1482
Study	Race				Sex		Age (years)		Total	
	Caucasian	Black	Hispanic	Other	Female	Male	< 65	> 65		
011 Outpatient Dose Response	310	63	40	2	135	280	343	72	415	
021 ABPM (QD vs. BID)	89	0	0	1	32	58	74	16	90	
043 RAAS Effects	24	0	0	1	8	17	19	6	25	
044 Captopril Comparison	97	3	0	9	45	64	94	15	109	
045 Atenolol Comparison	112	3	16	3	59	75	118	16	134	
050 Mild to Moderate HTN	205	30	12	3	88	162	202	48	250	
055 Felodipine in Elderly	52	0	10	27	46	41	0	89	89	
064 Double Blind Severe HTN	25	22	2	1	19	31	45	5	50	
065 BID vs. QD	250	49	13	8	113	207	277	43	320	
TOTAL	1164 (79%)	170 (11%)	93 (6%)	55 (4%)	547 (37%)	935 (63%)	1172 (79%)	310 (21%)	1482	

Fifty-eight percent of the female and fifty percent of the male subjects experienced at least one adverse event. There was no difference in the overall incidence of patients experiencing adverse events based on age. Blacks had a slightly higher incidence of patients with adverse experiences compared to non-blacks, 58% versus 52%. Tables SS.5a. and SS.5b. lists the incidence of individual adverse events for subgroups based on age, sex, race and treatment group. In general, there appear to be little difference in the incidence of adverse events between subgroups. Gout, hemoglobinuria, insomnia decreased libido and flank pain occurred only in non-black patients. Headache, upper respiratory infection, dizziness and asthenia/fatigue were the most common adverse events reported with losartan occurring in 13.6%, 7.4%, 4.2% and 4.0% respectively. Cough occurred in 3.4% of patients.

SS.5a. Adverse Event Incidence from Nine Studies by Sex, Race and Age. [Includes adverse events that have a incidence > 1% in at least one treatment group, have potential serious clinical implications, are characteristic in ACE Inhibitors or may have clinical relevance based on the mechanism of action of losartan]

	Sex		Race		Age		TOTAL
	F	M	Blacks	Non-Black	< 65	>64	
Patients Randomized	547	935	170	1312	1172	310	1482
Patients with at Least 1 AE	318	468	99	687	621	165	786
Percent with at least 1 AE	58%	50%	58%	52%	53%	53%	53%
Adverse Experience							
HEADACHE	15.50%	12.50%	17.60%	13.10%	14.70%	9.70%	13.60%
URI	7.90%	7.20%	6.50%	7.50%	7.80%	6.10%	7.40%
DIZZINESS	4.90%	3.70%	5.30%	4.00%	4.60%	2.60%	4.20%
ASTHENIA/FATIGUE	4.60%	3.70%	3.50%	4.10%	4.20%	3.50%	4.00%
COUGH	3.70%	3.30%	3.50%	3.40%	2.90%	5.50%	3.40%
ALT INCREASED	1.30%	2.90%	1.80%	2.40%	2.60%	1.30%	2.30%
DIARRHEA	2.40%	1.90%	0.60%	2.30%	2.00%	2.60%	2.10%
NAUSEA	3.30%	1.30%	1.80%	2.10%	1.60%	3.50%	2.00%
EDEMA/SWELLING	2.60%	1.50%	4.10%	1.60%	1.60%	2.90%	1.90%
PAIN, BACK	2.40%	1.60%	1.80%	1.90%	1.60%	2.90%	1.90%
CONGESTION, NASAL	1.60%	1.80%	2.40%	1.70%	1.80%	1.60%	1.80%
PHARYNGITIS	2.60%	1.40%	1.80%	1.80%	1.70%	2.30%	1.80%
PAIN, ABDOMINAL	2.90%	1.00%	2.40%	1.60%	1.70%	1.60%	1.70%
AST INCREASED	0.70%	1.60%	1.20%	1.30%	1.50%	0.60%	1.30%
DYSPEPSIA	1.60%	1.10%	1.80%	1.20%	1.10%	1.90%	1.30%
PAIN, CHEST	1.50%	1.20%	2.40%	1.10%	1.40%	1.00%	1.30%
SINUS DISORDER	1.50%	1.10%	1.80%	1.10%	1.30%	1.00%	1.20%
INSOMNIA	1.50%	1.00%	0.00%	1.30%	1.00%	1.60%	1.10%
PAIN, LEG	1.30%	0.70%	0.60%	1.00%	1.00%	0.60%	0.90%
HEMATURIA	0.70%	0.50%	1.20%	0.50%	0.50%	1.00%	0.60%
GOUT	0.20%	0.60%	0.00%	0.50%	0.60%	0.00%	0.50%
LIBIDO DECREASED	0.20%	0.50%	0.00%	0.50%	0.50%	0.00%	0.40%
CREATININE INCREASED	0.40%	0.40%	0.60%	0.40%	0.30%	0.60%	0.40%
HYPOKALEMIA	0.50%	0.20%	0.00%	0.40%	0.30%	0.60%	0.30%
PAIN, FLANK	0.00%	0.40%	0.00%	0.30%	0.30%	0.00%	0.30%
HEMOGLOBINURIA	0.40%	0.10%	0.00%	0.20%	0.20%	0.30%	0.20%
EDEMA, EYELID	0.20%	0.00%	0.00%	0.10%	0.00%	0.30%	0.10%
EDEMA, FACIAL	0.40%	0.00%	0.00%	0.20%	0.10%	0.30%	0.10%
HYPERKALEMIA	0.20%	0.10%	0.00%	0.20%	0.20%	0.00%	0.10%

SS.5b. Adverse Event Incidence from Nine Studies by Dose. [Includes adverse events that have a incidence > 1% overall, have potential serious clinical implications, are characteristic in ACE Inhibitors or may have clinical relevance based on the mechanism of action of losartan.]

	10 mg	25 mg	50 mg	100 mg	150 mg	variable	25 mg bid	50/100 mg	50 mg bid	Total
Patients Randomized	80	201	341	134	84	382	106	123	31	1482
Patients with at Least 1 AE	41	112	184	58	47	201	60	69	14	786
Percent with at least 1 AE	51 %	56 %	61 %	43 %	56 %	53 %	57 %	56 %	45 %	
Adverse Experience										
HEADACHE	13.80%	17.40%	12.30%	12.70%	13.10%	12.00%	17.00%	15.40%	9.70%	13.50%
URI	1.30%	9.50%	7.00%	6.90%	8.30%	7.10%	10.40%	8.10%	9.70%	7.40%
DIZZINESS	2.50%	4.50%	4.10%	0.70%	2.40%	6.50%	3.80%	3.30%	3.20%	4.20%
ASTHENIA/FATIGUE	3.80%	2.50%	3.50%	3.00%	4.80%	6.00%	5.70%	1.60%	3.20%	4.00%
COUGH	6.30%	4.00%	2.60%	3.00%	3.60%	3.10%	2.80%	4.90%	3.20%	3.40%
ALT INCREASED	3.80%	3.00%	1.50%	3.70%	3.60%	1.00%	0.00%	4.90%	6.50%	2.30%
DIARRHEA	3.80%	2.00%	2.90%	1.50%	2.40%	1.30%	1.90%	1.60%	3.20%	2.10%
NAUSEA	1.30%	2.00%	2.60%	0.70%	0.00%	2.90%	0.00%	2.40%	3.20%	2.00%
EDEMA/SWELLING	1.30%	1.50%	2.90%	0.70%	0.00%	2.60%	0.00%	2.40%	0.00%	1.90%
PAIN, BACK	3.80%	2.00%	2.10%	1.50%	2.40%	2.10%	0.90%	0.80%	0.00%	1.90%
CONGESTION, NASAL	0.00%	1.50%	2.60%	2.20%	3.60%	0.30%	2.80%	1.60%	6.50%	1.80%
PHARYNGITIS	1.30%	2.00%	4.10%	0.70%	0.00%	1.60%	0.00%	0.00%	3.20%	1.80%
PAIN, ABDOMINAL	3.80%	1.00%	2.10%	1.50%	1.20%	2.40%	0.00%	0.80%	0.00%	1.70%
AST INCREASED	2.50%	2.00%	1.20%	0.70%	1.20%	0.50%	0.00%	2.40%	6.50%	1.30%
DYSPEPSIA	1.30%	1.00%	0.90%	0.70%	3.60%	1.60%	1.90%	3.80%	0.00%	1.30%
PAIN, CHEST	1.30%	2.00%	1.20%	0.70%	1.20%	1.60%	1.90%	0.00%	0.00%	1.30%
SINUS DISORDER	2.50%	1.00%	1.50%	1.50%	2.40%	0.30%	0.90%	2.40%	0.00%	1.20%
INSOMNIA	1.30%	1.50%	1.80%	0.70%	0.00%	1.30%	0.90%	0.00%	0.00%	1.10%
PAIN, LEG	2.50%	1.00%	1.50%	0.70%	0.00%	0.50%	0.00%	1.60%	0.00%	0.90%
HEMATURIA	0.00%	0.00%	0.90%	1.50%	1.20%	0.30%	0.00%	0.80%	3.20%	0.60%
GOUT	0.00%	0.00%	0.60%	0.70%	1.20%	0.30%	0.90%	0.80%	0.00%	0.50%
LIBIDO DECREASED	1.30%	0.50%	0.60%	0.00%	0.00%	0.00%	1.90%	0.00%	0.00%	0.40%
CREATININE INCREASED	0.00%	0.00%	0.30%	0.00%	0.00%	1.30%	0.00%	0.00%	0.00%	0.40%
HYPOKALEMIA	1.30%	0.00%	0.30%	0.00%	0.00%	0.80%	0.00%	0.00%	0.00%	0.30%
PAIN, FLANK	0.00%	0.00%	0.30%	1.50%	1.20%	0.00%	0.90%	0.00%	0.00%	0.30%
HEMOGLOBINURIA	0.00%	1.00%	0.00%	0.00%	0.00%	0.00%	0.90%	0.00%	0.00%	0.20%
EDEMA, EYELID	0.00%	0.00%	0.00%	0.00%	1.20%	0.00%	0.00%	0.00%	0.00%	0.10%
EDEMA, FACIAL	0.00%	0.00%	0.00%	0.00%	1.20%	0.30%	0.00%	0.00%	0.00%	0.10%
HYPERKALEMIA	0.00%	0.00%	0.00%	0.00%	1.20%	0.30%	0.00%	0.00%	0.00%	0.10%

A complete listing of all adverse events in these nine trial can be found in the appendix.

Table SS.6 lists the number of subjects receiving losartan therapy who were withdrawn prematurely from the clinical trials and the reason for withdrawal. This does not include patients in long term follow-up studies. One hundred and ninety patients on losartan monotherapy withdrew prematurely from the clinical trials. Seventy-four withdrew for clinical or laboratory adverse events. Fifty-three patients withdrew as lost to follow-up or "patient withdrew".

Table SS.6. Reasons for Premature Discontinuations from Clinical Trials in Patients Treated with Losartan (Does not include Studies 048, 049, 054, 073 and long term follow-up studies. See Dr. Knudson's Review.) [Reviewer's Note: Studies 002, 004, 007, 012, 022, 023, 024, 033, 034, 060, 063, 067, 072, 074 and 075 did not have any premature withdrawals.] (doc. excel file disca11.exe)

Study	Clinical AE	Lab AE	Lost To Followup	Protocol Deviation	Patient Uncooperative	Therapy Ineffective	Did Not Meet Eligibility	Clinical and Lab AE	Clinical and ECG AE	Patient Withdrew	Clinical AE/Continuing	Therapy Ineffective/Continuing	Protocol Violations/Continuing	Total
001 Dupont Angiotensin II Infusion	0	0	1	0	0	0	0	0	0	0	0	0	0	1
003 Dupont Single Dose Safety	2	1	0	0	0	0	0	0	0	0	0	0	0	3
005 Inpatient Multiple Dose	1	0	0	0	0	0	0	0	0	0	0	0	0	1
006 Dupont High Dose Angiotensin II Infusion	1	0	0	0	0	0	0	0	0	0	0	0	0	1
011 Outpatient Dose Response	7	1	3	3	1	9	0	1	0	8	1	1	0	35
014 Urinary Protein Excretion	1	0	0	0	0	0	0	0	0	0	0	0	0	1
015 Food Interaction	0	0	2	1	0	0	0	0	0	0	0	0	0	3
016 HF Hemodynamics	0	0	0	0	0	0	0	0	0	0	0	1	0	1
018 12 Week Prostaglandin Synthesis	0	0	0	0	0	0	0	0	0	0	0	0	0	1
019 Low Sodium Diet	1	0	0	1	0	0	0	0	0	1	0	0	0	3
021 ABPM (QD vs. BID)	4	0	0	2	0	0	0	0	0	0	0	0	0	6
035 Forearm Blood Flow	0	0	0	0	1	0	0	0	0	0	0	0	0	1
043 RAAS Effects in Hypertensives	1	0	0	0	0	0	0	0	0	0	0	0	0	1
044 Captopril Comparison	10	0	1	1	0	0	0	0	0	1	0	0	0	13
045 Atenolol Comparison	2	0	2	1	0	4	0	0	0	2	0	0	0	11
047 HF Hemodynamics	13	0	0	0	0	1	0	0	0	0	1	0	0	15
050 Mild to Moderate Hypertension	7	0	4	3	1	2	0	0	0	3	0	5	1	26
055 Felodipine in Elderly	3	0	1	0	0	1	0	0	0	0	0	0	0	5
056 Multicenter Cough	1	0	0	0	0	0	0	0	0	0	0	0	0	1
058 Renal Impairment	2	0	0	1	0	2	1	0	0	6	0	0	0	12
059 Open Severe Hypertension	5	0	1	0	0	1	0	0	1	1	0	0	0	9
064 Double Blind Severe Hypertension	0	0	3	2	1	0	0	0	0	0	0	0	0	6
065 BID vs. QD	4	2	4	5	0	9	0	0	0	7	0	0	0	31
070 Coumadin Interaction	0	0	0	0	0	0	0	0	0	1	0	0	0	1
079 Digoxin Interaction	0	1	0	0	0	0	0	0	0	1	0	0	0	2
TOTAL	65	5	22	21	4	29	1	1	1	31	2	7	1	190

(In reasons for discontinuation, continuing means that despite withdrawal prematurely, patients entered open label losartan study.)

At the request of the FDA, the sponsor submitted (document 20-386/BM submitted 1/8/94) additional information on the 53 patients withdrawn because of "lost to follow-up" or "patient withdrew". Table SS.7 provides details of the information included in the submission. Twenty-four patients had adequate explanations for discontinuing. Eighteen patients had no additional information. Four patients could have been listed as treatment failures (inadequate response to therapy as determined by the patient). Four could have been listed as experiencing adverse events. Four patients could be listed as adverse events or treatment failures.

Table SS.7. Reason for Discontinuation in Patients Withdrawn as Patient Withdrew or Lost to Follow-up.

	Study # / Patient #					
	11/192	11/496	45/4058	50/2291	50/2394	55/5160
No Additional Information	50/5528	64/4518	64/4559	65/1676	65/1685	65/1407
	65/1628	44/3092	50/2284	50/2119	58/373	11/552
Therapeutic Failure (TF)	64/462	65/1386	65/1420	65/1351		
Adverse Event (AE)	50/2110	64/4617	45/4167	65/1310		
AE or TF	58/463	58/552	59/5517			

A complete list of losartan treated hypertensive patients withdrawn from clinical trials due to adverse experiences is located in the appendix. There was one healthy subject in study 007 worth noting. Patient #13 experienced hemolytic anemia, palmar desquamation and increased creatinine while receiving losartan. A relationship between losartan and this adverse event has not been ruled out. A complete description of this adverse event can be found in the summary for study 007.

Adverse Events - Open Label Trials

The CANDA contains the data for the long term follow-up studies 011, 021, 049, 050 and 054. This is summarized in the review of these trials. The integrated summary of safety includes additional information on long term follow-up studies 063, 073, 018 and 059. Table SS.7a is a partial list of adverse events in patients enrolled in open label trials. However, the sponsor can not identify time point up to which this data was collected. As noted earlier, the CANDA and paper NDA submission only contain data for long term follow-up of studies 011, 021, 049, 050 and 054 reportedly because these were the only studies with CRF's in house by the NDA cut-off date of 3/31/93. Serious adverse events from the sponsors WAES data base were included up to 6/30/93. Thus, it is not clear where and when the data for long term follow-up for studies 063, 073, 018 and 059 is derived. [Reviewer's Note: Compare this table with data in the summary of the long term follow-up of studies 011, 021, 049, 050 and 054. (summary is located in open label trials section)]

Table SS.7a. Clinical Adverse Experiences (%)^a Hypertensive Patients by Treatment Group (Open-Label)

	Losartan (n=831)	Losartan Plus HCTZ (n=601)	Losartan Plus HCTZ Plus Other Antihypertensive Agents (n=212)
Body System			
Body as a Whole			
Asthenia/Fatigue	3.4	2.8	1.9
Edema/Swelling	1.9	1.3	6.6
Flu-Like Illness	0.4	1.5	0.5
Pain, Abdominal	2.3	2.3	0.5
Pain, Chest	2.0	3.0	0.9
Digestive System			
Diarrhea	3.1	2.0	1.4
Dyspepsia	1.1	1.3	1.4
Nausea	1.9	1.3	0.5
Musculoskeletal System			
Cramp, Muscle	0.4	1.0	1.4
Myalgia	1.2	0.5	0.5
Pain, Back	2.2	2.7	1.4
Pain, Leg	1.0	0.3	0.0
Pain, Shoulder	0.6	1.5	0.5
Nervous System and Psychiatric			
Anxiety	0.8	0.8	1.9
Depression	1.2	0.2	0.5
Dizziness	3.7	5.8	4.2
Headache	12.5	8.5	7.5
Insomnia	1.3	1.0	0.0
Paresthesia	0.7	1.3	0.0
Respiratory System			
Bronchitis	0.7	1.5	0.5
Congestion, Nasal	1.1	2.0	0.9
Cough	2.5	2.7	1.9
Infection, Respiratory, Upper	9.1	6.7	6.6
Influenza	0.5	1.0	0.9
Pharyngitis	2.5	2.0	1.4
Sinus Disorder	1.3	0.8	0.0
Sinusitis	1.8	0.7	0.5
Skin and Skin Appendage			
Flushing	0.2	0.5	2.8
Rash	2.0	1.5	0.9
Urogenital System			
Impotence	0.6	1.2	1.4
Infection, Urinary Tract	1.7	1.3	0.9

^a Occurring in $\geq 1\%$ hypertensive patients in at least one of the losartan treatment groups.

Fifty-seven patients withdrew due to adverse events from open-label trials while being treated with losartan +/- combination. A listing of these patients can be found in the appendix

Adverse Events - Cough

Angiotensin converting enzyme inhibitors (ACEI) cause cough possibly related to its interaction with the bradykinin system. Since losartan acts on the RAAS system but not the bradykinin system, it is of interest to determine whether losartan increases the risk for cough in patients. Study 056 exams this in patients who have a previous history of lisinopril induced cough. In this study, losartan significantly decreased the incidence of cough in patients with ACEI induced cough. The limitation of the study is the short duration of exposure, up to 4 weeks, and the likelihood that the dose of lisinopril and losartan used in this trial were not equipotent (in terms of lowering DBP). The latter limitation may be irrelevant if ACEI induced cough is not a dose dependent phenomena.

Four double-blind, controlled clinical trials of 6 to 12 weeks in duration included an ACEI and losartan as treatment groups. These trials were 011, 043, 044 and 064. Table SS.8 lists the number of patients randomized to each group in these trials, the number of patients with cough as an adverse event and the number of patients with cough or other adverse events that probably presented with cough (cough, bronchitis, respiratory infection, upper respiratory infection, lower respiratory infection) as an adverse event. The rationale for looking at this is that in the ACEI's initially approved, cough was not known to be a side effect. It became apparent post-marketing. One possible reason it was not found to be a problem in the NDA controlled data base is that patients with cough were classified as having a respiratory infection. In the four studies, the overall incidence of cough reported as an adverse event was 2.2%, 4.6% and 7.4% for placebo, losartan and ACEI respectively (not significantly different; Chi-square Test: losartan vs. placebo $p = 0.292$, losartan vs. ACEI, $p = .148$). If respiratory infection adverse events, that are likely to cause cough, are included with cough, 13.3% of placebo, 13.9% of losartan and 15.9% of ACEI patients respiratory adverse events or cough.

Table SS.8. Number of Patients Randomized in Studies 011, 043, 044 and 064, Incidence with Cough and Incidence with Cough or Other Respiratory Infections.

	Placebo	Losartan	ACEI
Study 011. # Randomized	78	415	83
Study 043. # Randomized	12	51	14
Study 044. # Randomized	-	109	54
Study 064. # Randomized	-	50	25
Total Randomized	90	625	176
# With Cough as and Adverse Event	2	29	13
% with Cough	2.2%	4.6%	7.4%
# With cough or bronchitis or respiratory infection or lower respiratory infection or upper respiratory infection as an adverse event	12	87	28
% With cough or bronchitis or respiratory infection or lower respiratory infection or upper respiratory infection	13.3%	13.9%	15.9%

Adverse Events - Cancer

Thirteen patients were diagnosed with cancer while enrolled in losartan or losartan/HCTZ clinical trials. Table SS.9 lists the patients and the type of cancer. Twelve of the patients were on losartan or losartan combination therapy. One patient in the WMA database is listed with renal cancer. A complete review of the relationship between losartan and renal cell cancer is summarized in a separate review and in a consultation by Dr. Greg Burkhart from the Division of Epidemiology.

Table SS.9. Patients Diagnosed with Cancer in Losartan Trials

Study	Patient #	Sex	Age	Race	Day Discontinued	AE Drug Dose	Adverse Experience	AE Start Day
L11 LT	666	F	58	Caucasian	22	100 mg Losartan	SKIN, MALIGNANT	66
49	7418	M	64	Caucasian	57	100 mg Losartan/25 mg HCTZ	INTESTINAL, MALIGNANT	42
L11 LT	508	M	66	Caucasian	476	150 mg Losartan/12.5 mg HCTZ	MELANOMA	498
L11 LT	27	M	57	Caucasian	343	150 mg Losartan/25 mg HCTZ	SKIN, MALIGNANT	403
49	7280	M	62	Black	54	25 mg Losartan/25 mg HCTZ	LUNG, MALIGNANT	48
65	1421	M	66	Caucasian	43	Placebo	INTESTINAL, METASTATIC	43
65	1194	M	64	Caucasian	84	50 mg Losartan	MALIGNANT NEOPLASM	15
L11 LT	71	M	49	Caucasian	458	50 mg Losartan	SKIN, MALIGNANT	237
L49 LT	7279	M	52	Caucasian	254	50 mg Losartan	TONGUE, MALIGNANT	267
L50 LT	2022	M	56	Caucasian	279	50 mg Losartan/12.5 mg HCTZ/5 mg Felodipine	PROSTATE, MALIGNANT	336
49	7288	F	34	Black	84	50 mg Losartan/25 mg HCTZ	UTERINE, BENIGN	38
L11 LT	828	M	65	Caucasian	373	50 mg Losartan	SKIN, MALIGNANT	133
L49 LT	7411	M	61	Caucasian	287	50 mg losartan/ 25 mg HCTZ	KIDNEY, MALIGNANT	233

Laboratory - Mean Changes

There was no clinically significant change in mean laboratory values in the acute (12 weeks or less), double blind, placebo controlled studies except for a consistent decrease in mean uric acid levels. There were some trends in mean values that are worth noting (Table SS.10.). Mean uric acid levels tended to decrease with losartan therapy. It is unclear that this is clinically important since there did not appear to be a decrease in the incidence of acute attacks of gout with losartan treatment. Mean serum potassium increased slightly and mean urine pH decreased slightly.

Table SS.10. Mean Change in Labs

	Placebo Change	Losartan Change (range)
Uric Acid (mg/dl)		
Study 011	.05	.1 to -.33
Study 050	.18	-.08 to -.12
Study 065	-.16	-.24 to -.35
Urine pH		
Study 011	.12	.04 to -.32
Study 050	-.2	.01 to -.23
Study 065	-.06	-.16 to -.39
Serum Potassium (mEq/L)		
Study 011	-.14	.01 to -.12
Study 050	-.02	.05 to .09
Study 065	-.03	0 to .13

Laboratory Adverse Experiences

There was not a clinically significant change in mean creatinine in the controlled clinical studies. However, there are instances where serum creatinine increased in some individuals. Table SS.11 lists three patients from study 044 (2 losartan, 1 captopril) that experienced elevated creatinine during therapy. In the both losartan cases, baseline BUN was increased.

Table SS.11. Patients With Increased Creatinine from Study 044.

Patient	Treatment	Baseline Creatinine (mg/dl)	Maximum Creatinine (mg/dl)	Comment
3181	losartan	1.4	2.3	Creatinine decreased, but not to baseline, after losartan discontinued. Baseline BUN = 61 mg/dl, Maximum BUN = 72 mg/dl.
3238	losartan	1.1	1.5	Creatinine decreased, but not to baseline, after losartan discontinued. Baseline BUN = 26 mg/dl, Maximum BUN = 53 mg/dl.
3023	captopril	1.25	2.4	Creatinine decreased, but not to baseline, after captopril discontinued. Baseline BUN = 17 mg/dl, Maximum BUN = 32 mg/dl.

There are three patients in long term follow-up studies who experienced elevations in serum creatinine while receiving losartan in combination with HCTZ. Patient #2212 in study L50 had a baseline creatinine of 1.2 mg/dl. On study day 198, the creatinine was 2.8 mg/dl (BUN = 35 mg/dl; baseline BUN = 10 mg/dl). The patient received losartan/HCTZ until day 191.

The database does not provide any creatinines between days 191 and 198. Thus, until shown otherwise, one must presume that the elevated creatinine and BUN is due to losartan/HCTZ. On day 209, the creatinine was 1.4 mg/dl. Patient #646 in study L011 had a creatinine of 2.4 mg/dl on day 134 (losartan 150 mg/HCTZ 12.5 mg). The creatinine was 1.4 mg/dl on day 119 and 1.2 mg/dl at baseline. Patient #594 in study L011 had an elevated creatinine of 2.4 mg/dl on day 377 (Losartan 150 mg/HCTZ 25 mg). Baseline creatinine was 1.2 mg/dl. The creatinine improved after the HCTZ was discontinued. Patient #5274 in study 055 had a creatinine of 1.6 mg/dl on day 83 (losartan 100 mg). These examples provide evidence that losartan with or without HCTZ can cause reversible elevations in serum creatinine.

There were no patients with serious laboratory adverse experiences who died. Two patients had non-fatal serious adverse events. Patient # 0548, a 52-year-old male, developed elevations of total serum bilirubin, AST, ALT, serum LDH, serum GGT while participating in protocol 011 and was subsequently found to be serologically positive for acute hepatitis A. Patient # 5188, a 68-year-old female, developed hypokalemia (3.0 mmol/L) while participating in protocol 055. Previous serum potassiums were in the normal range. The patient had developed minor flu complaints and headache with reduced appetite.

Table SS.12 provides a detailed listing of the laboratory adverse experiences leading to patient discontinuation in losartan-treated patients during the double-blind phase of clinical trials with hypertensive patients.

Table SS.12. Discontinuations Due to Laboratory Adverse Experiences in Losartan-Treated Hypertensive Patients (Double-Blind)

Protocol #/ Study #	Patient #	Age/Sex	Treatment	Daily Dose (mg)	Relative Day of Onset	Relative Day Discontinued	Adverse Experience
011/006	0115	76/M	Losartan	25	14	32	Platelet Count Decrease
065/003	1599	44/F	Losartan	50	84	84	AST Increased
			Losartan	50	84	84	ALT Increased
048/001	0193	53/M	Losartan	50	28	28	Eosinophilia
			Losartan	50	28	28	Hemoglobin Decreased
			Losartan	50	28	28	Hematocrit Decreased
048/001	0194	55/M	Losartan	50	14	13	Proteinuria
048/018	6336	68/M	Losartan	50	10	11	Hyperglycemia
065/023	1750	45/M	Losartan	50	90	90	Hyperglycemia
011/027	0548	52/M	Losartan	150	28	34	Total Serum Bilirubin Increased*
			Losartan	150	28	34	AST Increased
			Losartan	150	28	34	ALT Increased
			Losartan	150	34	34	GGT Increased
			Losartan	150	34	34	LDH Increased
			Losartan	150	34	34	Hepatitis A Antibody Positive
			Losartan	150	34	34	Total Serum Bilirubin Increased
			Losartan	150	34	34	AST Increased
			Losartan	150	34	34	ALT Increased
			Losartan	150	35	34	Total Serum Bilirubin Increased
			Losartan	150	35	34	AST Increased
			Losartan	150	35	34	ALT Increased
			Losartan	150	35	34	GGT Increased

* Serious Adverse Event

Brief narratives describing the events in these seven patients follow:

Patient # 0115, a 76-year-old male, developed "thrombocytopenia" ($118,000/\text{mm}^3$, normal range $130,000$ to $400,000/\text{mm}^3$) after approximately 5 weeks of participation in protocol 011. The platelet count at baseline (prior to randomization) was normal, $198,000/\text{mm}^3$. The patient was noted to have had a platelet count that was at the lower limit of normal ($139,000/\text{mm}^3$, normal range $130,000$ to $394,000/\text{mm}^3$) approximately 5 months prior to entering the study. The patient subsequently recovered (platelet count $168,000/\text{mm}^3$) approximately 3 weeks after discontinuation of the study drug.

Patient # 1599, a 44-year-old female, developed mild elevations of ALT (56 U/L, normal range 6-34 U/L) and AST (73 U/L, range 9-34 U/L) while participating in protocol 065. The patient was discontinued. A follow-up evaluation revealed persistent mild elevation of these laboratory parameters (ALT 68 U/L and AST 78 U/L).

Patient # 0193, a 53-year-old male, developed a decreased hemoglobin (13.7 gm/dL and hematocrit 40.0%) and increased eosinophils (4.5%) while participating in protocol 048. The decreased hemoglobin and hematocrit was felt to be due to bleeding hemorrhoids; there was no evidence of a bleeding diathesis. The increased eosinophils which resolved on discontinuation of the study drug were felt to be drug related.

Patient # 0194, a 55-year-old male, developed worsening proteinuria (from 2 units at baseline to 3 units during the study) while participating in protocol 048. The patient was a known insulin-dependent diabetic with mild renal insufficiency at baseline (creatinine 1.3 mg/dL).

Patient # 6336, a 68-year-old male, developed hyperglycemia (12.1 mmol/L) while participating in protocol 048. The patient was a known diabetic at baseline.

Patient # 1750, a 45-year-old male, developed hyperglycemia (326 mg/dL, range 70-115 mg/dL) while participating in protocol 065. The patient was a known diabetic at baseline with an elevated baseline glucose 268 mg/dL.

Patient # 0548, a 52-year-old male, developed elevations of total serum bilirubin, AST, ALT, serum LDH, serum GGT while participating in protocol 011 and was subsequently found to be serologically positive for acute hepatitis A.

Drug Interaction - Warfarin

Clinical pharmacology trials assessing the effect of phenobarbital and cimetidine on the pharmacokinetics of losartan were performed and are discussed in the clinical pharmacology summary. Additionally, the sponsor studied the effect of losartan on the pharmacokinetics of warfarin in study 70. Study 70 does not provide sufficient information on the pharmacodynamics of warfarin to conclude that no interaction with losartan occurs. In the NDA, fifty-seven patients received concomitant anti-coagulants while receiving losartan. Sixteen patients received single doses of losartan in study 016. Forty-one patients received multiple doses of losartan while on anti-coagulants. Prothrombin and partial thromboplastin times were not obtained on case report forms as part of the laboratory parameters collected (as per submission 20-386/BM; received 10/7/94). Patient 1031 in study 047 experienced gingival bleeding on losartan 2.5 mg and warfarin. Apparently the prothrombin time was increased to 29.4 seconds at the time of bleeding (day 22). Baseline prothrombin times are not provided. In addition to losartan, lovastatin was the only other medication started after randomization and continued through the time of the gingival bleeding. It is not clear whether losartan played a role in the increase in the prothrombin time in this patient. Unless the sponsor provides additional information, a pharmacodynamic interaction between warfarin and losartan can not be ruled out.

Placebo Controlled Multi-Dose Trials in Hypertensive Patients						
Study #	Design/ Patient Population	Treatment Groups	N	Primary Endpoint	Other Measures	Page
005	- r, db, pc, ac, 5 day Rx period - non-black hypertensives	- placebo - losartan 50 mg - losartan 100 mg - losartan 150 mg - enalapril 10 mg	23 20 18 20 19	- change in suDBP	- 6 hour post dose DBP - plasma renin - aldosterone - Angiotensin II - withdrawal BP	24
011*	- r, db, pc, p, mc, 8 wk Rx period - hypertensives (limited to $\leq$ 25% black) - open label extension optional	- placebo - losartan 10 - losartan 25 - losartan 50 - losartan 100 - losartan 150 - enalapril 20 mg	78 80 82 79 90 84 83	- Trough sup DBP at week 8	- losartan levels - peak blood pressure (6 hours post-dose) - response rate - PRA	34
050*	- r, db, pc, p, mc, dose titration, 12 wk Rx period - hypertensives (limited to $\leq$ 30% black) - open label extension optional	- placebo - losartan 50/100 mg - losartan 50/P	116 123 127	- Trough si DBP at week 12	- peak blood pressure (5 - 8 hours post-dose) - response rate - PRA	47
065*	- r, db, pc, 12 wk Rx period - hypertensive, no more than 30% black, 30% with moderate hypertension - open label extension optional	- placebo - losartan 25 mg daily - losartan 25 mg bid - losartan 50 mg daily	108 108 106 106	- Trough siDBP at week 12	- Response Rate - BP change at peak - Difference in BP change between losartan 50 od and 25 bid	57
021	- r, db, pc, p, 6 wk Rx period - non-black hypertensives - Ambulatory Blood Pressure Monitoring (ABPM) - open label extension	- placebo - losartan 50 mg - losartan 100 mg - losartan 50 mg bid	32 29 30 31	- change in ABPM blood pressure at 4 weeks		69
043*	- r, db, pc, ac, 6 wk Rx period - non black hypertensives	- losartan 25 mg od - losartan 100 mg od - placebo - enalapril 20 mg od	11 14 12 14	- plasma renin - plasma angiotensin II	- losartan levels - E-3174 levels - plasma and urine aldosterone - plasma and urine NE and Epi. - supine DBP and SBP - rebound hypertension	128

* Summarized in Clinical Pharmacology Section

wk = week, db = double-blind, ol = open label, od = once a day, bid = twice a day, r = randomized, ac = active control, pc = placebo control, nc = no control, p = parallel, co = crossover, hx = history, HTN = hypertension, ACEI = angiotensin converting enzyme inhibitor, NE = norepinephrine, Epi = epinephrine, PRA = plasma renin activity

* = designated pivotal by the sponsor, ** = does not include data from 1 of 17 centers due to cut-off date restrictions.

Study 005. A Multicenter, Double-Blind, Placebo-Controlled, Two Panel, Parallel Group, Inpatient Study to Investigate the Safety and Antihypertensive Efficacy of Multiple Doses of AII Antagonist Losartan in Patients with Mild-to-Moderate Essential Hypertension

Protocol

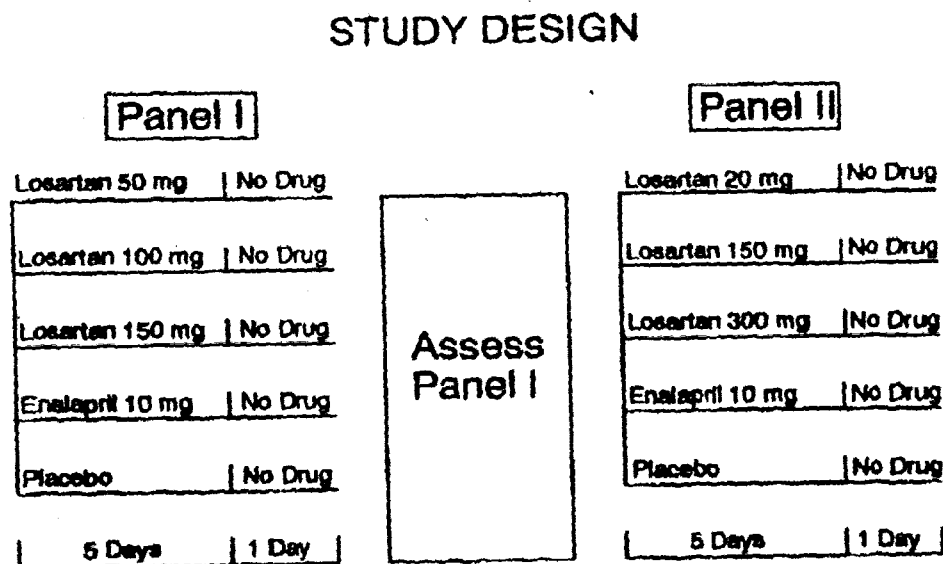
This was a multicenter, randomized, double-blind, placebo-controlled, two-panel, parallel, multiple-dose study in mild to moderate hypertensive patients. The objectives of this phase II study were to establish safety, obtain preliminary dose response data, estimate the duration of effect, assess the withdrawal effect and measure various metabolic parameters. The study enrolled non-black patients, age 21 - 70 years, within 30% of ideal body weight and with no other active medical problems. The study consisted of a 2 week single-blind, outpatient, placebo baseline period, a 2 day in-patient placebo baseline period, a 5 day in-patient double-blind treatment period and a 1 day in-patient withdrawal period.

Following discontinuation of all antihypertensive medications for at least 1 week, patients were eligible to enter a 2-week outpatient, single-blind placebo period to document blood pressure, provided their supine diastolic blood pressure (suDBP) was ≥ 90 mmHg. After 1 and 2 weeks of placebo therapy, a patient's suDBP had to be in the range of 95-120 mmHg with the two readings not differing by more than 7 mmHg in order for the patient to continue in a 2-day in-patient placebo period. In addition, supine systolic blood pressure (suSBP) could not exceed 200 mmHg on more than 2 successive visits. Patients who were eligible were to return to the clinic within 5 days for inpatient placebo screening.

During the 2-day in-patient screening period, blood pressure readings were obtained at various intervals between 0.5 - 24 hrs postdose. Readings with an automated device were also obtained only if the procedure did not interfere with the quality or timing of the mercury sphygmomanometer readings. In order to be randomized to receive double-blind drug, the suDBP at Hours 23, 23.5 and 24 on the second inpatient day had to be between 95-120 mmHg without varying by more than 7 mmHg from the mean. In addition, on both placebo days, 6 of the first 9 mercury measurements of suDBP (Hours 5-12) as well as Hours 23, 23.5 and 24 on the second placebo day, had to be in the range of 95-120 mmHg. None of the first 9 readings could be < 90 mmHg. Also, a blood sample for the measurement of plasma renin activity, aldosterone, angiotensin II and safety was drawn at various time points on the second day of placebo.

Patients who met all the eligibility criteria during the placebo days were randomized at the completion of the second placebo day to 1 of the 5 parallel groups as shown in Figure 5.1. Each patient was to participate in 1 panel only.

Figure 5.1



Note: n=20/Group,100/Panel ...

Patients received 5 days of therapy and then participated in an off-drug day while remaining inpatients to assess whether there were any major shifts in blood pressure. After the 1-day off-drug period, patients could resume conventional antihypertensive therapy.

The second panel was to be initiated upon the completion of Panel I after the clinical safety and preliminary efficacy data had been assessed by the clinical monitor. Upon completion of Panel I it was determined that a maximum efficacy dose had been found, and that it was not appropriate to proceed with the second panel.

Table 5.1 identifies the clinical and laboratory measurements that were obtained during the study and the time at which they were obtained.

Table 5.1 Clinical Observations and Laboratory Measurements

	Outpatient				Inpatient								Follow-Up 3 - 7 days after discharge	
	Pre-study	Baseline			Baseline		Double-Blind					Off Drug		
		Start of Outpatient Placebo Period	Week -1	Week -2	Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6		
Medical History	X													
Physical Exam	X											X	X	
Body Weight	X		X	X										
Body Height	X													
BP and HR ¹	X		X	X	X ²	X ³	X ³	X ⁶	X ⁶	X ⁶	X ³	X ¹¹		
ECG	X			X		X ⁵	X ¹⁰			X ⁵		X ¹³		
Laboratory Screen	X			X		X		X			X	X ¹²	X	
Stool Sample	X					X				X	X	X		
Discontinue Anti-hypertensive Meds	X													
Urine Drug Screen, HIV and Hepatitis Screen		X		X ¹⁴										
Blood Draw (PRA, All and Aldosterone)						X ⁴	X ⁸				X ⁴	X ¹²		
Measurement Urine Volume					X	X ⁹	X ⁹	X	X	X	X ⁹	X ⁹		
Bleeding Time						X				X				
Blood Draw (ACE Activity)							X ⁷				X ⁷			
Determination of Electrolytes, Creatinine, Total Protein, Cortisol and Aldosterone						X	X				X	X		

¹Measurements made in both the supine and standing positions

²Hours -1, -0.5, 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 23, 23.5 and 24=Dinamap, Hours 0, 6, 8, 12, and 24=mercury sphygmomanometer

³Hours 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 23, 23.5 and 24=Dinamap, Hours 6, 8, 12 and 24=mercury sphygmomanometer

⁴Hours -1, 5, 13, and 23

⁵Hours 0, 16 and 24

⁶Hours 1, 2, 4, 6, 8, 12, 16, 20, 23 and 24=Dinamap; Hours 6, 8, 12 and 24=mercury sphygmomanometer

⁷Hours -1 and 5

⁸Hours 5, 13 and 23

⁹pH of Urine Immediately after Voiding

¹⁰Hours 6 and 24

¹¹Hours 1, 2, 4, 6, 8, 12, 16, 20, 23 and 24=Dinamap; Hours 6, 12, and 24=mercury sphygmomanometer

¹²After rising (Hour 23)

¹³Hours 0 and 24

¹⁴Repeat Screen within 5 days of Inpatient Period

When evaluated as inpatients, the mercury sphygmomanometer was used as the primary measurement device. A comparison between the Dinamap® automated blood pressure monitor (only if measurements did not interfere with the quality or timing of the mercury sphygmomanometer readings) and the mercury sphygmomanometer was to be made. [Note: Due to inaccuracies in blood pressure readings taken with the automated device when compared to readings taken with the mercury sphygmomanometer obtained at the same time, results obtained with the automated device were not analyzed.]

The statistical analysis performed are outlined in table 5.2. The Type I error rate was set at $\alpha=0.05$ for all formal hypothesis testing.

Table 5.2. Statistical Analysis.

Parameter	Statistical Analysis
Blood Pressure and Heart Rate Change (within group mean changes)	Paired t-test
Blood Pressure Change (between group mean changes)	Least significant difference procedure Linear and Quadratic Dose Response Evaluations
Signed Area of change Maximum decrease in first 12 hours postdosing Time to maximum decrease in blood pressure	Pairwise comparison Dose Response
Laboratory Tests (outside pre-defined limit of change)	Fisher's Exact Test (2 tailed)
Bleeding Time	ANOVA with respect to least square mean changes

Results

Demographics

One hundred non-black patients, 60 males and 40 females, mean age 54.3 ± 9.8 years from 10 clinics entered this study. The number of patients per treatment group ranged from 18 to 23. The number of patients randomized per center ranged from 3 to 16. No more than 5 patients in any one treatment group received an ACE inhibitor prior to entering this trial. Variations in between-clinic baseline measurements did differ significantly for mean blood pressures, pulse (except standing pulse 24-hour), serum aldosterone, plasma renin activity, and in serum potassium. There were no statistically significant differences (overall F-test) between the treatment groups with respect to mean blood pressure, heart rate, weight, serum aldosterone, plasma renin activity, serum potassium, serum creatinine, and serum uric acid levels as recorded for the patients on Day -1.

Disposition

Four of the 100 patients who entered the study did not complete the study as "per protocol". They are listed in Table 5.3.

Table 5.3. Patients Who Did Not Complete The Study As "Per Protocol"

Patient	Treatment	Study Day	Reason
118	Placebo	4	Clinical Adverse Experience (discontinued)
39	losartan 150 mg	2	Clinical Adverse Experience (discontinued)
124	Enalapril	1	Clinical Adverse Experience (discontinued)
168	Enalapril	6	Received one extra (sixth) dose of treatment, completed study

Efficacy [Note: Efficacy data for study 005 was not included in the CANDA.]

On study Days -1, 1, 2, 3, 4, 5, and 6, supine diastolic and systolic blood pressures, standing diastolic and systolic blood pressures, and supine and standing heart rates were collected over 24 hours following a single morning dose of the allocated treatment. Timepoint-by-timepoint changes from Day -1 were calculated at the 14 timepoints (0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 23, 23.5, 24 hours) postdosing over which 24-hour blood pressure and heart rate readings were taken on Days 1, 2, 3, 4, 5, 6. Hours 6 and 24 were chosen by the sponsor as clinically meaningful timepoints to evaluate. [Note: The sponsor contends that "the 24-hour blood pressure lowering effect is smooth and not associated with an excessive reduction in blood pressure at the peak time of efficacy"....and "because of this smooth profile, first-dose hypotension is rarely seen".]

Table 5.4 shows the mean change in suDBP from baseline for days 1, 5 and 6. Significant changes from baseline for all treatment groups at 6 and 24 hours post dosing are noted. A dose response is not present among losartan treatment groups unless placebo is included (model and time post dosing dependent). Figure 5.2 depicts the change in suDBP at each timepoint post-dosing day 1 and 5. The placebo subtracted decline from baseline at trough on day 5 ranged from 6.7 mmHg to 8.1 mmHg for losartan therapy. The changes in blood pressure between losartan groups are indistinguishable.

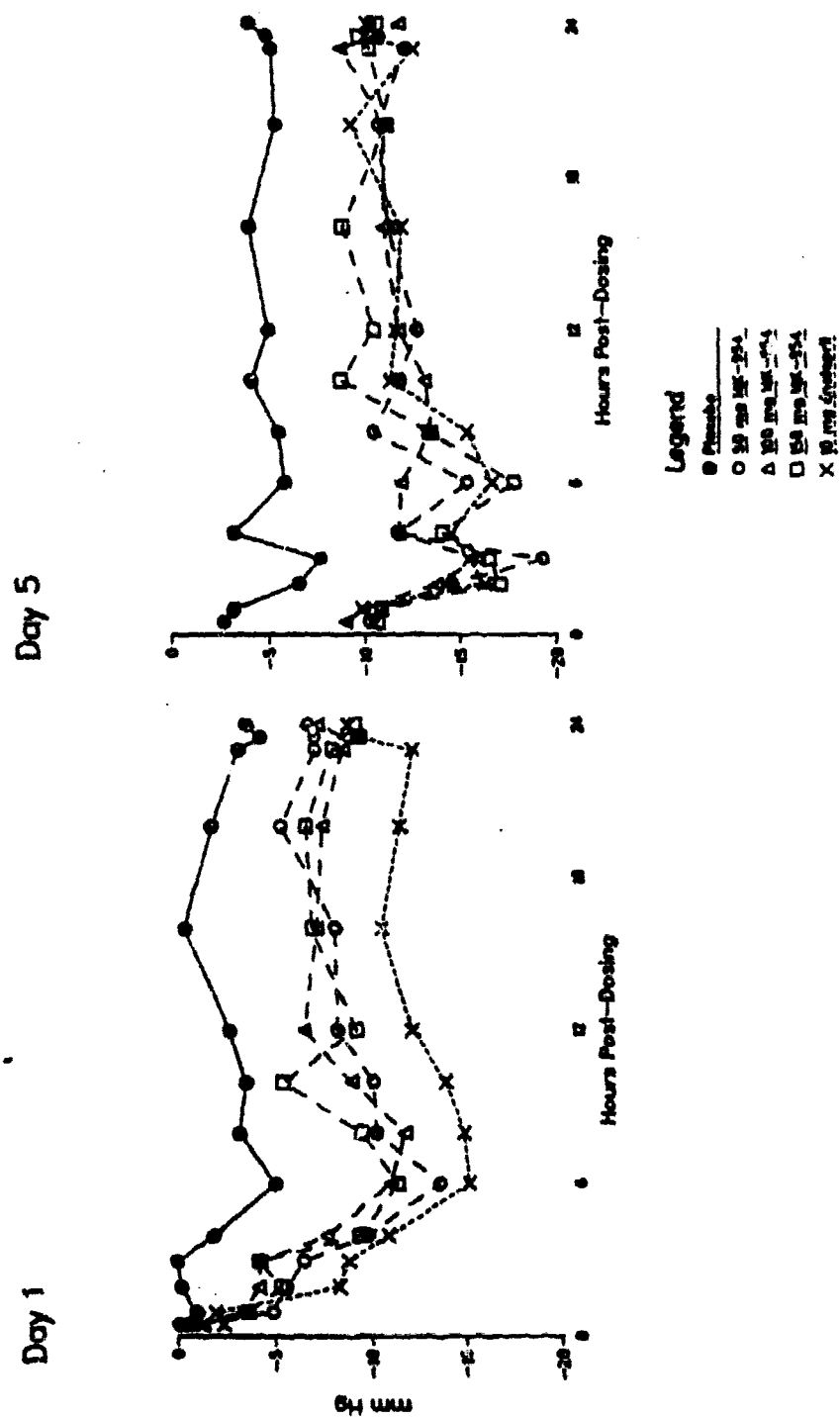
Table 5.4. Supine Diastolic Blood Pressure (mmHg). Mean^(a) Changes from Day -1

	Day 1				Day 5				Day 6				Day 6 - 5			
	Hr. 6		Hr. 24		Hr. 6		Hr. 24		Hr. 6		Hr. 24		Hr. 6		Hr. 24	
Treatment	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Placebo	23	-5.2**	22	-4.2**	23	-5.9**	23	-4.3**	23	-6.4**	23	-4.4**	23	-0.5	23	-0.1
Losartan 50 mg	20	-13.9**	20	-7.8**	20	-15.6**	20	-11.0**	20	-9.7**	20	-7.0**	20	+5.9**	20	+4.0**
Losartan 100 mg	18	-11.6**	18	-8.4**	18	-12.2**	18	-12.4**	18	-10.3**	18	-9.1**	18	2	18	+3.3*
Losartan 150 mg	20	-11.7**	20	-10.0**	19	-17.9**	19	-11.3**	19	-9.8**	19	-9.2**	19	+8.1**	19	2.1
10 mg Enalapril	19	-15.4**	18	-9.6**	18	-16.9**	18	-10.2**	18	-10.9**	18	-8.5**	18	+6.0**	18	1.7
p values																
Day 1 Day 5 Day 6 Day 6 - 5																
Hr. 6 Hr. 24 Hr. 6 Hr. 24 Hr. 6 Hr. 24 Hr. 6 Hr. 24																
Dose Response																
Pbo	50	100	150	L	0.039	0.01	0.0003	0.002	0.21	0.023	0.0096	0.33				
Pbo	50	100	150	Q	0.026	0.53	0.29	0.016	0.33	0.46	0.92	0.047				
	50	100	150	L	0.43	0.32	0.43	0.904	0.97	0.34	0.43	0.31				
	50	100	150	Q	0.63	0.8	0.073	0.54	0.83	0.65	0.036	0.86				
Pairwise vs. Placebo																
Pbo		150			0.014	0.0085	<0.001	0.0021	0.204	0.035	0.0013	0.25				
Pbo		100			0.018	0.063	0.023	0.0005	0.16	0.045	0.34	0.071				
Pbo	50				0.0012	0.099	0.0004	0.0026	0.21	0.24	0.013	0.026				

L = Linear Component, Q = Quadratic Component

Δ = .05 < p ≤ .10; * = p ≤ .05; ** = p ≤ .01; (a) Least Squares Means

Figure 5.2. Mean^a Changes from Day -1 Supine Diastolic Blood Pressure



From the change curves in figure 5.2, signed area about zero over 24 hours, maximum decrease in the first 12 hours postdosing, and the time of the maximum decrease in the first 12 hours were calculated. The results for these measurements are listed in table 5.5.

Table 5.5. Supine Diastolic Blood Pressure (mmHg)

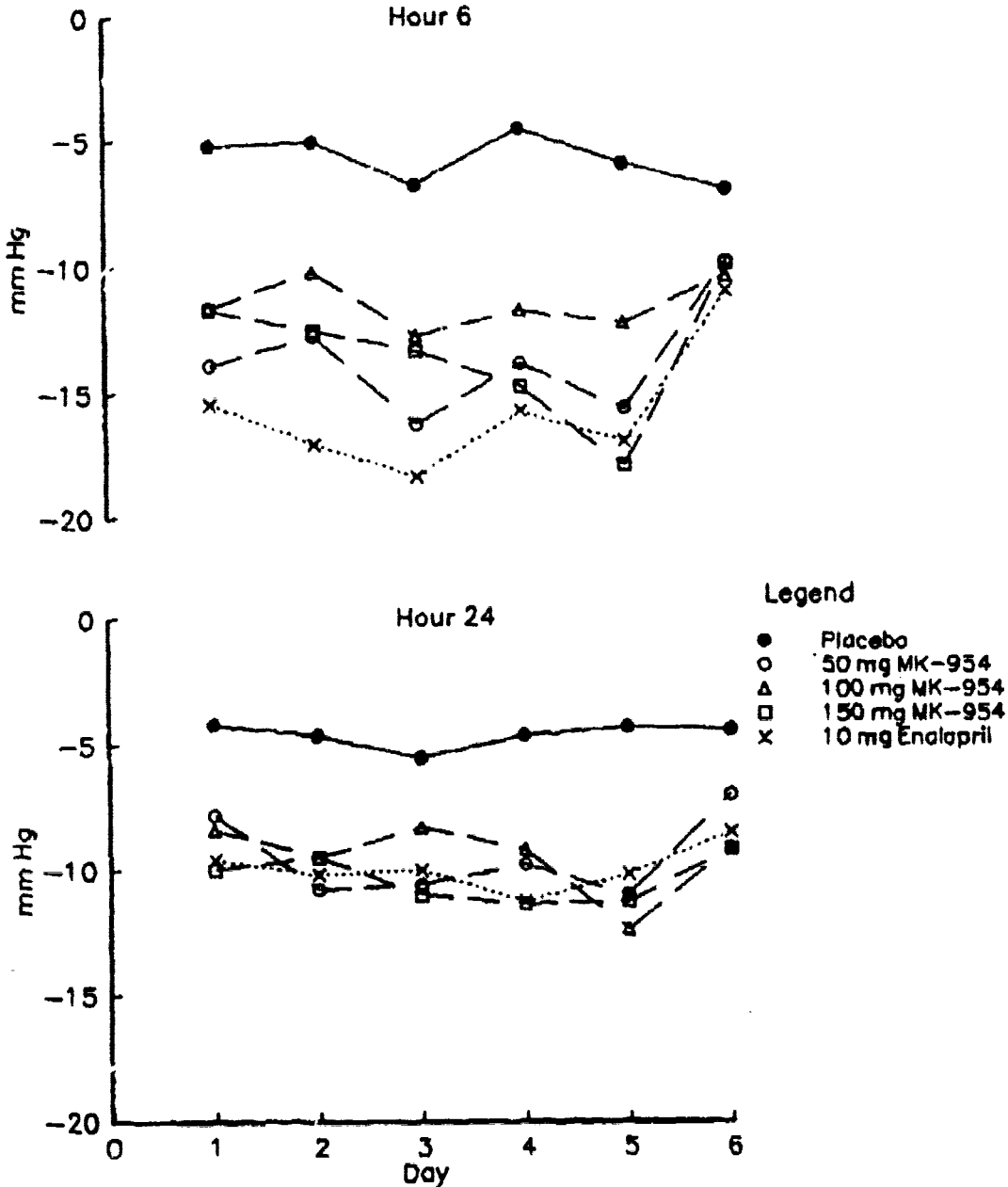
Treatment	Changes from day -1											
	Mean (a) Area ^(b) About Zero				Mean ^(a) Maximum Decrease in First 12 Hours Postdosing				Mean ^(a) Hours Post Dosing of Maximum Decrease			
	Day 1		Day 5		Day 1		Day 5		Day 1		Day 5	
N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	
Placebo	23	-45.7*	23	-111.9**	23	-10.8**	23	-14.5**	23	7.0**	23	5.1**
Losartan 50 mg	20	-189.2**	20	-282.9**	20	-18.9**	20	-23.5**	20	7.4**	20	4.7**
Losartan 100 mg	18	-174.9**	18	-266.7**	18	-17.0**	18	-22.8**	18	7.1**	18	5.8**
Losartan 150 mg	20	-167.9**	19	-260.3**	20	-17.2**	19	-24.2**	20	7.3**	19	3.7**
10 mg Enalapril	19	-268.6**	18	-283.0**	19	-21.2**	18	-22.9**	19	7.3**	18	5.6**

(a) Least Squares Means; (b) $\int_{-24}^{24}$ Hours.* = $p \leq 0.05$; ** = $p \leq 0.01$

The sponsor contends that the area under the curve below (or above) zero was analyzed, revealing that after the first dose of losartan potassium, total reduction in measured blood pressure was not as great with the three losartan potassium doses as with enalapril 10 mg. After 5 days, there was no obvious difference between the groups and all were significantly different from placebo. They claim that this data suggests that losartan potassium has a slower onset of action in lowering BP than enalapril 10 mg, but that after 5 days the effects are equivalent in these patients. This could be interpreted as losartan potassium 50, 100 and 150 mg potentially having less first-dose hypotension when compared to enalapril 10 mg. It is difficult to conclude this from the data for the following reasons. First, area under the curve data is clinically meaningless. Second, five mg and not ten mg of enalapril is the recommended starting dose for enalapril. Since anti-hypertensive medications are titrated from the lowest effective dose, one can not consider this conclusion unless the initial recommended starting doses of enalapril and losartan are compared, and they are not in this trial. Third, the definition of first dose hypotension is subjective but is usually not assessed by measuring mean changes in blood pressure or mean area under the curve. First dose hypotension is better measured by defining what constitutes first dose hypotension and determining the incidence for each therapy. They have not shown anything with this data.

Figure 5.3 shows the 6 and 24 hour post dose changes in sDBP for each treatment group. The changes in blood pressure appear to be stable within the first five days of therapy.

Figure 5.3. Mean^(a) Change from Day -1: Supine Diastolic Blood Pressure Hour 6



(a) Least Squares Means

Table 5.6 lists the mean changes in suSBP at days 1, 5 and 6. Figure 5.4 depicts the change in suSBP over day 1 and day 5 for each treatment group.

Table 5.6. Supine Systolic Blood Pressure (mmHg). Mean^(a) Changes from Day -1

Treatment	Day 1		Day 5		Day 6		Day 6 - 5	
	Hr. 6	Hr. 24	Hr. 6	Hr. 24	Hr. 6	Hr. 24	Hr. 6	Hr. 24
Placebo	N 23 Mean -3.5	N 22 Mean -7.6**	N 23 Mean -1.6	N 23 Mean -10.2**	N 23 Mean -6.1*	N 23 Mean -4.7	N 23 Mean -4.5*	N 23 Mean +5.5*
losartan 50 mg	N 20 Mean -14.8**	N 20 Mean -12.4**	N 20 Mean -19.7**	N 20 Mean -11.2**	N 20 Mean -11.1**	N 20 Mean -6.0*	N 20 Mean +8.6**	N 20 Mean +5.2*
losartan 100 mg	N 18 Mean -12.3**	N 18 Mean -10.3**	N 18 Mean -14.8**	N 18 Mean -17.5**	N 18 Mean -14.4**	N 18 Mean -10.6**	N 18 Mean 0.4	N 18 Mean +6.9**
losartan 150 mg	N 20 Mean -12.1**	N 20 Mean -15.3**	N 19 Mean -18.9**	N 19 Mean -18.4**	N 19 Mean -10.5**	N 19 Mean -13.6**	N 19 Mean +8.4**	N 19 Mean +4.8*
Enalapril 10 mg	N 19 Mean -19.6**	N 18 Mean -14.8**	N 18 Mean -18.2**	N 18 Mean -15.4**	N 18 Mean -10.9**	N 18 Mean -10.3**	N 18 Mean +7.4*	N 18 Mean +5.1*

(a) Least Squares Means; Δ = .05 < p ≤ .10; * = p ≤ .05; ** = p ≤ 0.01

Figure 5.4. Mean Changes from Day -1: Supine Systolic Blood Pressure

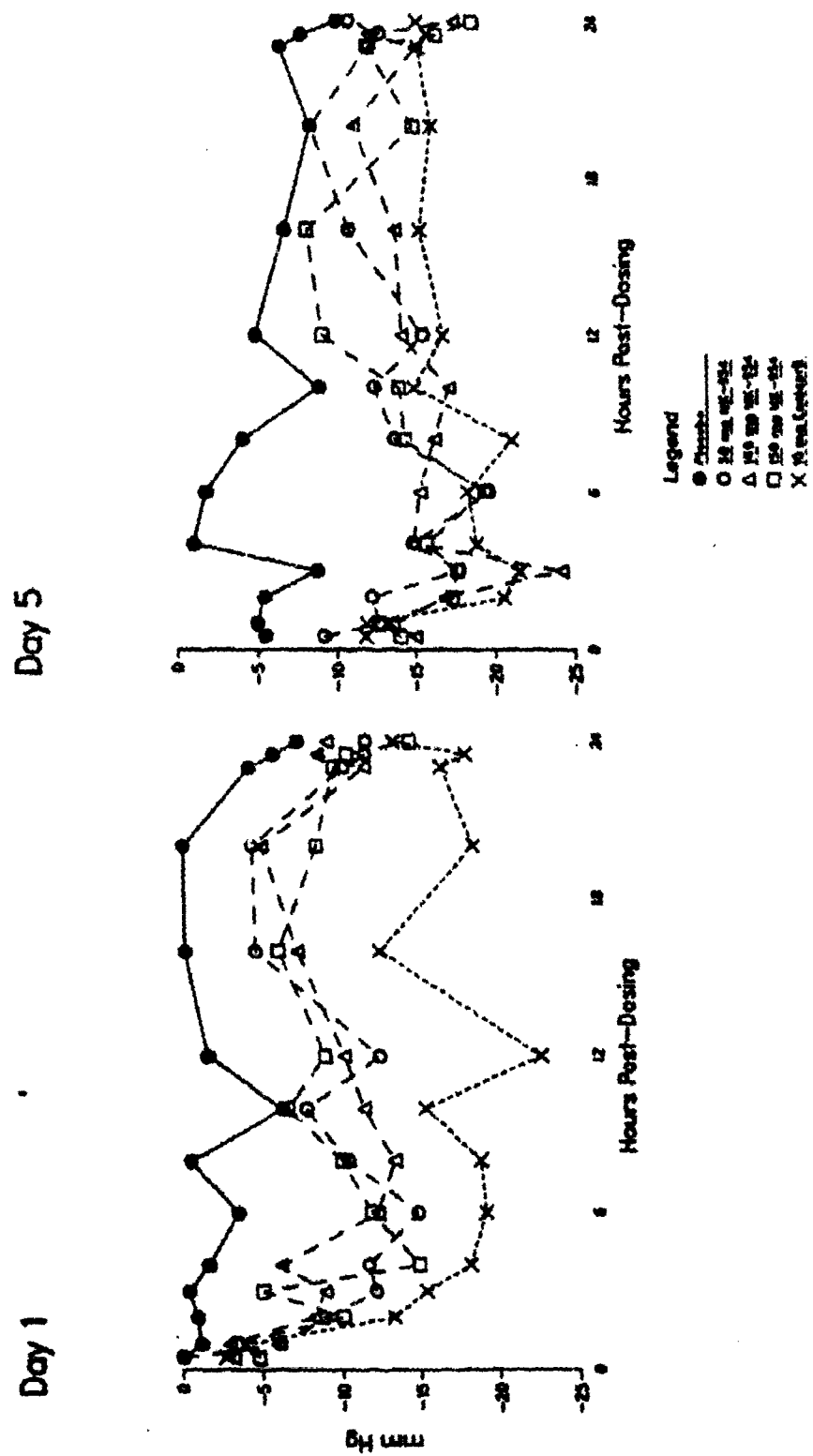


Table 5.8 and 5.9 show the standing DBP for the treatment groups. The difference from placebo is not as pronounced as for suDBP. The effect for each losartan dose at trough on day 5 are not different.

Table 5.8. Standing Diastolic Blood Pressure (mmHg). Mean^(a) Changes from Day -1

Treatment	Day 1				Day 5				Day 6				Day 6 - 5			
	Hr. 6		Hr. 24		Hr. 6		Hr. 24		Hr. 6		Hr. 24		Hr. 6		Hr. 24	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Placebo	23	-4.5*	22	-3.8*	23	-4.8*	23	-5.3**	23	-7.7**	23	-2.8 Δ	23	-2.9	23	2.5
losartan 50 mg	20	-10.6**	20	-5.6**	20	-15.1**	20	-8.5**	20	-8.5**	20	-5.8**	20	+6.6**	20	2.7
losartan 100 mg	18	-9.8**	18	-7.8**	18	-12.6**	18	-10.2**	18	-9.9**	18	-7.9**	18	2.7	18	2.4
losartan 150 mg	20	-11.0**	20	-7.7**	19	-14.3**	19	-8.4**	19	-10.2**	19	-6.0**	19	+4.1 Δ	19	2.4
Enalapril 10 mg	19	-13.7**	18	-7.9**	18	-15.0**	18	-2.2**	18	-8.2**	18	-6.7**	18	+6.9**	18	2.5

$\Delta = .05 < p \leq .10$, * = $p \leq .05$, ** = $p \leq .01$, a = least Square means

Table 5.9. Standing Diastolic Blood Pressure (mmHg). Mean^(a) Changes from Day -1

Treatment	Day 2				Day 3				Day 4			
	Hr. 6		Hr. 24		Hr. 6		Hr. 24		Hr. 6		Hr. 24	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Placebo	23	-6.4**	23	-3.1*	23	-7.3**	23	-6.4**	23	-6.0**	23	-5.4**
Losartan 50 mg	20	-13.5**	20	-9.3**	20	-14.2**	20	-9.1**	20	-11.3**	20	-6.9**
Losartan 100 mg	18	-10.2**	18	-7.6**	18	-11.6**	18	-6.7**	18	-10.3**	18	-7.3**
Losartan 150 mg	20	-12.7**	20	-5.0**	20	-11.3**	20	-7.8**	20	-13.1**	20	-7.4**
10 mg Enalapril	18	-14.0**	18	-7.5**	18	-16.1**	18	-7.1**	18	-10.8**	18	-9.3**

$\Delta = .05 < p \leq .10$; * = $p \leq .05$; ** = $p \leq .01$, a = least Square means

Pulse rate is not significantly affected by losartan.

Plasma renin was increased in the losartan groups on day 1 and day 5 as illustrated in table 5.10

Table 5.10. Plasma Renin Activity (ng/mL/hr)

Treatment	Mean ^(a) Changes from Day -1							
	Day 1				Day 5			
	Hr. 5		Hr. 23		Hr. 5		Hr. 23	
	N	Mean	N	Mean	N	Mean	N	Mean
Placebo	23	+0.35	23	-0.02	22	-0.11	23	+0.45
50 mg LOSARTAN	19	+1.9*	20	+1.3*	19	+4.9*	19	+1.8*
100 mg LOSARTAN	18	+1.5	18	+1.4*	18	+3.9 Δ	18	+2.0*
150 mg LOSARTAN	20	+2.3*	20	+1.5**	19	+4.5 Δ	20	+1.7 Δ
10 mg Enalapril	18	+2.3*	18	+1.4*	17	+7.7**	16	+2.7**
P-Values								
Dose Response	Hr. 5		Hr. 23		Hr. 5		Hr. 23	
Pbo 50 100 150 L	.13		.042		.16		.24	
Pbo 50 100 150 Q	.62		.27		.28		.30	
50 100 150 L	.76		.74		.89		.95	
50 100 150 Q	.56		.97		.78		.79	
Pairwise vs. Placebo	Hr. 5		Hr. 23		Hr. 5		Hr. 23	
Pbo 150	.084		.035		.11		.24	
Pbo 100	.32		.062		.16		.16	
Pbo 50	.16		.073		.08		.23	
(a) Least Squares Means			L = Linear Component			$\Delta = .05 < p \leq .10$		
			Q = Quadratic Component			* = $p \leq .05$		
						** = $p \leq .01$		

Aldosterone levels generally decreased with losartan and enalapril treatment as table 5.11 illustrates. The magnitude of the change from baseline was less on day 5 as opposed to day 1.

Table 5.11. Serum Aldosterone (pg/mL)

Treatment	Mean ^(a) Changes from Day -1								
	Day 1				Day 5				
	Hr. 5		Hr. 23		Hr. 5		Hr. 23		
	N	Mean	N	Mean	N	Mean	N	Mean	
Placebo	23	-3.9	23	+9.1	22	+31.1	23	+55.7 Δ	
50 mg LOSARTAN	18	-96.9**	19	-16.5	19	-42.5 Δ	18	-8.7	
100 mg LOSARTAN	18	-87.4**	18	-49.0*	18	-36.6	18	-25.0	
150 mg LOSARTAN	20	-53.8**	20	-39.8 Δ	19	+7.7	20	-15.7	
10 mg Enalapril	18	-76.1	19	-32.3	17	-21.6	16	-30.9	
Dose Response	P-Values								
	Hr. 5		Hr. 23		Hr. 5		Hr. 23		
Pbo 50 100 150 L	.081		.047		.49		.088		
Pbo 50 100 150 Q	.0009		.40		.0066		.24		
50 100 150 L	.10		.43		.098		.88		
50 100 150 Q	.60		.42		.47		.74		
Pairwise vs. Placebo									
Pbo 150	.048		.082		.43		.092		
Pbo 100	.0016		.046		.026		.065		
Pbo 50	.0005		.37		.014		.14		
Pairwise vs. Enalapril									
150 E	.40		.80		.35		.74		
100 E	.67		.58		.63		.90		
50 E	.44		.59		.50		.64		
Pbo E	.0061		.15		.087		.057		
Mean Squared Error	6,407.7		8,141.6		8,472.0		18,155.5		
(a) Least Squares Means		L = Linear Component		Q = Quadratic Component		$\Delta = .05 < p \leq .10$		* = $p \leq .05$	
								** = $p \leq .01$	

Serum uric acid tended to decrease with losartan treatment as shown in Table 5.12. It is unclear whether this is a clinically meaningful change.

Table 5.12. Mean Uric Acid Labs

Variable	Treatment	Mean ^(a) Changes from Day -1						P-Values: Pairwise vs. Placebo		
		Day 2		Day 5		Day 6		Day 2	Day 5	Day 6
		N	Mean	N	Mean	N	Mean			
S. Uric Acid (mg/dl)	Placebo	23	-0.103	23	-0.153	23	-0.053			
	Losartan 50 mg	19	-.367**	19	-.945**	17	-.769**	0.0019	0.003	0.016
	Losartan 100 mg	17	-.287*	18	-1.133**	18	-.742**	0.27	0.0004	0.0019
	Losartan 150 mg	19	-.618**	19	-.944**	19	-.581**	0.1	0.0029	0.0017
	10 mg Enalapril	17	0.111	17	-0.129	16	-0.146	0.2	0.93	0.68
S. Uric Acid (mg/dl)	Dose Responses						P-Values			
	Pbo 50 100 150 L	0.0052		0.0026		1.025				
	Pbo 50 100 150 Q	0.78		0.011		0.0062				
	50 100 150 L	0.14		0.99		0.41				
	50 100 150 Q	0.18		0.43		0.74				
Pairwise vs. Enalapril										
	150	<.0001		0.0051		0.067				
	100	0.027		0.0097		0.014				
	50	0.007		0.0048		0.011				
	Mean Squared Error	0.2613		0.6833		0.4563				

(a) Least Squares Means; (b) Over 24 Hours; L = Linear Component; Q = Quadratic Component;
 $\Delta = .05 < p \leq .10$; * = $p \leq .05$; ** = $p \leq .01$

ACE activity was measured before patients received their first dose of study medication on day 1 and then five hours after the dose. Measurements were taken again on day 5, at one hour before and five hours after patients received their dose. Table 5.13 shows that the mean ACE activity after enalapril decreased and that there was essentially no change after losartan.

Table 5.13. ACE Activity

		Mean Changes from Baseline (Hr -1)						P-Values: Pairwise vs. Placebo		
		Day 1			Day 5			Day 1 Hour 5	Day 5 Hour -1	Day 5 Hour 5
		Hour 5		Hour -1		Hour 5				
		N	Mean	N	Mean	N	Mean			
ACE Activity (U/L)	Placebo	21	-4.1	21	-1.5	20	-3.3			
	Losartan 50 mg	18	-3.2	18	-1.9	18	-2.2	0.838	0.932	0.819
	Losartan 100 mg	17	-3	17	-0.6	17	-0.7	0.808	0.852	0.61
	Losartan 150 mg	20	-2.7	19	1.8	19	-4.3	0.737	0.467	0.842
	10 mg Enalapril	15	-30.9**	15	31.9**	15	-35.9**	0	0	0
	Mean Square Error		191.1		200.4		229.7			

(a) Least Squares Means

Within Treatment Change equal to zero: # = .010 < p < .100; * = p < .050; ** = p < .010

Safety

Table 5.14 lists three patients discontinued from the study due to adverse experiences. Patient #118 had standing heart rates generally in the 80's and 90's until day 4. The majority of standing heart rates on day 4 were greater than 100 with a maximum as high as 136 beats per minute. There was not a significant decline in blood pressure that could precipitate this increase in heart rate. Patient #039 had standing SBP on day -1 range from 117 to 180 and standing DBP range from 95 to 111 mmHg. On the day the patient complained of lightheadedness on standing, the standing DBP was as low as 72 mmHg and the standing SBP was as low as 112 mmHg. Standing blood pressures were not lower than supine blood pressures. Patient 124 had baseline standing blood pressures range from 141/89 to 191/108. On the first day of treatment with 10 mg of enalapril, the standing blood pressure was as low as 87/59 mmHg. Day 2 blood pressure data is not provided.

Table 5.14. Patients Discontinued Due to a Clinical Adverse Experience

Patient Allocation	Sex/Age	Drug	Relative Day of Onset	Adverse Experience	Duration	Severity	Outcome
0118	M/69	Placebo	4	Orthostatic tachycardia	12 hrs.	Moderate	Recovered
0039	F/68	Losartan 150 mg	2	Lightheadedness on standing	23.8 hrs.	Moderate	Recovered
0124	F/72	enalapril	1	Postural Hypotension	6 hrs.	Mild	Recovered

Table 5.15 lists the incidence of adverse experiences reported during the 6 day treatment period. Forty-eight percent of placebo and fifty-five to sixty percent of losartan patients complained of

Table 5.15. Clinical Adverse Experience Summary

Number (%) of Patients	Placebo (N=23)	Losartan 50 mg (N=20)	Losartan 100 mg (N=18)	Losartan 150 mg (N=20)	Enalapril 10 mg (N=19)
With any Clinical AE	11 (48)	12 (60)	10 (56)	11 (55)	12 (63)

A summary of clinical adverse experiences by body system, along with individual adverse experiences reported in at least two patients are summarized in Table 5.16. The most common adverse experience reported was headache. The incidence of headache was significantly higher in the losartan potassium 150 mg group (40%) than in the placebo group (13%). Dizziness was also common in the active treatment groups, with the losartan potassium 100 mg (28%) and enalapril 10 mg (37%) groups reporting significantly higher incidence than the placebo group (0%).

Table 5.16. Clinical Adverse Experiences by Body System and Individual Adverse Experiences Occurring in at Least Two Patients. () - % of patients with AE; [] - indicates number of Drug-Related Adverse Experiences

Adverse Experience	Placebo (N=23)			Losartan 50 mg (N=20)			Losartan 100 mg (N=18)			Losartan 150 mg (N=20)			Enalapril 10 mg (N=19)		
Body as a Whole	4	(17)	[2]	5	(25)	[1]	2	(11)	[2]	4	(20)	[3]	4	(21)	[3]
Asthenia	1	(4)	[0]	1	(5)	[0]	2	(11)	[2]	4	(20)	[2]	3	(16)	[2]
Cardiovascular	3	(13)	[3]	1	(5)	[1]	3	(17)	[3]	0	(0)	[0]	1	(5)	[0]
Tachycardia	3	(13)	[3]	1	(5)	[1]	3	(17)	[3]	0	(0)	[0]	0	(0)	[0]
Digestive	0	(0)	[0]	4*	(20)	[0]	2	(11)	[1]	3**	(15)	[1]	1	(5)	[0]
Nausea	0	(0)	[0]	1	(5)	[0]	1	(6)	[1]	2	(10)	[1]	1	(5)	[0]
Musculoskeletal/	3	(13)	[1]	2	(10)	[0]	1	(6)	[0]	1	(5)	[0]	1	(5)	[0]
Nervous System/															
Psychiatric	4	(17)	[2]	8	(40)	[4]	7	(39)	[4]	9 [#]	(45)	[5]	9*	(47)	[7]
Dizziness	0	(0)	[0]	0	(0)	[0]	5*	(28)	[4]	2	(10)	[2]	7**	(37)	[5]
Headache	3	(13)	[1]	7	(35)	[4]	5	(28)	[2]	8 [#]	(40)	[4]	7	(37)	[5]
Respiratory	1	(4)	[0]	0	(0)	[0]	2	(11)	[1]	1	(5)	[0]	2	(11)	[0]
Skin and Skin															
Appendage	2	(9)	[0]	2	(10)	[0]	2	(11)	[2]	1	(5)	[0]	3	(16)	[2]
Special Senses	1	(4)	[0]	0	(0)	[0]	1	(6)	[0]	1	(5)	[1]	2	(11)	[2]
Urogenital	0	(0)	[0]	1	(5)	[0]	1	(6)	[1]	0	(0)	[0]	0	(0)	[0]

[#] Difference from placebo noted, p≤0.100; *, ** Significant difference vs. placebo, p≤0.050, p≤0.010 respectively.

Note: This table contains counts of patients. If a patient reported a particular adverse experience more than once, the patient was counted only once with that adverse experience. If a patient had more than one adverse experience in a body system category, the patient was counted only once in the body system total.

Excluding mean changes in uric acid (see efficacy summary for study 005), there were no significant differences in mean changes of laboratory parameters from baseline. There is no trend in the number of patients with laboratory parameters outside pre-defined limits. There was no significant effect on ECG intervals at trough.

Study 011. A Double-Blind Randomized, Parallel, Placebo-Controlled Study to Investigate the Antihypertensive Efficacy and Safety of Different Doses of Losartan

Protocol

Design

This was a multicenter, randomized double-blind, placebo-controlled, parallel study in patients with mild to moderate essential hypertension (supine diastolic blood pressure 100-115 mmHg). The primary objective of the trial was to evaluate the antihypertensive efficacy of the AII antagonist losartan at different doses (10, 25, 50, 100 or 150 mg) as compared to placebo and 20 mg enalapril.

Inclusion Criteria

1. Mild to moderate uncomplicated essential hypertension characterized by an untreated supine diastolic blood pressure (suDBP) 100 to 115 mmHg. The patient's Prestudy (Day -29) suDBP must be >90 mmHg, Week -3 suDBP must be ≥95 mmHg, and the means of the Week -3 and Week -1 suDBP readings cannot vary from each other by more than 7 mmHg.
2. The patient is at least 21 years of age at the time of entrance into the baseline period.
3. The patient is within 30% of ideal weight for his/her height and body build 4. The patient has no active medical problems other than essential hypertension, that might of themselves or their treatment affect blood pressure.
5. The patient is receiving no drug therapy that might affect blood pressure.
6. The patient's prestudy laboratory screen shows no clinically important abnormalities.
7. No more than 25% of the patient population studied at each site can be Black (3 of 14 patients).

Exclusion Criteria

1. Prior exposure to losartan.
2. Secondary hypertension of any etiology, such as unilateral or bilateral renal disease, coarctation of the aorta or pheochromocytoma. History of malignant hypertension. Supine systolic blood pressure >210 mmHg.
3. History of cerebrovascular accident (stroke) or history of transient ischemic attacks.
4. Documented history of myocardial infarction or angina pectoris (prior or active).
5. Clinically significant AV conduction disturbance, i.e., second- or third-degree AV block, or left bundle branch block. Sick-sinus syndrome or clinically significant bradycardia (resting heart rate <45 beats/minute).
6. Atrial flutter or atrial fibrillation and an accessory bypass tract (e.g., Stokes-Adams Syndrome or Wolff-Parkinson-White Syndrome).
7. History of congestive heart failure or a known left ventricular ejection fraction <40%.
8. Prior known sensitivity to ACE inhibitors.
9. Concomitant use of β-blockers (excluding ophthalmic preparations) or digitalis, or any agent that may cause a lowering of blood pressure (e.g. diuretics, angiotensin converting enzyme inhibitors, nitrates, calcium channel blockers) is not permitted.

during the study. Patients taking major psychotropic agents or anti-depressants will be excluded. Regular use of nonsteroidal anti-inflammatory agents (NSAIDs) and high-dose aspirin are not permitted. Acetaminophen is permitted. One or two aspirins taken regularly as a cardioprotective agent is permitted.

10. Evidence of significant renal or hepatic dysfunction as indicated by history or recent laboratory:

BUN	>35 mg/dl
Serum Creatinine	>1.7 mg/dl
Proteinuria	>TRACF
SGPT/SGOT	>50% above normal

11. Clinically significant laboratory values outside of the established normal range including but not limited to any of the following parameters: hematocrit, hemoglobin, platelet count or white blood count.

12. White blood count below 3000 mm^3 , platelet count below $100,000 \text{ mm}^3$.

13. Serum potassium <3.5 or $>5.5 \text{ mEq/L}$.

14. Known positive test for AIDS (positive HIV) or Hepatitis B surface antigen.

15. History of clinically important malabsorption or gastrointestinal resection.

16. Patients being treated for acute ulcer disease. The H_2 -antagonists, famotidine or ranitidine are allowed on a PRN basis.

17. History of chronic liver disease.

18. Actively treated diabetes mellitus. Fasting glucose levels up to 150 mg/dl will be permitted.

19. Other concurrent severe disease, such as neoplasm which could preclude participation or survival.

20. Any known bleeding or platelet disorder.

21. The absence of one kidney.

22. Women of childbearing potential or who are currently breastfeeding, i.e., those who are not postmenopausal or have not been surgically sterilized; (postmenopausal women receiving chronic estrogen treatment are allowed. The dose should be kept constant).

23. The patient is currently abusing or has a history of alcoholism, drug addiction, or abuse of other substances.

24. Mentally or legally incapacitated patients.

25. Patient has participated in another drug trial, including one using marketed drugs, within the 28 days prior to initiation of placebo baseline.

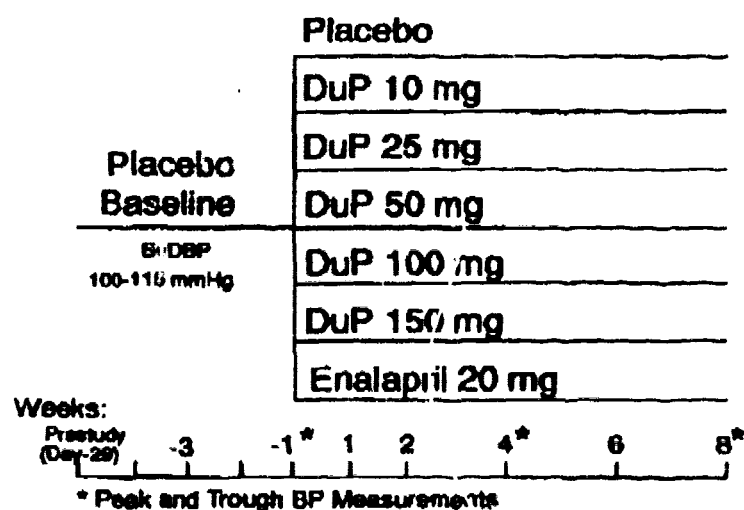
26. Patients who, in the opinion of the investigator, will not cooperate fully, keep appointments or are generally unreliable.

27. Patients who will not be able to complete the study due to economic or social problems.

Study Description

The trial consisted of a two to four week single-blind placebo period and a double-blind 8 week treatment period. Prior to entry into the study, the patient's prestudy (Day -29) supine diastolic blood pressure (suDBP) had to be $> 90 \text{ mmHg}$. All antihypertensive medications were discontinued, and the patients were given placebo for 2 weeks (Weeks -4 through -3). After 2 weeks of placebo therapy, the patient's Week -3 suDBP had to be $\geq 95 \text{ mmHg}$ in order for the patient to continue with the final 2 weeks of placebo baseline therapy (Weeks -2 through -1). If at the end of the 4-week placebo baseline period a patient's suDBP was 100 to 115 mmHg and the means of the Week -3 and Week -1 suDBP readings did not vary from each other by more than 7 mmHg, the patient entered the 8-week treatment period (Weeks 1 through 8). If during the placebo baseline period the patient's suDBP exceeded 115 mmHg at any visit, then the investigator could enter the patient into the active-treatment period. Patients were randomized to one of seven possible treatment groups as outlined in figure 11.1.

FIGURE 11.1 Study Outline (DuP = Losartan).



Patients could, at the investigator's discretion, be randomized after 2 weeks of placebo provided there are at least 2 sets of blood pressure data within the acceptable range (suDBP 110-115 mmHg), not less than 3 days apart, and the difference between the readings is ≤ 7 mmHg. If during the placebo baseline period the patient's suDBP exceeds 115 mmHg at any visit, the patient should not be entered into the active-treatment period. If during the active-treatment period the supine DBP is inadequately controlled (supine DBP >120 mmHg or a rise of >15 mmHg from baseline on two successive measurements separated by at least 3 days), the investigator could discontinue the patient from the study and provide alternative therapy. At the end of the 8-week double-blind treatment phase, centers could elect to participate in an open-label extension phase of the study, which was ongoing. Results from the open-label extension will be presented as a separate clinical study report.

Primary Objectives

A. To investigate the antihypertensive efficacy, safety (clinical and laboratory), and dose response relationship of Losartan compared to placebo. Week 8 supine diastolic blood pressure 24 hours postdose results will be used as primary efficacy determinants.

Secondary Objectives

- B. To investigate the length of time (weeks) on drug necessary to establish a stable reduction in blood pressure.
- C. To investigate the safety and antihypertensive efficacy of Losartan at various doses in the following subsets of the patient population studied.
- Elderly (≥ 65 years) vs. young (<65 years)
 - Non-black vs. Black
 - Male vs. Female
 - Mild (100-105 mmHg suDBP) vs. Moderate (106-115 mmHg suDBP)
- D. To investigate the antihypertensive efficacy of various doses of Losartan in the patient population studied stratified by the patients' predose ambulatory renin status (PRA levels).
- E. To investigate the effects of Losartan on metabolic parameters (glucose, sodium, potassium, creatinine, uric acid, HDL and total cholesterol).
- F. To investigate the trough to peak ratio of antihypertensive efficacy.
- G. To investigate the safety and efficacy of Losartan compared to enalapril (20 mg).
- H. To determine an ineffective dose of Losartan.

Statistical Analysis

Efficacy Analyses was performed using the "All-Patients-Treated" and "Per-Protocol" analysis. The "all patients treated" analysis included all patients with at least one treatment period measurement. The last measurements of withdrawn patients were carried forward to subsequent timepoints. For patients with data missing from a visit, the missing data is estimated by carrying forward data from the last visit at which it was available (excluding the baseline visit). For the "per protocol" analysis, patients with protocol violations are excluded. Patients who withdraw prior to an analyzed timepoint are not included.

The sample size estimation provided in the protocol is quite confusing and difficult to interpret as illustrated in table 11.1.

Table 11.1. Sample Size Estimation

Approximately 40 sites will be used to enter a total of up to 840 patients; at least 357 (51 per treatment group) are expected to complete the study. Assuming a standard deviation of 9 mmHg or less, 51 patients per treatment group will be sufficient to detect a 5 mmHg difference between the treatments with the highest and lowest responses; i.e., in mean reduction in suDBP with 80% probability at the 5% level of significance (two-sided test).

If 420 (504) patients complete the study, 60 (72) patients per treatment group will be sufficient to detect a 5 mmHg difference in mean reduction in suDBP between the treatments with the highest and lowest responses with 86% (92%) probability at the 5% level of significance (two-sided test).

The sample size (51 per group) will also provide approximately 95% power for detecting a slope of -2 mmHg for the regression of change from baseline in suDBP on the log of Losartan dose; i.e., to detect a 2 mmHg decrease with each doubling of the dose. This statement assumes a standard deviation in change from baseline in suDBP of 9 mmHg for a one-sided, 5% level of significance test. It is believed that a slope of this magnitude would indicate a dose-response relationship.

Outline of Procedures

Table 11.1a outlines the procedures performed during the trial.

Table 11.1a. Clinical and Laboratory Measurements

Procedure	Study Week							
	Baseline			Treatment				
	Prestudy	-3	-1	1	2	4	6	8
Medical History	X							
Complete Physical Exam	X							X
Body Weight	X	X	X	X	X	X	X	X
Trough BP and HR ¹	X	X	X	X	X	X	X	X
Peak BP and HR ¹			X			X		X
Chest X-ray ²		X						
Fasting Laboratory		X			X	X		X
12-lead ECG		X			X			X
"Peak time" PRA			X					X
Plasma Drug Levels								X

1 = Measurements made in both the supine and standing positions. 2 = Unless x-ray from 1 year period prior to study participation was available for review

Trough supine and standing blood pressure and heart rate were measured at the beginning of every clinic visit, 22-26 hours post the previous day's dose of medication. Peak supine and standing blood pressure and heart rate were also measured 5-6 hours post that day's dose of study medication at Weeks -1, 4 and 8, as indicated in Table 1.

The pulse rate over at least 30 seconds was taken after 5 minutes in the supine position and again after 2 minutes in the standing position, prior to blood pressure measurement.

Ambulatory plasma renin activity (PRA) was measured in samples obtained from patients at peak clinic visits at Weeks -1 and 81. Prior to venipuncture, the patient had to remain ambulatory for at least 30 minutes.

Results

A planned interim analysis of this study consisting of data summarizations was performed when approximately 40% of the patients in the final analysis had completed the double-blind phase. This analysis was for the purpose of selecting doses for future hypertension studies and included summarizations of blood pressure, adverse experience information and laboratory test results. Two additional blood pressure summarizations [Reviewer's Note: These additional analysis were not pre-specified.] occurred for the same purpose as noted above when approximately 60% and 90% (study was complete at this point, but not all data were available) of the double-blind data were available. The study remained blinded (patient-treatment assignments were not reported) until validation of the data was complete. No adjustments to final statistical p-values were made. [Reviewer's Note: Enrollment for this trial was complete by the time the first interim analysis was performed. (Information obtained from Larry Bell on 1/11/95)]

Demographics/Patient Disposition

Five hundred and seventy-six patients were randomized to 41 centers. A listing of investigators can be found in the appendix. The number of patients screened during the baseline period is not provided. The number of patients randomized per treatment group ranged from 78 - 90. Table 11.2 summarizes the demographic parameters among treatment groups. The mean age was 53 years. Two-thirds of the patients were male. The percentage of black patients in each treatment group ranged from 6% to 19%. The percentage of hispanic patients ranged from 6% to 14% per treatment group.

Table 11.2. Baseline Patient Demographic Characteristics

	PBO (N=78)	Losartan						Total (N=576)
		10 (N=80)	25 (N=82)	50 (N=79)	100 (N=90)	150 (N=84)	ENAL 20 (N=83)	
Sex								
Female	31 (40%)	29 (36%)	27 (33%)	26 (33%)	31 (34%)	22 (26%)	27 (33%)	193 (34%)
Male	47 (60%)	51 (64%)	55 (67%)	53 (67%)	59 (66%)	62 (74%)	56 (67%)	383 (66%)
Age (Years)								
Mean	52.3	53.9	52.8	52.8	54.0	53.9	51.9	53.1
S.D.	11.6	12.3	12.2	10.3	10.2	10.8	11.1	11.2
Median	53.0	55.0	53.0	53.0	52.5	56.0	53.0	53.0
Range	28-77	22-88	25-76	27-73	29-75	29-77	27-73	22-88
Racial Origin								
Caucasian	64 (82%)	60 (75%)	63 (77%)	57 (72%)	66 (73%)	64 (76%)	64 (77%)	438 (76%)
Black	5 (6%)	10 (13%)	14 (17%)*	11 (14%)	17 (19%)*	11 (13%)	7 (8%)	75 (13%)
Hispanic	9 (12%)	9 (11%)	5 (6%)	11 (14%)	7 (8%)	8 (10%)	10 (12%)	59 (10%)
Other	0	1 (1%)	0	0	0	1 (1%)	2 (2%)	4 (1%)
Duration of Hypertension (years)								
<1	3 (4%)	5 (6%)	2 (2%)	3 (4%)	2 (2%)	3 (4%)	5 (6%)	23 (4%)
1-5	11 (14%)	13 (16%)	27 (33%)	25 (32%)	22 (24%)	24 (29%)	23 (28%)	145 (25%)
5.01-10	29 (37%)	21 (26%)	21 (26%)	17 (22%)	26 (29%)	19 (23%)	24 (29%)	157 (27%)
>10	35 (45%)	41 (51%)	32 (39%)	33 (42%)	39 (43%)	38 (45%)	31 (37%)	249 (43%)
Unknown	0	0	0	1 (1%)	1 (1%)	0	0	2 (0%)
Mean	11.9	11.6	10.0	10.1	10.7	9.8	9.8	10.5
S.D.	8.8	8.4	7.4	7.8	7.1	6.7	7.5	7.7
Median	10.0	10.3	8.3	7.5	10.0	10.0	8.5	10.0
Range	0.5-44	0.1-46	0.6-30	0.1-35	0.5-32	0.1-28	0.1-36	0.1-46
Supine Diastolic Blood Pressure (mmHg)								
<105 (mild)	61 (78%)	57 (71%)	64 (78%)	58 (73%)	65 (72%)	66 (79%)	68 (82%)	439 (76%)
>105 (moderate)	17 (22%)	23 (29%)	18 (22%)	21 (27%)	25 (28%)	18 (21%)	15 (18%)	137 (24%)
Mean	103.3	104.3	103.3	104.0	104.1	103.4	103.1	103.7
S.D.	3.8	3.9	3.7	3.7	4.2	3.4	3.7	3.8
Median	102.0	103.0	102.0	103.0	103.0	102.0	101.0	102.0
Range	100-113	100-115	100-114	100-115	99-115	100-114	100-115	99-115

* Statistically significantly different from PLACEBO treatment group, p<0.05

Fifty patients withdrew prematurely during the 8 weeks of double blind therapy. The number of dropouts ranged from 3 to 11 per treatment group. Discontinuations due to adverse experiences are divided into clinical adverse experience, laboratory adverse experience and both. A total of 14 patients withdrew due to adverse experiences. Eleven patients are listed as simply "patient withdrew". Six withdrew in the losartan 100 mg group for this reason. Six patients were lost to follow-up. Three hundred and seven patients continued into the open label follow-up study. A listing of patients withdrawn prematurely can be found in the appendix. Table 11.3 lists the number of patients discontinued based on treatment.

Table 11.3. Patient Accounting

	PBO (N=78)	Losartan						ENAL 20 (N=83)
		10 (N=80)	25 (N=82)	50 (N=79)	100 (N=90)	150 (N=84)		
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Completed DB/No OL	28 (35.9)	31 (38.7)	37 (45.1)	33 (41.8)	32 (35.6)	30 (35.7)	31 (37.3)	
Completed DB/ Entered OL	39 (50.0)	41 (51.3)	38 (46.3)	43 (54.4)	48 (53.3)	47 (56.0)	48 (57.8)	
Discontinued DB Prematurely	11 (14.1)	8 (10.0)	7 (8.5)	3 (3.8) ^a	10 (11.1)	7 (8.3)	4 (4.8)	
Clinical Adverse Experience	0	2 (2.5)	1 (1.2)	1 (1.3)	1 (1.1)	3* (3.6)	1* (1.2)	
Laboratory Adverse Experience	2 (2.6)	0	1 (1.2)	0	0	0	1 (1.2)	
Clinical & Laboratory AE	0	0	0	0	0	1 (1.2)	0	
Therapy Ineffective	3 (3.8)	5* (6.3)	2 (2.4)	0	0 ^b	3 (3.6)	0 ^b	
Patient Uncooperative	2 (2.6)	0	0	0	1 (1.1)	0	0	
Patient Withdrew	2 (2.6)	1 (1.3)	1 (1.2)	0 ^c	6 (6.7)	0 ^c	1 (1.2)	
Protocol Deviation	0	0	1 (1.2)	1 (1.3)	1 (1.1)	0	0	
Lost to Follow-up	2 (2.6)	0	1 (1.2)	1 (1.3)	1 (1.1)	0	1 (1.2)	

* One patient in this treatment group continued into the extension period of the study after discontinuing the double-blind phase.

^a: Statistically significantly different from PBO treatment group, p<0.05.; DB = Double Blind Phase^b: Statistically significantly different from LOS 10 treatment group, p<0.05.; OL = Open Label Phase^c: Statistically significantly different from LOS 100 treatment group, p<0.05.

Supine Blood Pressure Changes - Trough and Peak

Three patients, # 376 (losartan 50 mg; lost to follow up), #190 (losartan 100 mg; protocol deviation) and #124 (enalapril; patient withdrew), did not have any treatment period blood pressure measurements and could not be included in the "all-patients-treated" analysis.

The mean change in trough supine diastolic blood pressure at week 8 is listed in table 11.4. [NOTE Adjusted means (for baseline DBP and clinic) are provided in this table since baseline was included as a covariate in the model and the pairwise comparisons were based upon these adjusted means]. Although losartan 10 mg showed a significant difference from placebo, the relative change was only 2.3 mmHg. This difference was numerically greater than the difference between losartan 25 mg and placebo. There is no difference in treatment effect between losartan 50 mg, 100 mg and 150 mg. Enalapril was not significantly different from the three highest doses of losartan.

Table 11.4. Mean Change in Trough Supine Diastolic Blood Pressure at Week 8. (All-Patients-Treated Approach)

Treatment	N	Baseline		Treatment		Change		Change Adj Mean	Comparison					
		Mean	S.D	Mean	S.D.	Mean	S.D.		VS. B	VS. C	VS. D	VS. E	VS. F	VS. G
Placebo (A)	78	103.3	3.8	97.8	8.8	-5.6	7.8	-5.3	*	NS	**	**	**	**
LOS 10 (B)	80	104.3	3.9	96.3	9.7	-7.9	7.6	-7.8	--	NS	*	NS	NS	**
LOS 25 (C)	82	103.3	3.7	96.5	9.5	-6.8	7.9	-6.4	--	--	**	**	**	**
LOS 50 (D)	78	104.1	3.7	94	8.5	-10.1	7	-10.1	--	--	--	NS	NS	NS
LOS 100 (E)	89	104.1	4.3	94.2	8	-9.9	6.9	-9.9	--	--	--	--	NS	NS
LOS 150 (F)	84	103.4	3.4	93.7	9.4	-9.7	8	-9.5	--	--	--	--	--	NS
ENAL 20 (G)	82	103.1	3.8	91.9	8.2	-11.2	6.7	-10.8	--	--	--	--	--	--

NS -- Not statistically significant, * -- Treatment difference statistically significant, $p < 0.05$; ** -- Treatment difference statistically significant, $p < 0.01$

Table 11.5 lists the change in supine systolic blood pressure. Losartan doses greater than 25 mg are significantly different from placebo. There is no dose response with losartan.

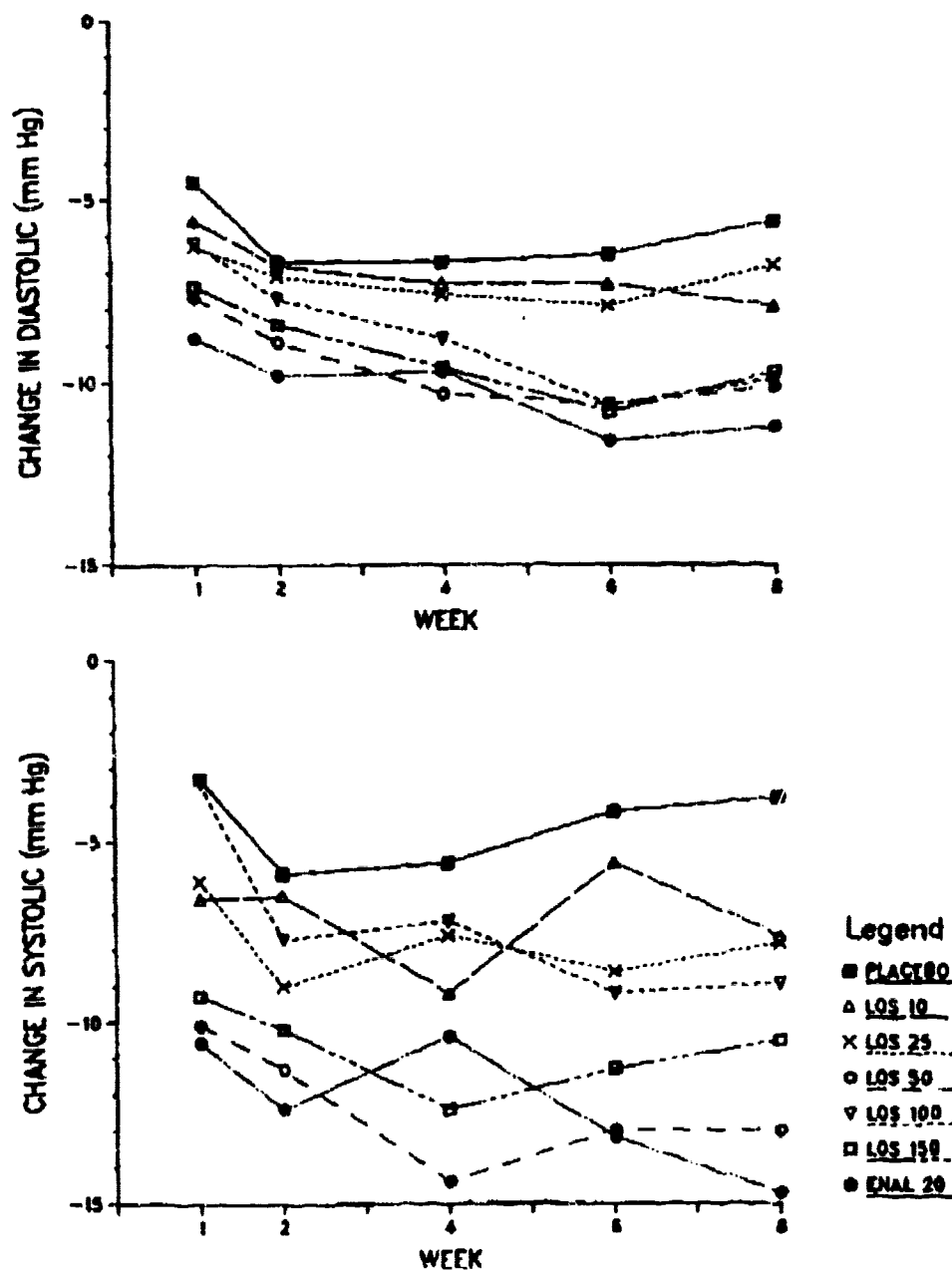
Table 11.5. Mean Change in Trough Supine Systolic Blood Pressure at Week 8 (All-Patients-Treated Approach)

Treatment	N	Baseline		Treatment		Change		Change Adj Mean	Comparison					
		Mean	S.D	Mean	S.D.	Mean	S.D.		VS. B	VS. C	VS. D	VS. E	VS. F	S. G
Placebo (A)	78	157.9	14.5	154.1	17.7	-3.8	11.7	-3.9	NS	*	**	**	**	**
LOS 10 (B)	80	160.7	16.7	153.1	19.2	-7.6	12.6	-6.7	--	NS	**	NS	NS	**
LOS 25 (C)	82	158.7	16.2	151	18.7	-7.8	13.8	-7.9	--	--	**	NS	NS	**
LOS 50 (D)	78	158.3	14.9	145.3	15.4	-13	12.7	-13.2	--	--	--	NS	NS	NS
LOS 100 (E)	89	156.3	16.6	147.4	16.7	-8.9	13.6	-9.4	--	--	--	--	NS	**
LOS 150 (F)	84	158.6	16	148	18.5	-10.5	13.3	-10.5	--	--	--	--	--	*
ENAL 20 (G)	82	155.4	14.9	140.7	17.3	-14.7	13.6	-15.4	--	--	--	--	--	--

NS -- Not statistically significant, * -- Treatment difference statistically significant, $p < 0.05$; ** -- Treatment difference statistically significant, $p < 0.01$

The maximum effect on suDBP appears to stabilize after 6 weeks of therapy as shown in figure 11.2. The effect on suSBP stabilizes after 4 weeks of therapy.

Figure 11.2. Mean Change in Trough Supine Blood Pressures by Week (All-Patients-Treated Approach)



The "per-protocol" analysis for trough suDBP at week 8 was similar to the "all-patients-treated" approach.

Peak supine and standing blood pressures were obtained approximately 6 hours post dosing. Tables 11.6 and 11.7 list the mean change in peak supine DBP and SBP at week 8. Enalapril had a significantly greater effect on week 8 supine DBP at peak compared to any dose of losartan. Paradoxically, losartan 150 mg had a significantly greater effect on week 8 supine DBP than losartan 100 mg but not losartan 50 mg.

Table 11.6. Mean Change in Peak Supine Diastolic Blood Pressure at Week 8 (All-Patients-Treated Approach)

Treatment	N	Baseline		Treatment		Change		Change Adj Mean	Comparison						
		Mean	S.D.	Mean	S.D.	Mean	S.D.		VS. B	VS. C	VS. D	VS. E	VS. F	VS. G	
Placebo (A)	75	99.0	5.5	94.4	8.9	-4.7	8.7	-4.7	NS	**	**	**	**	**	**
LOS 10 (B)	79	99.8	6.0	92.5	10.3	-7.3	9.4	-7.3	--	NS	**	*	**	**	**
LOS 25 (C)	80	100.2	5.4	90.3	10.3	-9.9	8.5	-9.7	--	--	NS	NS	*	**	**
LOS 50 (D)	77	100.1	6.4	88.3	10.3	-11.9	9.2	-12.0	--	--	--	NS	NS	**	**
LOS 100 (E)	87	100.5	6.7	90.1	9.2	-10.4	8.9	-10.3	--	--	--	--	*	**	**
LOS 150 (F)	81	99.9	6.4	86.8	10.7	-13.1	9.0	-13.1	--	--	--	--	--	*	**
ENAL 20 (G)	82	100.4	6.2	84.2	10.1	-16.2	10.4	-16.0	--	--	--	--	--	--	--

NS -- Not statistically significant; * -- Treatment difference statistically significant, $p \leq 0.05$; ** -- Treatment difference statistically significant, $p \leq 0.01$.

Table 11.7. Mean Change in Peak Supine Systolic Blood Pressure at Week 8 (All-Patients-Treated Approach)

Treatment	N	Baseline		Treatment		Change		Change Adj Mean	Comparison						
		Mean	S.D.	Mean	S.D.	Mean	S.D.		VS. B	VS. C	VS. D	VS. E	VS. F	VS. G	
Placebo (A)	75	152.1	12.9	151.3	15.9	-0.8	12.0	-1.2	**	**	**	**	**	**	**
LOS 10 (B)	79	157.4	15.3	148.9	18.1	-8.5	14.5	-7.6	--	NS	**	*	**	**	**
LOS 25 (C)	80	155.0	16.1	143.4	17.3	-11.6	14.5	-11.5	--	--	NS	NS	NS	**	**
LOS 50 (D)	77	154.6	13.6	139.9	15.1	-14.7	11.8	-14.6	--	--	--	NS	NS	*	**
LOS 100 (E)	87	154.5	15.4	142.2	16.8	-12.3	14.4	-12.2	--	--	--	--	NS	**	**
LOS 150 (F)	81	152.1	15.1	138.6	18.0	-13.5	11.9	-14.2	--	--	--	--	--	*	**
ENAL 20 (G)	82	152.9	15.8	134.2	16.6	-18.7	15.4	-18.9	--	--	--	--	--	--	--

NS -- Not statistically significant; * -- Treatment difference statistically significant, $p \leq 0.05$; ** -- Treatment difference statistically significant, $p \leq 0.01$.

The trough/peak ratio was obtained by using the mean adjusted change in supine DBP at week 8 (placebo subtracted; carry forward analysis; from table 10 and 17 of the clinical summary report). The results are depicted in figure 11.3 and table 11.8. The ratio for 50 - 150 mg of losartan is $\geq$ to .5.

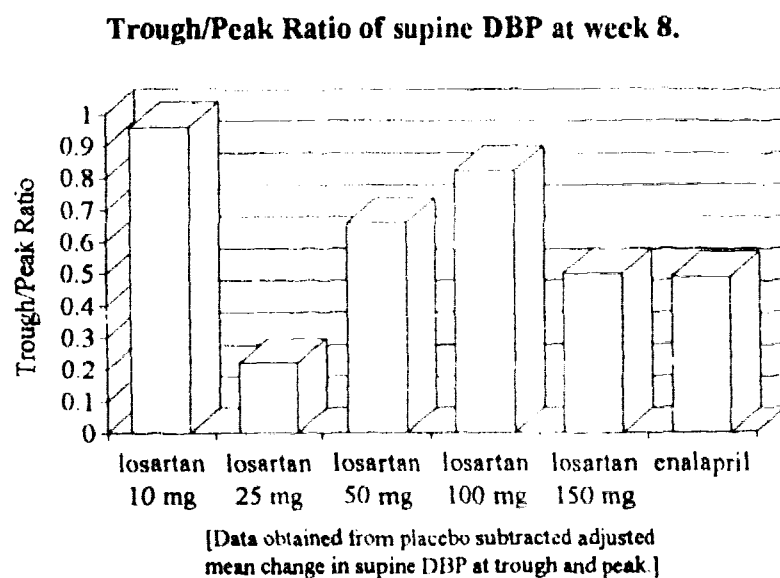
Figure 11.3. Supine DBP Trough/Peak Ratio at week 8.

Table 11.8. Trough-to-Peak Ratios for Supine Diastolic Blood Pressure at Week

N	Treatment	Mean Change (mmHg)		T:P Ratio	T:P Ratio (PBO Adjusted)
	Group	Trough	Peak		
75	Placebo	-5.8	-4.7	125%	—
79	LOS 10	-7.9	-7.3	108%	78%
80	LOS 25	-7.0	-9.9	71%	23%
77	LOS 50	-10.2	-11.9	86%	60%
86	LOS 100	-10.0	-10.5	95%	72%
81	LOS 150	-10.0	-13.1	76%	49%
82	ENAL 20	-11.2	-16.2	69%	47%

NOTE: Only patients with both trough and peak measurements were included in this table.

Mean changes in peak blood pressures for the "per-protocol" approach were similar to those obtained for the "all-patients-treated" approach.

Subgroup Analysis - Supine DBP

Subgroup analysis of suDBP was performed on patients based on gender, age and race. In figure 11.4 and table 11.9, the carry forward analysis of suDBP (placebo subtracted) based on gender suggests that in female patients the 100 and 150 mg doses of losartan are less effective than the 50 mg dose. However, these results are not statistically different. Each treatment group was comprised of approximately one-third women. The carry forward result is similar to the non-carry forward analysis (Reviewer's Note: The non-carry forward analysis includes only suDBP measurements available at week 8.).

Figure 11.4

Mean Change in suDBP by gender at week 8.

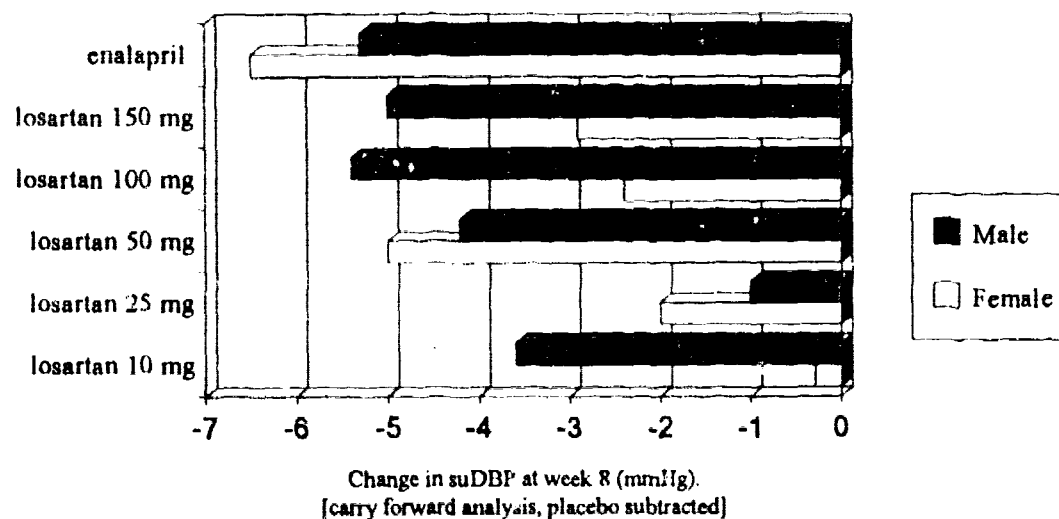


Table 11.9. Mean Change in Trough Supine Diastolic Blood Pressure at Week 8 by Sex (All-Patients-Treated Approach)

Sex	Treatment	N	Baseline Mean	Treatment Mean	Change Mean	95% Confidence Interval for Mean Change
Female	Placebo	31	102.4	96.0	-6.5	(-9.0, -4.0)
	LOS 10	29	104.7	97.9	-6.8	(-9.2, -4.4)
	LOS 25	27	102.8	94.3	-8.5	(-11.5, -5.5)
	LOS 50	25	103.2	91.6	-11.5	(-14.0, -9.0)
	LOS 100	31	103.1	94.2	-8.9	(-11.6, -6.2)
	LOS 150	22	103.0	93.6	-9.4	(-12.4, -6.4)
	ENAL 20	27	102.8	89.8	-13.0	(-15.8, -10.2)
Male	Placebo	47	104.0	99.0	-5.0	(-7.4, -2.6)
	LOS 10	51	104.0	95.4	-8.6	(-10.8, -6.4)
	LOS 25	55	103.6	97.6	-6.0	(-8.1, -3.9)
	LOS 50	53	104.5	95.1	-9.4	(-11.3, -7.5)
	LOS 100	58	104.6	94.2	-10.4	(-12.0, -8.8)
	LOS 150	62	103.5	93.7	-9.8	(-11.9, -7.7)
	ENAL 20	55	103.3	93.0	-10.3	(-12.0, -8.6)

The mean change in suDBP (placebo subtracted, carry forward analysis) at week 8 based on race is depicted in figure 11.5. The analysis is limited by the small number of patients in some black and hispanic patient treatment groups. The black treatment groups ranged in size from 5 to 17 patients. The hispanic treatment group ranged in size from 7 to 11 patients. An analysis that did not include carry forward data showed even less of a treatment effect in black patients. Table 11.9a shows the non-carry forward analysis of the change from baseline in suDBP at week 8 in black patients compared to the carry forward analysis. Losartan therapy is essentially no different from placebo. The major limiting factor in concluding anything from the race subgroup analysis is that only 5 black patients were randomized into the placebo group.

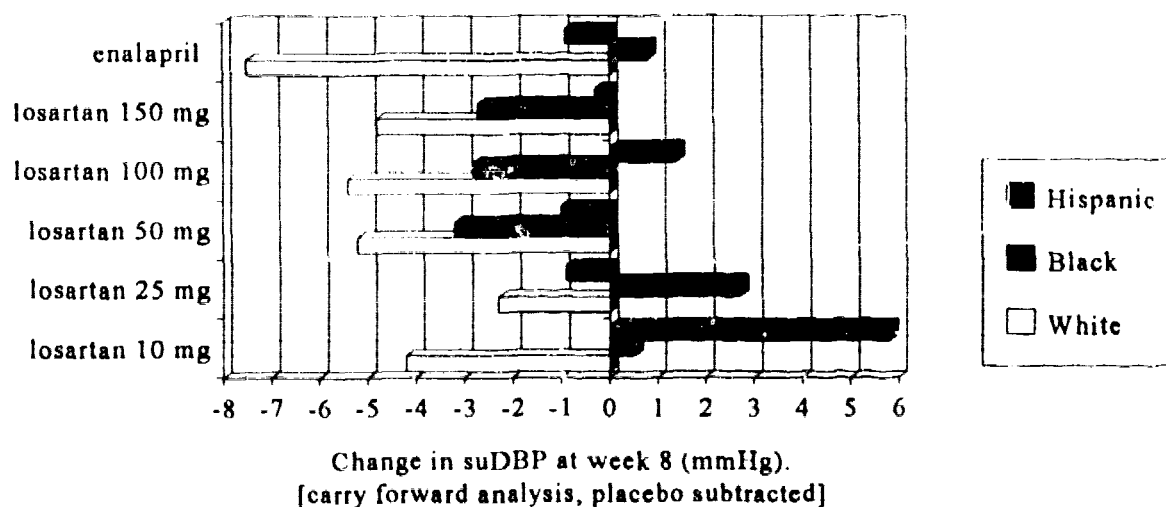
Figure 11.5.**Change in suDBP by Race at week 8.**

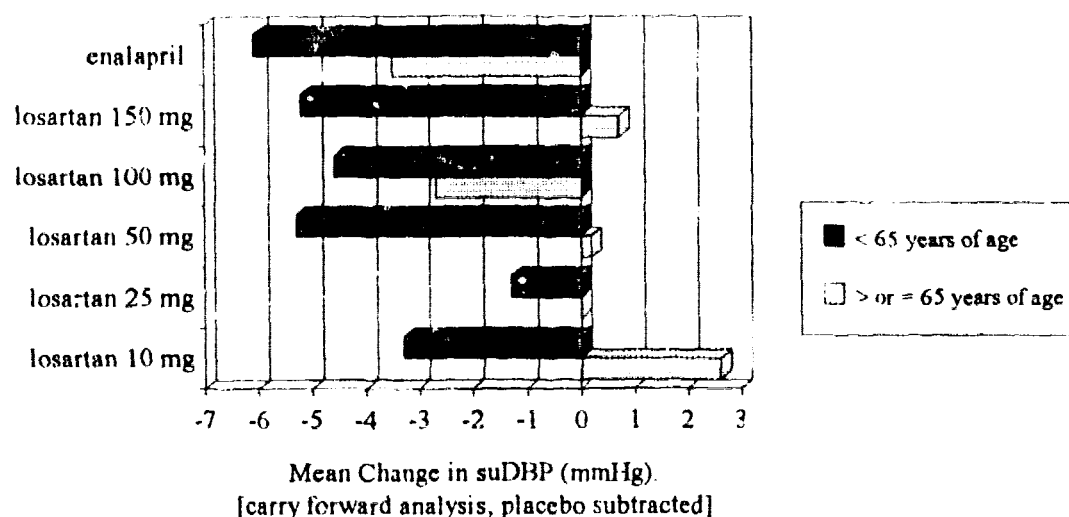
Table 11.9a. Change in supine DBP in black patients at week 8

Treatment	N	Change in suDBP (S.D.) [mm Hg] (non-carry forward analysis)*	Placebo Subtracted Change in suDBP [mm Hg] (non-carry forward analysis)	N	Change in suDBP (S.D.) [mm Hg] (carry forward analysis)**	Placebo Subtracted Change in suDBP [mm Hg] (carry forward analysis)
placebo	4	-7.5 (4.5)	-	5	-5.2	-
enalapril	7	-4.4 (8.3)	3.1	7	-4.4	.8
losartan 10 mg	9	-4.3 (7.8)	3.2	10	-4.7	.5
losartan 25 mg	12	-3.7 (7.2)	3.8	14	-2.7	2.5
losartan 50 mg	10	-8.4 (6.0)	-0.9	10	-8.4	-3.2
losartan 100 mg	13	-8.0 (6.6)	-0.5	17	-8.0	-2.8
losartan 150 mg	9	-8.3 (9.8)	-0.8	11	-7.5	-2.3

* obtained from the CANADA database by eliminating carry-forward data

** obtained from the sponsor's clinical summary report page 48, table 13

Figure 11.6 depicts the change in suDBP based on age. For patients ≥ 65 years of age, 11 to 18 were present in each treatment group. Patients ≥ 65 years of age responded poorly to losartan in this study.

Figure 11.6.**Mean Change in suDBP by Age at Week 8.**

In general, patients with moderate hypertension (DBP > 105 mmHg) had less of an anti-hypertensive effect compared to patients with mild hypertension (DBP < 105 mmHg) in all treatment groups (placebo excluded).

Adverse Experience

No patients died during this phase of the study. A summary of overall clinical adverse experiences (AEs) is given in Table 11.10. There appeared to be no dose-related trend for losartan with respect to the percentage of patients with one or more AE.

Table 11.10. Clinical Adverse Experience Summary

	PBO	Losartan 10	Losartan 25	Losartan 50	Losartan 100	Losartan 150	ENAL 20
Number of Patients Randomized	N=78	N=80	N=82	N=79	N=90	N=84	N=83
With One or More AE	40 (51%)*	38 (48%)	40 (49%)	32 (41%)	32 (36%)	46 (55%)*	39 (47%)
With Serious AE	1 (1%)	1 (1%)	0	0	0	2 (2%)	0
Withdrawn Due to AE	0	2 (3%)	1 (1%)	1 (1%)	1 (1%)	4** (5%)	1 (1%)

* Statistically significantly different from LOSARTAN 100 treatment group, $p < 0.05$, ** AN 548 discontinued due to a clinical and a laboratory adverse experience.

Interpretation of each individual adverse event is difficult. Table 11.10a list the adverse events that occurred in greater than 1% of the patients randomized. Cough occurred most often in patients on enalapril (8%) compared to losartan (4%) and placebo (1%). Patient #667 (enalapril) was discontinued due to cough. Dizziness and vertigo was not reported in the placebo patients but was reported by 8 (2%) and 6 (1%) of losartan patients respectively.

Table 11.10a. Adverse Events in > 1% of Patients Randomized

	losartan 10 mg	losartan 25 mg	losartan 50 mg	losartan 100 mg	losartan 150 mg	enalapril 20 mg	placebo	total
ALT INCREASED	3	2	0	5	3	1	3	17
AST INCREASED	2	2	0	1	1	1	1	8
ASTHENIA/FATIGUE	3	2	3	3	4	5	5	25
CONGESTION, NASAL	0	1	4	1	3	0	0	9
COUGH	5	2	2	2	3	7	1	22
DIARRHEA	2	0	3	1	2	4	2	15
DIZZINESS	2	1	2	0	2	0	2	9
DYSPEPSIA	1	0	0	1	3	1	0	6
FLUSHING	0	0	0	1	3	1	1	6
HEADACHE	11	15	10	8	11	8	10	73
HEMATURIA	0	0	2	2	1	2	0	7
URI	1	9	2	7	7	9	7	42
INSOMNIA	1	2	2	1	0	0	0	6
NAUSEA	1	1	0	1	0	2	5	10
ORTHOSTATIC EFFECTS	0	0	2	3	3	0	0	8
PAIN, ABDOMINAL	3	0	1	2	1	1	2	10
PAIN, BACK	3	0	2	0	2	1	2	10
PAIN, CHEST	1	2	0	1	1	1	3	9
PAIN, LEG	2	1	2	0	0	1	0	6
PHARYNGITIS	1	1	3	1	0	2	2	10
PROTEINURIA	1	0	2	1	0	2	2	8
PYURIA	1	1	0	1	2	0	1	6
VERTIGO	1	1	0	2	2	0	0	6

Table 11.10b. lists several other adverse events that are worth discussing. Five patients had decreased leukocytes but in no cases was the total count less than 2900/mm³. Total serum bilirubin was increased in three losartan patients. Data for this lab is not available in the CANADA.

Table 11.10 b. Adverse Events

	losartan 10 mg	losartan 25 mg	losartan 50 mg	losartan 100 mg	losartan 150 mg	enalapril 20 mg	placebo	total
EDEMA, EYELID	0	0	0	0	1	0	0	1
EDEMA, FACIAL	0	0	0	0	1	0	0	1
EDEMA/SWELLING	0	1	1	1	0	0	0	4
LEUKOCYTES DECREASED	0	2	0	1	1	0	1	5
TOTAL SERUM BILIRUBIN INCREASED	1	0	0	0	2	0	0	3

Four patients had adverse clinical experiences that were considered serious. Table 11.11 lists the serious clinical adverse experiences which occurred in this study. These adverse events are further described in the narrative paragraphs which follow:

Table 11.11. Serious Clinical Adverse Experiences

Patient #	Sex	Age	Dosage	Rel Day Of Onset	Adverse Experience(s)	Duration (Days)	Severity	Outcome
0649	F	66	PBO	21	Asthenia/Fatigue	12	Moderate	Recovered
0399*	M	64	LOS 10 mg	32	Angina Pectoris	5	Moderate	Still Present**
				15	Edema	22	Moderate	Still Present**
				32	Exertional Dyspnea	5	Moderate	Still Present**
0033*	M	56	LOS 150 mg	1	Chest Pain	20	Mild	Recovered
0548*	M	52	LOS 150 mg	28	Hepatitis A Infection	139	Moderate	Recovered

* Discontinued; ** Information obtained after correction cutoff date indicated AE was resolved as of July 9, 1991. Patient recovered.

Patient AN 0649 was a 66-year-old hypertensive female patient was treated with placebo for 21 days during the double-blind portion of the study when she was hospitalized for moderate asthenia/fatigue secondary to her development of hypokalemia. The patient was discontinued from the study due to the development of hypokalemia and recovered after receiving potassium replacement therapy.

Patient AN 0399 was a 64-year-old male hypertensive patient had been treated for 32 days with losartan (10 mg) when he was hospitalized for moderate angina pectoris, edema and exertional dyspnea. The patient was discontinued from the study. The day after discontinuation from the study, the patient underwent cardiac catheterization. A diagnosis of a high grade obstruction of the left main coronary artery was made from the test. Bypass surgery was performed 13 days after discontinuation; the patient recovered.

Patient AN 0033 was a 56-year-old male hypertensive patient had been treated for 17 days with losartan (150 mg) when he was discontinued from the study due to chest pain and a positive thallium stress test result. The patient had a documented history of chest pain due to both gastroesophageal reflux and ischemic heart disease, which had resulted in angioplasty in 1987. After 2 weeks of participation in the placebo baseline phase of this study, the patient began to experience mild burning chest pain, which continued into the double-blind treatment phase. This was initially attributed to epigastric

reflux. However, due to the patient's history of ischemic heart disease, the investigator performed the thallium stress test, which was positive. The patient was discontinued from the study. Angioplasty was performed 10 days after the patient's discontinuation; the chest pain resolved.

Patient AN 0548 was a 52-year-old male hypertensive patient had been treated for 28 days with losartan (150 mg) when he was diagnosed as having contracted an acute moderate hepatitis A infection. The patient was discontinued from the study after 34 days of double-blind therapy and eventually recovered.

A total of 10 patients were discontinued for clinical adverse experiences. Table 11.12 lists pertinent data for these patients. There appeared to be no dose-related trend for losartan with respect to the percentage of patients withdrawn for a clinical adverse experience, although the largest number of patients (n=4) were discontinued from the losartan 150 mg group. Patient 0488 (losartan 150 mg) discontinued for what appears to be angioneurotic edema.

Table 11.12. Patients Discontinued for Clinical Adverse Experiences

Patient	Age (Yrs)	Sex	Dose (mg/Day)	Adverse Reaction	Onset (Day)	Duration (Days)	Relative Day of Discontinuation	Intensity	Outcome
0033	56	M	LOS 150	Chest Pain	1	0	17	Mild	Recovered
0085	64	F	LOS 50	Asthma	30	6	34	Mild	Recovered
0294	65	M	LOS 100	Hematuria	34	0.5	36	Moderate	Recovered
0399	64	M	LOS 10	Angina Pectoris	32	5	36	Moderate	Still Present ¹
				Exertional Dyspnea	32	5	35	Moderate	Still Present ¹
				Edema	15	22	36	Moderate	Still Present ¹
0488	73	F	LOS 150	Edema, Eyelid	18	8	20	Moderate	Recovered
				Edema, Facial	18	8	20	Moderate	Recovered
0489	69	F	LOS 10	Rash	24	2	25	Severe	Recovered
				Tremor	24	2	25	Moderate	Recovered
				Increased Intraocular Pressure	24	2	25	Moderate	Recovered
0548*	52	M	LOS 150	Hepatitis A	28	139	34	Moderate	Recovered
				Asthenia/Fatigue	30	46	34	Moderate	Recovered
				Malaise	30	46	34	Moderate	Recovered
				Fever	30	13	34	Mild	Recovered
0617	43	M	LOS 150	Tachycardia	28	2	28	Moderate	Recovered
0667	56	M	ENAL	Cough	10	38	47	Moderate	Still Present
0684	52	F	LOS 25	Headache	34	15	41	Severe	Recovered

¹ Information obtained after correction cut-off date indicated AE was resolved as of July 9, 1991. Patient recovered.

* Patient also discontinued due to laboratory AE, see Table 30.

Five patients were withdrawn due to adverse laboratory experiences. Pertinent data for these patients is listed Table 11.13. Three patients experienced elevated AST and ALT > 100 U/L simultaneously. In addition to patients #548 and #802, patient #574 (placebo) had increases in ALT and AST (ALT = 182 U/L (baseline = 77 U/L), AST = 96 U/L (baseline = 43 U/L) on day 56; ALT = 200 U/L, AST = 101 U/L on day 63)

Table 11.13. Patients Discontinued due to Laboratory Adverse Experiences

Patient #	Age (Yrs)	Sex	Dose (mg/Day)	Adverse Reaction	Normal Range	Baseline Value	Highest (Lowest) Value	Study Day ¹ of Highest (Lowest) Value	Day Discontinued
0115	76	M	LOS 25	Platelet Count Decreased	130-400 thb/mm ³	198	(118)	24	32
0321	53	M	ENAL 20	Hyperglycemia	80-125 mg/dL	114	129	31	41
				Alkaline Phosphatase Increased	20-140 U/L	144	155	31	41
0548*	52	M	LOS 150	Tot. Serum Bilirubin Increased	0.2-1.2 mg/dL	0.80	13.0**	42	34
				AST Increased	0-50 U/L	23.0	3530**	42	34
				ALT Increased	0-55 U/L	27.0	7600**	42	34
				GGT Increased	0-65 U/L	N.D.	213**	49	34
				LDH Increased	0-250 U/L	N.D.	629	34	34
				Hepatitis A Antibody Positive	Negative	N.A.	Positive	34	34
0649	66	F	Placebo	Hypokalemia	3.5-5.3 mEq/L	3.9	(3.10)	14	28
0802	63	M	Placebo	AST Increased	0-50 U/L	25	129	47	43
				ALT Increased	0-55 U/L	14	124	47	43

¹ = Study day of highest (lowest) value = relative day of test; * Patient was also discontinued due to clinical AE, see Table 26.

** Patient's Day 28 and/or Day 35 laboratory values for these tests also listed as "reason discontinued"

Tot. Serum Bilirubin (Day 28) = 0.9 mg/dL

Tot. Serum Bilirubin (Day 35) = 4.60 mg/dL

AST (Day 28) = 113 U/L

AST (Day 35) = 1010 U/L

ALT (Day 28) = 140 U/L

ALT (Day 35) = 1390 U/L

GGT (Day 35) = 198 U/L

Mean changes in laboratory parameters suggest that with the losartan 100 and 150 mg treatment groups the mean serum uric acid decreased compared to placebo.

Patient 548 (losartan 150 mg) experienced marked elevations of liver function tests that was attributed to hepatitis A infection. Cough occurred in 1.3% of placebo, 3.4% of losartan and 3.4% of enalapril patients.

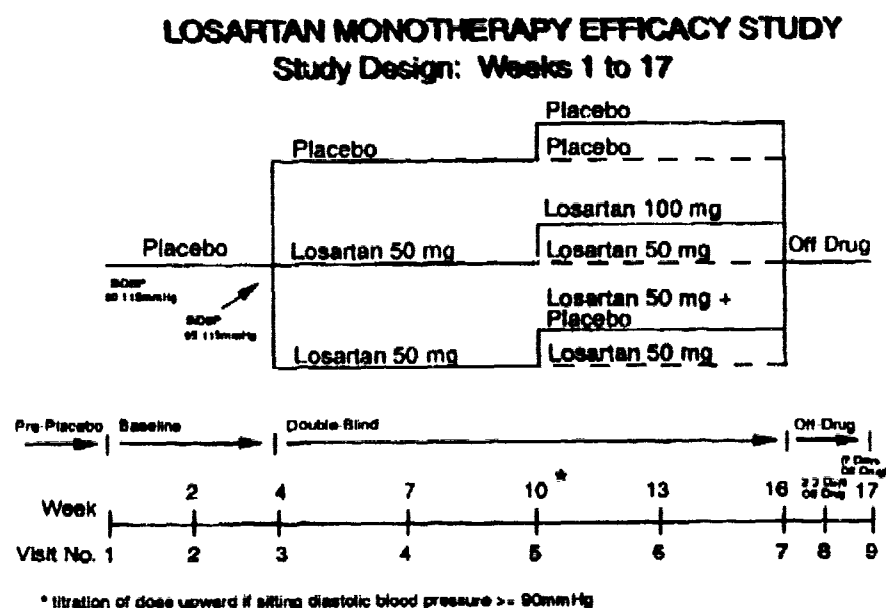
Study 050. A Multicenter, Double-Blind, Randomized, Placebo-Controlled Clinical Study to Evaluate the Antihypertensive Efficacy and Safety of Losartan (MK-954, DuP 753) in Patients with Mild-to-Moderate Hypertension

Protocol

Design

This is a randomized, double-blind, multicenter, placebo-controlled study of 17 weeks duration. A 4-week baseline period was followed by 12 weeks of double-blind treatment with either placebo or losartan. After 6 weeks of double-blind therapy, patients were titrated as outlined in the figure 50.1 based on blood pressure response. After the double-blind period, there was a 1-week off drug period. Patients then entered an open-label treatment period until Week 56.

Figure 50.1. Study 050 Design



Inclusion/Exclusion Criteria

Patients were excluded from enrollment in the study for pregnancy, history of renal disease, secondary hypertension, siSBP > 210 mmHg, MI within past year, other active medical problems (except for diabetes mellitus), conduction disturbances, CVA or TIA, significant arrhythmia, obstructive valvular disease, heart failure, history of unexplained syncope, concomitant medications as listed in the protocol, abnormal laboratory parameters at baseline and illicit drug use.

Patients were enrolled into the single-blind, 4 week, placebo baseline phase if they were > 21 years of age, were not receiving anti-hypertensive medication and had a siDBP of 90 -115 mmHg at visit 1. Hypertensive patients whose siDBP was 95-115 mmHg at the end of the Week 2 and Week 4 baseline period AND whose siDBP values at Week 2 and Week 4 did not differ by >7 mmHg were randomized (see table 50.1). Randomization was stratified based on the severity of hypertension [mild {95 - 105 mmHg} or moderate {106 - 115mmHg}] and race (Black or non-Black). No more than 30% of the patients enrolled in the trial could be black. Patients were randomized to either placebo (with a placebo titration dose), losartan 50 mg (with a losartan 50 mg titration dose) or losartan 50 mg (with a placebo titration dose). Titration occurred at week 6 of double-blind therapy if the siDBP was ≥ 90 mmHg. Patients received double-blind therapy for 12 weeks (until Week 16).

Table 50.1

Blood Pressure Criteria for Randomization.

Visit	Pre-Placebo	Trough Mean SiDBP*	
Baseline		90-115 mmHg	
Visit 2 (Week 2)		95-115 mmHg	Difference between SiDBP values at Week 2 and Week 4 must be ≤ 7 mmHg
Visit 3 (Week 4)		95-115 mmHg	
Period	Early entry into Double-Blind	Week 2: SiDBP 110-115 mmHg AND Readings must be confirmed (i.e., SiDBP 110-115 mmHg) at a second visit at least 3 days later.	

* Mean SiDBP: The calculated average of three consecutive readings at 1 minute intervals. All individual readings are to be read to the nearest 2 mmHg. None of the three readings may differ from the average by >5 mmHg.

The procedures performed during the trial are outlined in table 50.2.

Table 50.2 Flowchart of Study Visits For Losartan Monotherapy Efficacy: Pre-Placebo - Week 17

	Screen	Baseline			Double-Blind				Off-Drug	
Visit:	1	2	3	4	5	6	7	8	9	
Day:	1	14	28	49	70	91	112	115	119	
Week:	0	2	4	7	10*	13	16	17	17	
Medical History	X									
Complete Physical Examination	X						X		X	
Pregnancy Test			X ^l							
Sign Informed Consent	X									
Weight	X	X	X	X	X	X	X	X	X	
Clinic Visits ^a		X	X	X	X	X	X	X	X	
Sitting & Standing BP & HR ^c (Trough/Peak)	X ^{e,i}	T ^f	T ^{g,P}	T	T,P	T	T,P	X	X	
Laboratory Safety Tests ^h	X ^b	X			X		X		X ^m	
Additional Blood Draw ^o							T,P			
ECG (12-lead)		X			X		X		X ^m	
Chest X-ray		X ^j								
AE Evaluation		X	X	X	X	X	X	X	X	
Ophthalmology Examination			X ^k				X ^k			
Plasma Renin Activity			X			X	X	X		
Dispense Baseline Medication	X ⁱ	X								
Dispense Double-Blind Medication			X	X	X ⁿ	X				
Discontinue Double-Blind Medication							X			
Dispense Open-Label Medications								X		

a = Clinic Visits will occur as indicated between 6:30 and 10:00 a.m. Patients are to be in the fasted state at all clinic visits (i.e., no food is to be taken during the 8 hours prior to each clinic visit); b = Perform tests if patient does not have known history or if prior tests are not available.

c = Measurements are to be taken 24 hours (range 22 to 26 hours) after the last study dose; d = Repeat labs, if necessary.

e = Mean SiDBP must be 90-115 mmHg or patient cannot continue in the study; f = Mean SiDBP must be 95-115 mmHg or patient cannot continue in study.

g = Mean SiDBP must be 95-115 and Week 2 and Week 4 values must be ≤ 7 mmHg or patient cannot continue in study.

h = Fasting hematology, blood chemistry and urinalysis as described in Appendix 2.

i = Patient must be off antihypertension medication at least 7 full days or patient must return for another evaluation when an adequate washout period is achieved (refer to section IX.B)

j = Chest x-ray will be performed if one is not available from within the previous 6-month period.

k = To be performed by a qualified specialist, arrange appointment ahead of time; l = See Section VIII.B.1 for necessity and frequency of pregnancy tests.

m = Repeat at Week 17 only to be performed if lab or ECG at Week 16 indicated an AE; n = Dispense Bottles A and B if trough SiDBP <90 mmHg or Bottles C and D if trough SiDBP ≥ 90 mmHg.

o = Patients will also have additional blood drawn at both the Week 16 trough and peak clinic visits for possible future pharmacological and physiological analysis

T = Trough; P = Peak; * = Titration

NOTE: If a patient does not complete the study, all procedures scheduled for treatment Week 16 will be done on the day the patient discontinues treatment. In addition, a complete physical examination will be performed.

Sitting and standing blood pressure at peak and trough were measured. Trough BP measurements were performed 22 - 26 hours after dosing. The peak BP measurements were measured at Visits 3, 5 and 7 six hours (range 5 to 8 hrs) after dosing.

Primary Endpoint

The primary endpoint in the trial is the change in siDBP at week 12 of double-blind treatment. The projected enrollment was 300 patients. This assumes that 86 patients per treatment group completes the trial. The power to detect a 5 mm change in siDBP between treatment groups is 95 % (at the .05 significance level).

Results

[In the discussion of the results, the placebo with placebo titration is designated placebo, the losartan with placebo titration is designated losartan 50/P and the losartan with losartan titration is designated losartan 50/100.]

Patient Disposition

Three hundred sixty-six patients (366) were randomized to the three treatment groups at 22 centers (Placebo N = 116, Losartan 50/P N = 127, losartan 50/100 N = 123). A listing of investigators can be found in the appendix. No explanation was provided as to why more patients than projected in the protocol (100 per treatment group) were enrolled. The number of patients randomized at each center ranged from 12 to 30. Table 50.3 outlines the patient disposition throughout the trial. The projected enrollment in the trial was 300 patients. There is no explanation for the increased enrollment.

Table 50.3 Patient Disposition

[Table is from sponsor's summary and is corrected for one error. It has been validated in the CANDADA database except that 2 losartan 50/100 patients withdrew because therapy was ineffective. Thus, 14 and not 13 losartan 50/100 patients did not complete the double-blind phase of the study.]

	PBO (N= 116)	Losartan	
		50 (N=127)	50/100 (N=123)
	n (%)	n (%)	n (%)
Completed DB/ No OL	16 (13.8)	15 (11.8)	13 (10.6)
Completed DB/ Enter OL	82 (70.7)	100 (78.7)	96 (78.9)
Discontinued Double-Blind Phase	18 (15.5)	12 (9.4)	14 (10.6)
Clinical Adverse Experience	3 (2.6)	0 (0.0)	7 (5.7)
Laboratory Adverse Experience	0 (0.0)	0 (0.0)	0 (0.0)
Clinical & Laboratory AE	0 (0.0)	0 (0.0)	0 (0.0)
Therapy Ineffective	9 ⁺ (7.8)	6 ⁺ (4.7)	2 ⁺⁺ (0.8)
Patient Uncooperative	0 (0.0)	0 (0.0)	1 (0.8)
Patient Withdrew	2 (1.7)	1 (0.8)	2 (1.6)
Protocol Deviation	2 (1.7)	2 (1.6)	1 (0.8)
Lost to Follow-up	2 (1.7)	3 (2.4)	1 (0.8)

⁺ Four patients continued into extension after discontinuing double-blind phase.

⁺⁺ Patient continued into extension after discontinuing double-blind phase.

Forty-four patients did not complete the study. Eighteen placebo patients did not complete the study whereas twelve and fourteen patients did not complete the losartan treatment arms. Patients in the placebo and losartan 50/P group did not complete the study predominately due to lack of effectiveness. The predominate reason patients did not complete the losartan 50/100 treatment was clinical adverse experience. Some of the patients prematurely withdrawn from the double-blind phase continued into the open label extension. A listing of patients withdrawn prematurely can be found in the appendix.

Of the 44 patients discontinued from the study, 9 patients did not have any double-blind period blood pressure data: 2 patients in placebo group (# 2235, # 2385), 2 patients in the losartan 50 group (# 2282, # 2436), and 5 patients in the losartan 50/100 group (# 2160, # 2170, # 2266, # 2394, # 2397). These patients were protocol violators, lost to follow-up, experienced a clinical AE or withdrew prior to an efficacy measurement.

Demographics

Table 50.4 lists the demographic characteristics of the patients in each treatment group.

Table 50.4 Baseline Patient Demographic Characteristics

	Placebo (N=116)	Los 50 (N=127)	Los 50/100 (N=123)	Total (N=366)
Sex				
Female	42 (36%)	44 (35%)	45 (37%)	131 (36%)
Male	74 (64%)	83 (65%)	78 (63%)	235 (64%)
Age (years)				
<35	3 (3%)	7 (6%)	4 (3%)	14 (4%)
35-44	25 (22%)	19 (15%)	17 (14%)	61 (17%)
45-54	33 (28%)	41 (32%)	42 (34%)	116 (32%)
55-64	35 (30%)	41 (32%)	31 (25%)	107 (29%)
>65	20 (17%)	19 (15%)	29 (24%)	68 (19%)
Mean	53.8	53.2	55.1	54
Median	54	53	54	54
Range	26-78	28-75	28-76	26-78
Racial Origin				
Caucasian	92 (79%)	104 (82%)	101 (82%)	297 (81%)
Black	17 (15%)	14 (11%)	16 (13%)	47 (13%)
Hispanic	7 (6%)	8 (6%)	4 (3%)	19 (5%)
Indian	0	1 (1%)	0	1 (0%)
Oriental	0	0	2 (2%)	2 (1%)
Duration of Hypertension (years)				
<1	2 (2%)	3 (2%)	2 (2%)	7 (2%)
1-5	39 (34%)	42 (33%)	34 (28%)	115 (31%)
5.01-10	29 (25%)	35 (28%)	32 (26%)	96 (26%)
>10	46 (40%)	47 (37%)	55 (45%)	148 (40%)
Mean	10.3	10	11.8	10.7
Median	9	8	10	9
Range	0.5-41	0.5-52	0.5-48	0.5-52
Severity of Hypertension (sIDBP, mmHg)				
Mild (95-105)	89 (77%)	86 (68%)	85 (69%)	260 (71%)
Moderate (106-115)	27 (23%)	41 (32%)	38 (31%)	106 (29%)
sIDBP (mmHg)				
Mean	101.3	102.2	102.2	101.9
Median	100	101	101	101
Range	95-115	95-113	95-114	95-115

There were no statistically significant differences in baseline variables between treatment groups. The majority of patients enrolled in this trial were caucasian. Thirty-six percent were females and thirteen percent were black. Seventy-one percent of the patients had mild hypertension (95 - 105 mmHg). One hundred and seven patients received ACE inhibitor therapy prior to enrollment in the trial (31 placebo, 43 losartan 50/P, and 33 losartan 50/100).

Blood Pressure Results - Change in siDBP

Nine patients of the forty-four premature withdrawals did not have any blood pressures measured during the double-blind phase due to discontinuation. Of the remaining 35 premature discontinuations, eighteen did not have a double-blind week 6 visit (titration week). Table 50.5 lists the mean change in siDBP at weeks 6 and 12 for each treatment using an all patients treated (carry forward) analysis. At week 6, 87% of placebo patients, 68% of losartan 50/P patients and 71% of losartan 50/100 patients had the dose titrated. The placebo subtracted mean change in siDBP for losartan 50/P is 3.4 mmHg at both weeks 6 and 12. The placebo subtracted mean change in siDBP for losartan 50/100 is 4.4 and 4.1 mmHg at weeks 6 and 12 respectively. Both treatment's significantly changed siDBP compared to placebo.

Table 50.5 Mean Change In Trough Sitting Diastolic Blood Pressure At Weeks 6 And 12 (mmHg)

All-Patients-Treated Approach

WEEK	TREATMENT	N	Baseline		Treatment		Change		Change Adj Mean	Comparison	
			Mean	S.D.	Mean	S.D.	Mean	S.D.		vs. B	vs. C
6	PLACEBO(A)	114	101.3	4.9	97.8	7.5	-3.5	5.8	-3.5	**	**
	LOS 50 (B)	125	102.1	5.1	95.3	8.6	-6.9	7.0	-6.9	-	NS
	LOS 50/100(C)	118	102.2	5.0	94.3	8.4	-7.9	7.1	-7.9	-	-
12	PLACEBO(A)	114	101.3	4.9	97	7.7	-4.3	6.7	-4.5	**	**
	LOS 50 (B)	125	102.1	5.1	94.2	9.0	-7.9	7.6	-7.9	-	NS
	LOS 50/100(C)	118	102.2	5.0	93.6	8.3	-8.6	7.7	-8.6	-	-

NS -- NOT STATISTICALLY SIGNIFICANT ; * -- TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, P≤0.05

** -- TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, P≤0.01; ANALYSIS SPECS: OVERALL= RANOVA PA

The mean change in siSBP at weeks 6 and 12 are listed in table 50.6. Both losartan treatments caused significant changes in siSBP compared to placebo.

Table 50.6 Mean Change In Trough Sitting Systolic Blood Pressure At Weeks 6 And 12 (mmHg)
All-Patients-Treated Approach

WEEK	TREATMENT	N	BASELINE		POST VALUE		CHANGE		CHANGE	COMPARISON	
			Mean	S.D.	Mean	S.D.	Mean	S.D.	Adj Mean	vs. B	vs. C
6	PLACEBO(A)	114	153.3	16.3	151.8	17.7	-1.5	11.7	-1.7	**	**
	LOS 50 (B)	125	152.8	13.6	145.1	16.0	-7.7	12.0	-8.3	--	NS
	LOS 50/100(C)	118	157.1	18.5	147.3	19.5	-9.8	13.4	-9.4	--	--
12	PLACEBO(A)	114	153.3	16.3	152.5	18.0	-0.8	13.6	-1.2	**	**
	LOS 50 (B)	125	152.8	13.6	144.2	16.7	-8.6	13.9	-9.2	--	NS
	LOS 50/100(C)	118	157.1	18.5	147.4	22.4	-9.7	13.8	-9.4	--	--

NS -- NOT STATISTICALLY SIGNIFICANT

* -- TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, $P \leq 0.05$

** -- TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, $P \leq 0.01$

ANALYSIS SPECS: OVERALL = RANOVA PAIRWISE = LSMEANS, BASED ON RAW DATA

Subgroup analysis of interest include those based on race, gender and age. Table 50.7 lists the change in siDBP for black and non-black patients. The analysis is limited by the relatively small number of black patients enrolled in the trial. The losartan 50/P treatment in black patients showed no benefit in lowering siDBP compared to placebo at any week. The placebo subtracted mean change in siDBP at week 12 in blacks and non-blacks is listed in table 50.7a.

Table 50.7 Mean Change In Trough Sitting Diastolic Blood Pressure At Week 6 And 12 By Race (mmHg)
All-Patients-Treated Approach

WEEK	RACE	TREATMENT	N	BASELINE	TREATMENT	CHANGE	95% CONFIDENCE INTERVAL
				MEAN	MEAN	MEAN	FOR MEAN CHANGE
6	BLACK	PLACEBO	17	102.1	98.6	-3.5	(-5.9, -1.2)
		LOS 50	14	103.9	101.2	-2.7	(-6.3, 0.9)
		LOS 50/100	16	103.3	97.4	-5.9	(-10.5, -1.2)
	NON-BLACK	PLACEBO	97	101.2	97.7	-3.5	(-4.6, -2.3)
		LOS 50	111	101.9	94.5	-7.4	(-8.7, -6.1)
		LOS 50/100	102	102.0	93.8	-8.2	(-9.5, -6.9)
12	BLACK	PLACEBO	17	102.1	98.1	-4.0	(-6.3, -1.7)
		LOS 50	14	103.9	100.2	-3.7	(-7.4, 0.0)
		LOS 50/100	16	103.3	97.6	-5.6	(-10.2, -1.1)
	NON-BLACK	PLACEBO	97	101.2	96.8	-4.3	(-5.7, -3.0)
		LOS 50	111	101.9	93.5	-8.4	(-9.8, -7.0)
		LOS 50/100	102	102.0	93.0	-9.0	(-10.4, -7.6)

Table 50.7a. Mean change from baseline in siDBP at week 12. [Placebo Subtracted]

Treatment Group	Black	Non-Black
Losartan 50/P	+ .3 mmHg (N = 14)	- 4.1 mmHg (N = 111)
Losartan 50/100	- 1.6 mmHg (N = 16)	- 4.7 mmHg (N = 102)

Thirty-six percent of the patients enrolled in this trial were female. Table 50.8 lists the change in siDBP based on gender. In female patients, at 6 and 12 weeks of therapy, the change in siDBP was greater in the losartan 50/P group compared to the losartan 50/100 group.

Table 50.8 Mean Change In Trough Sitting Diastolic Blood Pressure At Weeks 6 And 12 By Sex (mmHg)
All-Patients-Treated Approach

WEEK	PATIENT SEX	TREATMENT	BASELINE		TREATMENT	CHANGE	95% CONFIDENCE INTERVAL FOR MEAN CHANGE
			N	MEAN	MEAN		
6	FEMALE	PLACEBO	41	100.0	95.2	-4.7	(-6.3, -3.1)
		LOS 50	44	102.1	94.7	-7.4	(-9.8, -5.1)
		LOS 50/100	41	100.1	93.6	-6.6	(-8.8, -4.3)
	MALE	PLACEBO	73	102.1	99.3	-2.8	(-4.1, -1.4)
		LOS 50	81	102.2	95.6	-6.6	(-7.9, -5.2)
		LOS 50/100	77	103.3	94.7	-8.6	(-10.1, -7.0)
12	FEMALE	PLACEBO	41	100.0	94.4	-5.6	(-7.4, -3.8)
		LOS 50	44	102.1	92.5	-9.6	(-12.2, -7.0)
		LOS 50/100	41	100.1	93.5	-6.6	(-9.2, -4.1)
	MALE	PLACEBO	73	102.1	98.5	-3.5	(-5.2, -1.9)
		LOS 50	81	102.2	95.2	-7.0	(-8.4, -5.5)
		LOS 50/100	77	103.3	93.7	-9.6	(-11.2, -8.0)

Table 50.9 lists the change in siDBP for patients < 65 years of age and patients $\geq$ 65 years of age. This analysis is limited by the disproportionate number of patients in the younger age group. At 12 weeks, the placebo subtracted change in siDBP was greater in patients $\geq$ 65 years of age for losartan 50/P (6.3 mmHg vs. 3.1 mmHg) and losartan 50/100 (5.1 mmHg vs. 4.2 mmHg).

Table 50.9 Mean Change In Trough Sitting Diastolic Blood Pressure At Weeks 6 And 12 By Age Category (mmHg)
All-Patients-Treated Approach

WEEK	AGE CATEGORY	TREATMENT	BASELINE		TREATMENT	CHANGE	95% CONFIDENCE INTERVAL FOR MEAN CHANGE
			N	MEAN	MEAN		
6	<65 YEARS	PLACEBO	94	101.5	98.1	-3.4	(-4.6, -2.2)
		LOS 50	106	102.3	95.5	-6.8	(-8.2, -5.4)
		LOS 50/100	90	102.5	94.9	-7.6	(-9.0, -6.3)
	$\geq$ 65 YEARS	PLACEBO	20	100.6	96.8	-3.8	(-5.8, -1.8)
		LOS 50	19	101.5	94.2	-7.3	(-9.8, -4.7)
		LOS 50/100	28	101.2	92.5	-8.7	(-11.9, -5.5)
12	<65 YEARS	PLACEBO	94	101.5	96.9	-4.6	(-6.0, -3.3)
		LOS 50	106	102.3	94.6	-7.7	(-9.1, -6.2)
		LOS 50/100	90	102.5	93.7	-8.8	(-10.3, -7.2)
	$\geq$ 65 YEARS	PLACEBO	20	100.6	97.8	-2.8	(-5.7, 0.2)
		LOS 50	19	101.5	92.4	-9.1	(-12.3, -5.9)
		LOS 50/100	28	101.2	93.3	-7.9	(-11.0, -4.8)

Patient response to therapy was divided into three categories as outlined in table 50.9a.

Table 50.9a. Response Categories

Category I:	siDBP <90 mmHg	
Category II:	siDBP $\geq$ 90 mmHg and a reduction of 1	more
Category III:	neither I nor II	

Table 50.9b lists the patient response to therapy at week 12 based on categories I, II and III. The distribution of responses across categories was modeled with Logistic regression including treatment. The percentage of patients in Category I/II in the LOS 50 group and the losartan 50/100 group was significantly greater than the placebo group at both Weeks 6 and 12 ($p \leq 0.01$). The percentage of patients in Category I/II was not significantly different between losartan 50 and losartan 50/100 groups. However, the percentage of patients in Category I/II was higher in the losartan 50/100 group at both Weeks 6 and 12. After 12 week, 27.1% of placebo patients, 46.4% of losartan 50/P patients and 51.6% of losartan 50/100 patients were responders.

Table 50.9b. Categories Of Antihypertensive Response (Trough siDBP) At Weeks 6 And 12[†]

WEEK	TREATMENT	ANTIHYPERTENSIVE RESPONSE CATEGORY			COMPARISON TOTAL	VS. B	VS. C
		I	II	III			
6	PLACEBO (A)	14(12.2%)	8 (7.0%)	92(80.7%)	114 (100%)	**	**
	LOS 50 (B)	37(29.6%)	20(16.0%)	68(54.4%)	125 (100%)	--	NS
	LOS 50/100 (C)	37(31.3%)	21(17.7%)	60(50.8%)	118 (100%)		
12	PLACEBO (A)	19(16.6%)	12(10.5%)	83(72.8%)	114 (100%)	**	**
	LOS 50 (B)	40(32.0%)	18(14.4%)	67(53.6%)	125 (100%)	--	NS
	LOS 50/100 (C)	37(31.3%)	24(20.3%)	57(48.3%)	118 (100%)		

NS - NOT STATISTICALLY SIGNIFICANT

* - TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, P<0.05

** - TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, P<0.01

[†] - NUMBERS ROUNDED TO NEAREST TENTH, THEREFORE, MAY NOT ADD TO 100%

Table 50.9c lists the response rates obtained from the database. Responders were defined as patients with week 12 siDBP decline from baseline greater or equal to 10 mmHg or siDBP less than 90 mmHg. Carry forward data was included. If there were more than one visit during week 12, only the last visit was counted in the analysis. There is little improvement in response rate when losartan 50 mg patients are given an additional 50 mg dose of losartan as opposed to placebo. Blacks are generally unresponsive to losartan compared to placebo. It is difficult to assess the response in female patients. One dose of losartan (losartan 50/P) suggests an improved response whereas another dose (losartan 50/100) suggests no difference from placebo. This is consistent with the mean change in siDBP for females. The response rates based on age suggest that patients < 65 years and ≥ 65 years have similar responses to therapy.

Table 50.9c. Responders at Week 12 Based on Demographic Variables. [Patients without any post-randomization blood pressure measurements are counted as treatment non-responders.]

Demographic Group	Placebo (N = 116)	Losartan 50/P (N = 127)	Losartan 50/100 (N = 123)
All Patients	34/116 (29%)	55/127 (43%)	57/123 (46%)
Caucasians	28/92 (30%)	48/104 (46%)	49/101 (49%)
Blacks	5/17 (29%)	3/14 (21%)	4/16(25%)
Male	19/74 (26%)	32/83 (39%)	40/78 (51%)
Female	16/42 (38%)	24/44 (55%)	17/45 (38%)
≥ 65 years of age	6/20 (30%)	8/19 (42%)	14/29 (48%)
< 65 years of age	28/96 (29%)	47/108 (44%)	43/94 (46%)

Table 50.10 lists the change in peak siDBP (obtained 5 - 8 hours after dosing) at week 6 and 12. Both losartan treatment groups exhibit significant changes in siDBP.

Table 50.10 Mean Change In Peak Sitting Diastolic Blood Pressure At Weeks 6 And 12 (mmHg)
All-Patients-Treated Approach

WEEK	TREATMENT	N	BASELINE		POST VALUE		CHANGE		CHANGE	COMPARISON	
			Mean	S.D.	Mean	S.D.	Mean	S.D.		Adj Mean	vs. B
6	PLACEBO(A)	108	98.6	6.3	94.5	7.7	-4.1	6.9	-4.2	**	**
	LOS 50 (B)	118	99.9	7.1	90.2	10.5	-9.7	8.7	-9.7	--	NS
	LOS 50/100(C)	111	99.1	5.9	90.3	9.6	-8.9	8.7	-9.0	--	--
12	PLACEBO(A)	108	98.6	6.3	93.9	8.8	-4.7	7.9	-4.6	**	**
	LOS 50 (B)	121	99.8	7.1	90.3	10.5	-9.5	9.2	-9.3	--	NS
	LOS 50/100(C)	113	99.2	6.0	89.1	9.1	-10.1	8.6	-10.1	--	--

NS -- NOT STATISTICALLY SIGNIFICANT

* -- TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, $P \leq 0.05$

** -- TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, $P \leq 0.01$

ANALYSIS SPECS: OVERALL= RANOVA PAIRWISE = LSMEANS, BASED ON RAW DATA

The placebo adjusted trough/peak ratio ranged from 73% to 78% for losartan groups at week 12 (Table 50.10a).

Table 50.10a. Trough-To-Peak Ratios For Sitting Diastolic Blood Pressure At Weeks 6 And 12

WEEK	N	TREATMENT GROUP	MEAN CHANGE (mmHg)		T:P RATIO	T:P RATIO (PBO ADJUSTED)
			TROUGH	PEAK		
6	108	PLACEBO	-3.5	-4.1	85%	--
	118	LOS 50	-7.1	-9.7	73%	63%
	111	LOS 50/100	-7.7	-8.9	87%	88%
12	108	PLACEBO	-4.4	-4.7	93%	--
	121	LOS 50	-8.2	-9.5	85%	78%
	113	LOS 50/100	-8.3	-10.1	82%	73%

The claims that there is a correlation (r) between baseline PRA and reduction in trough [peak] siDBP at Week 12 was significant in the active treatment groups: $r=0.28[-0.30]$, ($p \leq 0.01$) in the LOS 50 group, and $r=0.22[-0.20]$, ($p \leq 0.05$) in the LOS 50/100 group. That is, a higher baseline PRA corresponded with a larger reduction in both trough and peak siDBP at Week 12. PRA data could not be found in the CANDAs to validate this claim.

There were no significant changes in pulse, weight and ECG measurements with treatment.

Eighty-seven percent of patients had post-double-blind treatment visits. The percent of patients with post double-blind siDBP measurements greater than baseline is greatest in the placebo group. When the post-double-blind measurements for each treatment group are compared to baseline or to the last double-blind measurement or the number of patients with post-DB measurement > 110 mmHg are considered, there does not appear to be a significant difference between losartan and placebo. It is not unreasonable to conclude that rebound hypertension is not a problem.

Adverse Experience

There was no difference between treatment groups in the incidence of patients reporting at least one adverse experience. The incidence ranged from 52% to 52.8%. Seven losartan 50/100 patients and three of the placebo patients discontinued treatment prematurely due to adverse events. None of the losartan 50/P withdrew due to adverse events. Table 50.11 lists the patients withdrawn prematurely for clinical adverse events.

Table 50.11 Patients Discontinued Due To Clinical Adverse Experiences

Patient #	Age (yr)	Race	Gender	Day Discontinued	Treatment	Adverse Event	AE Start Day	AE Stop Day
2020	75	caucasian	M	36	losartan 50mg/100mg	HEADACHE	-1	20
						ANGINA PECTORIS	36	36
2028	68	black	M	23	placebo	DYSPNEA	-14	-1
						DYSPNEA	1	22
						HEART FAILURE	23	27
2149	78	caucasian	F	39	placebo	EDEMA, FACIAL	-3	17
						RASH	-3	17
						DYSPNEA	37	40
						NAUSEA	37	40
						PAIN, ABDOMINAL	37	40
						PAIN, CHEST	37	40
2160	42	caucasian	F	11	losartan 50mg/100mg	COUGH	-8	-3
						HEADACHE	-8	5
						URI	-8	-3
						FOLLICULITIS	11	12
						HEADACHE	11	12
2170	45	caucasian	F	1	losartan 50mg/100mg	BROWACHE	1	1
						CRAMP, MUSCLE	1	1
						DYSPHASIA	1	1
						DYSPNEA	1	1
						FLUSHING	1	1
						HEMIPARESIS	1	1
						NAUSEA	1	1
						PAIN, ARM	1	1
						VOMITING	1	1
						PARESTHESIA	3	3
						HEMIPARESIS	4	4
						NAUSEA	4	4
						2266	50	caucasian
ANGINA PECTORIS	32	38						
2271	63	caucasian	M	47	losartan 50mg/100mg	DIZZINESS	22	48
						HEADACHE	22	48
						NAUSEA	22	48
2292	59	caucasian	M	72	placebo	BLURRED VISION	8	8
						DYSARTHRIA	8	49
						NAUSEA	8	8
						SOMNOLENCE	28	49
						BLURRED VISION	37	37
						BLURRED VISION	38	38
						ASTHENIA/FATIGUE	70	74
						CONFUSION	70	73
						MEMORY IMPAIRMENT	70	74
2386	65	caucasian	M	21	losartan 50mg/100mg	CONGESTION, NASAL	9	26
						COUGH	9	26
						FEVER	9	26
						PAIN, MUSCULOSKELETAL	9	28
						GLYCOSURIA	26	
						HYPERGLYCEMIA	26	
						LEUKOCYTE COUNT INCREASED	26	
						PLATELET COUNT INCREASED	26	
						SINUS TACHYCARDIA	28	28
2397	75	caucasian	M	9	losartan 50mg/100mg	BRONCHITIS	4	8
						HEART FAILURE	5	9
						MYOCARDIAL INFARCTION	5	13

Eight patients (2.2%) had a clinical adverse experience that was considered serious by the investigator: 1 patient in the placebo group, 1 patient in the losartan 50 group and 6 patients in the losartan 50/100 group. Table 50.12 lists the patients with serious adverse experiences. Patient 2020 experienced a myocardial infarction and not just angina pectoris.

Table 50.12 Serious Clinical Adverse Experiences

Treatment Group	Patient #	Sex	Age	Dose	Day of Onset	Adverse Event	Duration	Resolved
Placebo	2028	M	58	Placebo	1	Dyspnea	22 Days	Yes
				Placebo	23	Heart Failure	4 Days	No
Losartan 50	2161	F	44	Losartan 50 mg	17	Pain, Abdominal	44 Days	Yes
				Losartan 50 mg	17	Menstruation Disorder	2 Days	Yes
Losartan 50/100	2020	M	75	Losartan 50 mg	36	Angina Pectoris	1 Day	No ¹
	2084	M	54	Losartan 50 mg	36	Tachycardia	1 Day	Yes
	2170	F	45	Losartan 50 mg	1	Dysphasia	30 Mins	Yes
				Losartan 50 mg	1	Hemiparesis	30 Mins	Yes
	2266	F	50	Losartan 50 mg	32	Angina Pectoris	1 Day	Yes
	2289	M	60	Losartan 50 mg	35	Hernia, Inguinal	44 Days	Yes
	2397	M	75	Losartan 50 mg	5	Myocardial Infarction	5 Days	No ²
Losartan 50 mg				5	Heart Failure	5 Days	No	

1 Information obtained after correction cutoff date indicated AE was resolved (date unknown). Patient recovered.

2 Information obtained after correction cutoff date indicated AE was resolved (as of 2/24/92). Patient recovered.

Twenty-three adverse experiences had an overall incidence greater than 1%. The incidence of these adverse experiences within each treatment group are provided in table 50.13. For most of these adverse experiences, a causal relationship to losartan is unlikely. However, dizziness occurred in 5 losartan 50/P, 4 losartan 50/100 and only 1 placebo patient. Cough did not appear to be increased in losartan patients compared to placebo. However, upper respiratory infections occurred in 14 losartan 50/P patients, 10 losartan 50/100 patients and 4 placebo patients. Gender does not play a role in predisposing a patient to an adverse event.

Table 50.13 Adverse Experiences in > 1% of the Patients Randomized.

Adverse Experience	losartan 50/P (N=127)	losartan 50/100 (N=123)	Placebo (N=116)	Total (N=366)
ALT increased	1	6	2	9
AST increased	1	3	0	4
Asthenia/Fatigue	6	2	8	16
Blurred Vision	1	1	2	4
Bronchitis	0	2	2	4
Nasal Congestion	5	2	2	9
Resp. Congestion	5	2	2	9
Cough	3	6	5	14
Muscle Cramp	1	3	1	5
Diarrhea	2	2	0	4
Dizziness	5	4	1	10
Dyspnea	1	3	3	7
Edema/Swelling	7	3	2	12
Headache	12	19	15	46
URI	14	10	4	28
Nausea	5	3	3	11
Abdominal Pain	1	1	3	5
Arm Pain	1	2	1	4
Back Pain	2	1	1	4
Chest Pain	2	0	2	4
Pharyngitis	4	0	3	7
Rash	2	1	1	4
Sinus Disorder	2	3	0	5

Twenty-five patients (flagged in the database) experienced laboratory adverse events (27 are listed in the clinical summary report). Nine of these patients had elevations of ALT. Seven of them received losartan. Patients #2362, #2230 and #2207 had elevations of both ALT and AST simultaneously. Patient #2230 had the highest elevations with the maximum ALT 171 U/L and maximum AST 109 U/L. Patient #2362 transaminases returned to normal despite continued therapy. None of the patients were reported to have clinical hepatitis.

There is no difference in the mean change in pulse, weight or ECG parameters between treatment groups. ECG adverse experiences were reported in 1 placebo, 2 losartan 50/P and 7 losartan 50/100 patients. Table 50.14 lists the ECG adverse experiences reported. Two losartan patients were reported to have prolongation of the QT interval. It is unlikely that the change in QT is related to losartan since losartan does not appear to change the mean QTc.

Table 50.14 ECG Adverse Experience.

Group	Treatment	AN	Adverse Experience
	Placebo	2428	Premature ventricular Contraction
	LOS 50	2326	Prolonged QT interval
		2338	Sinus bradycardia
	LOS 50/100	2056	Vascular disorder
		2103	AV block, first degree
		2215	AV block, first degree
			AV block, second degree
		2315	Left atrial hypertrophy
		2327	Axis disturbance
			Prolonged QT interval
		2336	Sinus bradycardia
		2386	Sinus tachycardia

Mean changes in laboratory parameters were unremarkable except for those listed in table 50.15. Mean uric acid appears to decrease as did total cholesterol. The decline in total cholesterol was due to a decrease in LDL cholesterol not HDL cholesterol. As expected, plasma renin levels increased with losartan

Table 50.15. Mean Changes For Laboratory Tests

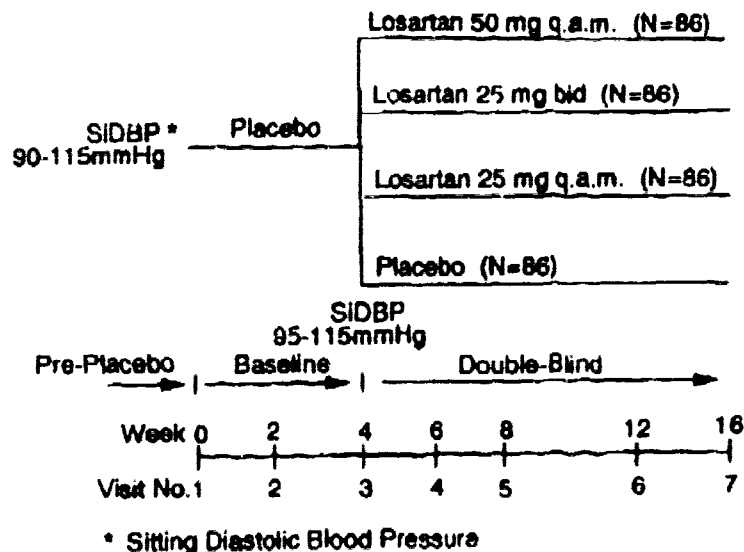
LABORATORY TEST	WEEK	TREATMENT	N	Baseline		Treatment		Change	
				Mean	S.D.	Mean	S.D.	Mean	S.D.
SERUM URIC ACID (mg/dl)	6	Placebo	102	6.34	1.43	6.45	1.61	0.12	0.82
		Losartan 50	114	6.16	1.59	5.91	1.5	-0.25	0.82
		Losartan 50/100	110	6.04	1.36	5.76	1.31	-0.29	0.85
	12	Placebo	94	6.33	1.46	6.51	1.6	0.18	0.71
		Losartan 50	111	6.15	1.6	6.07	1.68	-0.08	0.9
		Losartan 50/100	108	6.03	1.35	5.91	1.4	-0.12	0.7 ^a
TOTAL CHOLESTEROL (mg/dl)	12	Placebo	94	215.1	40	216.7	37.1	1.5	22.8
		Losartan 50	107	211.1	36.4	207.3	37.2	-3.9	21.4
		Losartan 50/100	106	212.6	38.8	204.8	34.9	-7.9	23.6
LDL CHOLESTEROL (mg/dl)	12	Placebo	90	131.3	36.9	129.2	34.4	-2	21.5
		Losartan 50	102	127.7	31.6	123.5	32	-4.2	18.7
		Losartan 50/100	95	126.3	35.5	117.9	31.9	-8.4	21.4
PLASMA RENIN ACTIVITY (mg/dl)	12	Placebo	81	1.028	0.918	1.21	1.688	0.181	1.752
		Losartan 50	99	1.3	1.114	2.889	2.884	1.589	2.341
		Losartan 50/100	96	1.473	2.253	3.724	5.242	2.251	3.69

Study 065. A Double-Blind Randomized, Parallel, Placebo-Controlled Study to Investigate the Antihypertensive Efficacy and Safety of Losartan Given Once or Twice Daily in Patients with Mild-to-Moderate Hypertension (Open Label Extension reviewed separately)

Protocol

Protocol 65 is a randomized, double-blind, placebo controlled trial in patients with mild to moderate hypertension. The primary objective was to show that losartan 50 mg once a day and losartan 25 mg twice a day decreased trough systolic blood pressure by a significantly greater amount than placebo after 12 weeks of therapy. The trial consisted of a 4 week placebo baseline period and a 12 week active treatment period as outlined in the figure 65.1 [Note: The N listed after each treatment in figure 65.1 is the projected enrollment.]

Figure 65.1 Study Design



Patients were enrolled into the baseline period (visit 1) if they had primary hypertension with a mean siDBP ≥ 90 mmHg (a patient could not have received antihypertensive drugs for at least 7 days prior to the start of the baseline period), were above the legal age to sign a consent and did not have active medical problems. The following conditions excluded patients from enrollment: pregnancy, secondary hypertension, siSBP ≥ 110 mmHg, history of CVA or TIA, MI within the past year, angina pectoris, significant AV block, sick sinus syndrome, ventricular tachyarrhythmias, unexplained syncope or a known syncopal disorder, accessory bypass tract (e.g., Wolff-Parkinson-White syndrome), current or prior history of heart failure or a known left ventricular ejection fraction $\leq 40\%$, hemodynamically significant obstructive valvular disease or hypertrophic cardiomyopathy, percutaneous coronary angioplasty or coronary artery bypass surgery within the past 6 months, concomitant use of β -blockers (except ophthalmic preparations) or any agent that may cause an alteration of blood pressure, use of phenothiazines and high-dose tricyclic anti-depressants, oral contraceptives, regular use of nonsteroidal anti-inflammatory agents (NSAIDs), renal or hepatic, hematological or metabolic dysfunction, regular use of nonsteroidal anti-inflammatory agents, obesity, abusing or previously abused alcohol or other drug substances within the past two year and absence of one kidney.

Patients whose mean SiDBP was 95-115 at the end of Week 2 and Week 4 of the placebo baseline period and whose mean siDBP values at Week 2 and Week 4 did not differ by >7 mmHg were stratified by degree of hypertension (mild or moderate) and by race (black or non-black) and were randomly assigned to 1 of 4 treatment groups: placebo q.a.m., losartan 50 mg q.a.m., losartan 25 mg b.i.d. and losartan 25 mg q.a.m. Patients took double-blind therapy for 12 weeks, i.e., until Week 16. Patients had the option of continuing in an open label follow-up study. The open label study is reviewed separately in the 4 month safety update.

The procedures performed in the trial are outlined in the table 65.1.

Table 65.1. Flowchart of Study Visits For Losartan QD and B.I.D. Efficacy: Pre-Placebo - Week 16

	Pre-Placebo	Baseline		Double-Blind Period			
Visit:	1	2	3	4	5	6	7
Day:		14	28	42	56	84	112
Week:		2	4	6	8	12	16
Medical History	X						
Complete Physical Examination	X						X
Pregnancy Test			X ^a				
Sign Informed Consent	X						
Weight	X	X	X	X	X	X	X
Clinic Visits ^b		X	X	X	X	X	X
Sitting & Standing BP & HR ^c (Trough/Peak)	X ^{d,e}	T ^{f,g}	T ^{f,g}	T	T	T	T,P
Laboratory Safety Test ^{h,i}	X ^j	X ^j					X
ECG (12-lead)		X					X
Chest X-ray		X ^k					
AE Evaluation		X	X	X	X	X	X
Dispense Baseline Medications	X ^e	X					
Dispense Double-Blind Medication			X		X	X	
Discontinue Double-Blind Study Medications							X
Dispense Open-Label Medications							X

^a See Section VIII.B.1 for necessity and frequency of pregnancy tests

^b Clinic Visits will occur as indicated between 6:30 and 10:30 a.m. Patients are to be in the fasted state at all clinic visits (for a minimum of 8 hours prior to each clinic visit).

^c Trough measurements are to be taken 24 hours (range 22 to 36 hours) after the last morning dose and 12 hours (10-14 hours) after the last p.m. dose

^d Mean siDBP must be 90-115 mmHg or patient cannot continue in the study.

^e Patient must not have taken antihypertension medication for at least 7 full days or patient must return for another evaluation when an adequate washout period is achieved (refer to section IX.B)

^f Mean siDBP must be 95-115 mmHg or patient cannot continue in study.

^g Mean siDBP must be 95-115 mmHg and Week 2 and Week 4 values must differ by ≤ 7 mmHg or patient cannot continue in study.

^h Fasting hematology, blood chemistry, PT, PTT and urinalysis as described in Appendix 3. At Visit 7 a trough and peak plasma sample (5 mg) will be obtained for possible additional physiological analysis.

ⁱ Perform tests only if patient does not have known history or if prior tests are not available.

^j Repeat labs, if abnormal at Visit #1.

^k Chest x-ray will be performed if one is not available from within the previous 6-month period.

NOTE: If a patient does not complete the study, all procedures scheduled for treatment Week 16 (Visit #7) were done on the day the patient discontinues treatment. All adverse experiences must be followed up until resolved or final status is ascertained.

Approximately 40 sites were to be used to ensure at least 344 patients complete the study. The study was powered so that if at least 86 patients per treatment group completed the study there would be 90% (80%) probability of detecting a 4 (3.4) mmHg difference between treatment groups with respect to change in blood pressure (assuming a standard deviation of 8 mmHg or less, and a 5% level of significance for a 2-sided test). Thirty percent of the patients enrolled had to have moderate hypertension (siDBP 106-115 mmHg) and no more than 30% of the patients could be black.

Endpoints

The primary endpoint of the study is the change in trough siDBP at week 12. Secondary endpoints included response rate at week 12, the change in siDBP for losartan 25 bid versus losartan 50 once a day and trough /peak assessments.

Results

Statistical Analysis

Table 65.1a describes the statistical tests performed by the sponsor on the data.

Table 65.1a. Statistical Tests Performed in Study 065.

Parameter	Statistical Analysis
Demographics - Categorical	Fisher's Exact Test
Demographics - Continuous	Analysis of Variance (Parameter = response variable; treatment group = independent variable)
Change in BP from baseline	Least Squares analysis of means - ANOCOVA for randomized block design (baseline BP = covariate, block = investigator) Pairwise Comparisons*: t-test on ranked data (error term obtained from an overall general linear model including treatment; was used). multifactor analysis of covariance on Week 12 changes from baseline in trough SiDBP was done using the "all-patients-treated" approach (factors: investigator**, treatment and baseline blood pressure, race (black/non-black), age category (>65 years/<65 years) and gender
Response Rate	cumulative logit model for the proportions of patients within each category of response (treatment group is the only independent variable; used carry forward data)
Safety	Lab (change from baseline): T-tests based on the ranked data. Lab (% outside pre-defined limit): Fisher's Exact test, Kruskal-Wallis test (based upon ndit scores) Adverse Experiences: Not specified

*As stated in the protocol the primary methodology used for treatment group comparisons was parametric in nature. Due to the presence of some extreme observations, a semi non-parametric analysis was also utilized to address the robustness of the conclusions.

**Investigators with fewer than 2 patients in any treatment group were combined into "one" investigator.

Demographics

Four hundred and twenty-eight (428) patients were randomized into four treatment groups (106-108 per treatment group) at 37 centers (4 centers received drug but did not randomize patients). A list of centers can be found in the appendix. Table 65.2 lists the mean demographic characteristics of each treatment group. The patients were generally similar among the treatment groups with respect to gender (65% male overall), age (combined mean age 53.5 years), race (78% Caucasian, 16% Black, 4% Hispanic across groups) and duration of hypertension (average 10.3 year history for all patients); however, there were significantly higher percentages of Blacks in the losartan 25 q.d. treatment group compared to the losartan 25 b.i.d. group ($p < 0.05$). The baseline trough mean sitting diastolic blood pressures (SiDBP) were similar among the 4 treatment groups, ranging from 101.5 to 102.4 mmHg (excluding patients at center #3; these patients were excluded from the efficacy analysis because times of drug doses and times that blood pressures were measured were found to be of questionable reliability and, in most cases, could not be verified). The number of patients randomized at each center ranged from 1 - 22.

Table 65.2. Baseline Patient Demographic Characteristics

		Placebo (N=108)	Losartan 25 qd (N=108)	Losartan 50 qd (N=106)	Losartan 25 bid (N=106)	Total (N=428)
Sex	Female	38 (35%)	41 (38%)	36 (34%)	36 (34%)	151 (35%)
	Male	70 (65%)	67 (62%)	70 (66%)	70 (66%)	277 (65%)
Age (years)	< 35	4 (4%)	4 (4%)	2 (2%)	5 (5%)	15 (4%)
	35-44	18 (17%)	19 (18%)	19 (18%)	19 (18%)	75 (18%)
	45-54	30 (28%)	38 (35%)	29 (27%)	32 (30%)	129 (30%)
	55-64	34 (31%)	31 (29%)	40 (38%)	39 (37%)	144 (34%)
	65-74	21 (19%)	13 (12%)	16 (15%)	10 (9%)	60 (14%)
	> 74	1 (1%)	3 (3%)	0	1 (1%)	5 (1%)
	Mean	54.6	53	54	52.4	53.5
Range	29-75	24-79	29-74	27-78	24-79	
Racial Origin	Caucasian	84 (78%)	79 (73%)	82 (77%)	89 (84%)	334 (78%)
	Oriental	1 (1%)	2 (2%)	2 (2%)	2 (2%)	7 (2%)
	Latin American	0	1 (1%)	0	0	1 (0%)
	Black	21 (19%)	22 (20%)	17 (16%)	10 (9%)	70 (16%)
	Hispanic	2 (2%)	4 (4%)	5 (5%)	4 (4%)	15 (4%)
	Vietnamese	0	0	0	1 (1%)	1 (0%)
Duration of HTN (years)	Mean	10	10.8	10.5	10	10.3
	Range	0.5-41	0.5-46	0.5-43	0.5-47	0.5-47
siDBP (mmHg)+	< 105 (Mild)	74 (70%)	78 (74%)	68 (66%)	73 (72%)	293 (70%)
	> 105 (Moderate)	32 (30%)	28 (26%)	35 (34%)	29 (28%)	124 (30%)
	Mean	101.5	101.8	102.4	102	101.9
	S.D.	5.1	5.5	6.4	5.3	5.6

+ These sample sizes do not include patients from investigator # 065003 which was excluded from all efficacy analyses

Disposition

The number of patients enrolled into the baseline period is not provided in the submission. Four hundred and twenty-eight patients were randomized. 86 of 108 placebo patients, 99 of 108 losartan 25 mg patients, 94 of 106 losartan 50 mg and 96 of 106 losartan 25 mg bid patients completed 12 weeks of double-blind therapy. Two hundred and eighty-eight patients continued into the open label follow-up study. Fifty-three patients withdrew from the double-blind phase prematurely. The majority of placebo patients withdrew due to clinical adverse experience or because therapy was ineffective. Seven patients, all in losartan groups, withdrew with no reason given. Four losartan patients were lost to follow-up. Table 65.3 outlines the disposition of patients in each treatment group. A listing of patients withdrawn from therapy prematurely during the double-blind treatment period can be found in the appendix.

Table 65.3. Patient Disposition.

	PBO	Losartan		
		25 mg q.d.	50 mg q.d.	25 mg b.i.d.
	(N=108)	(N=108)	(N=106)	(N=106)
	n (%)	n (%)	n (%)	n (%)
Completed DB/ No OL	20 (18.5)	19 (17.6)	26 (24.5)	22 (20.8)
Completed DB/ Enter OL	66 (61.1)	80 (74.1)	68 (64.2)	74 (69.8)
Discontinued Double-blind Phase	22 (20.4)	9 (8.3)	12 (11.3)	10 (9.4)
Clinical AE	10 (9.3)	0	1 (0.9)	3 (2.8)
Laboratory AE	0	0	2 (1.9)	0
Clinical & Laboratory AE	0	0	0	0
Therapy Ineffective	9 (8.3)	2 (1.9)	5 (4.7)	2 (1.9)
Patient Uncooperative	0	0	0	0
Patient Withdrew	0	3 (2.8)	1 (0.9)	3 (2.8)
Protocol Deviation	3 (2.8)	2 (1.9)	1 (0.9)	2 (1.9)
Lost to Follow-up	0	2 (1.9)	2 (1.9)	0

Efficacy

Eight patients did not have any treatment period data, and could not be included in the efficacy analysis: 4 patients in the placebo group (# 1219, # 1373, # 1308 and # 1655), 1 in losartan 25 mg q.d. group (# 1685), 2 in losartan 50 mg q.d. group (# 1628 and # 1301) and 1 in losartan 25 mg b.i.d. group (# 1310). When no data were available within a day range, the last available double-blind treatment measurements were used at that time point. Patients from center #3 (Dr. Arbeit, Leonard), were excluded from the efficacy analysis since the times of drug doses and times that blood pressures were measured were found to be of questionable reliability and, in most cases, could not be verified. This investigator had 11 patients: 2 in placebo group (# 1600 and # 1603), 2 in losartan 25 mg q.d. group (# 1598 and # 1610), 3 in losartan 50 mg q.d. group (# 1599, # 1601, and # 1608) and 4 in losartan 25 mg b.i.d. group (# 1597, # 1602, # 1607 and # 1609). Thus, there were a total of 409 patients evaluable for efficacy: 102 patients in the placebo group, 105 patients in the losartan 25 mg q.d. group, 101 patients in losartan 50 mg q.d. group and 101 patients in the losartan 25 mg b.i.d. group.

Table 65.4 lists the mean change in trough siDBP at week 12 using the all patients treated analysis. The placebo subtracted mean change is -3.8 mmHg, -4.3 mmHg and -6.0 mmHg for the losartan 25 mg, losartan 50 mg and losartan 25 mg bid groups respectively. Table 65.4 lists the mean change in trough siSBP at week 12 using the all patients treated analysis.

Table 65.4. Mean Change In Trough Sitting Diastolic Blood Pressure (mmHg) At Week 12. All-Patients-Treated Approach

Treatment	N	Baseline			Treatment			Change			Adj Mean	Comparison		
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.		vs. B	vs. C	vs. D
Placebo (A)	102	101.3	99.0	5.1	99.3	98.5	9.8	-2.0	-2.5	8.4	-2.1	**	**	**
Losartan 25 qd (B)	105	101.8	100.0	5.5	96.0	93.0	8.4	-5.8	-6.0	6.7	-5.9	-	NS	*
Losartan 50 qd (C)	101	102.3	100.0	6.3	96.0	95.0	9.5	-6.3	-7.0	7.4	-6.6	-	-	NS
Losartan 25 bid (D)	101	102.0	101.0	5.3	94.0	93.0	8.8	-8.0	-8.0	7.9	-8.3	-	-	-

NS - NOT STATISTICALLY SIGNIFICANT; * = TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, P<0.05

** = TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, P<0.01

Table 65.4a. Trough Sitting Systolic Blood Pressure (mmHg) At Week 12

Treatment	N	Baseline			Treatment			Change			Change			Comparison		
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	Adj Mean	vs. B	vs. C	vs. D		
Placebo (A)	102	156.3	153.5	18.3	156.0	154.0	19.6	-0.2	0.0	15.1	0.4	**	**	**		
Losartan 25 qd (B)	105	153.5	150.0	16.5	146.3	146.0	18.4	-7.2	-6.0	13.9	-7.7	-	NS	NS		
Losartan 50 qd (C)	101	155.1	154.0	15.8	147.6	146.0	17.5	-7.6	-8.0	12.6	-7.9	-	-	NS		
Losartan 25 bid (D)	101	150.5	149.0	15.4	141.8	139.0	17.1	-8.8	-9.0	13.0	-10.6	-	-	-		

NS -- NOT STATISTICALLY SIGNIFICANT, * = TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, $P \leq 0.05$

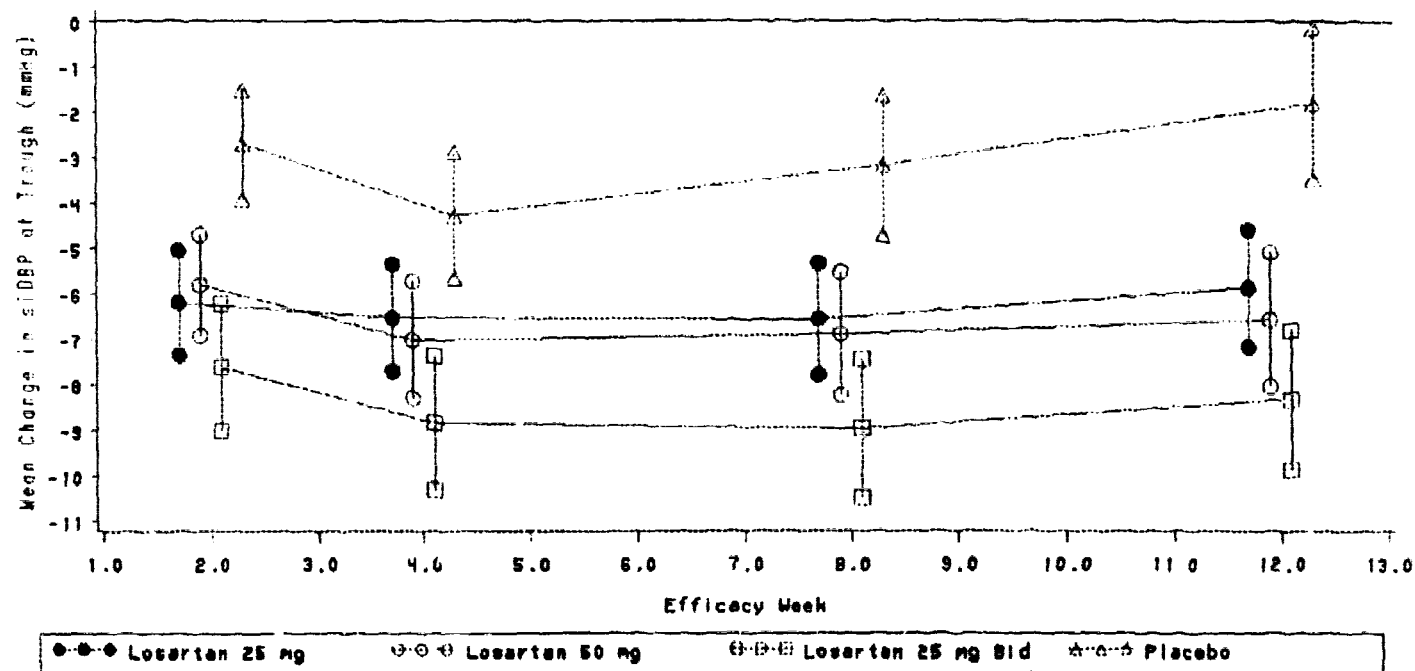
** = TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, $P \leq 0.01$

Figure 65.2 shows the mean change in trough siDBP from baseline for treatment weeks 2, 4, 8 and 12 using carry forward data (data from center #3 is included). The 95% confidence intervals are illustrated by the vertical lines at each time point for each treatment. Although there is no significant difference between losartan 25 mg bid and losartan

Figure 65.2

Study 65. Mean Change in siDBP at Trough

Carry Forward Data.



Tables 65.6 - 65.9 lists the week 12 change in siDBP (carry forward analysis) for subgroups based on race, degree of hypertension, age, and gender. In all subgroups except black patients, losartan caused a decline in trough siDBP compared to placebo. The larger decline in mean siDBP (though not statistically different) with losartan 25 mg b.i.d. compared to losartan 50 mg once a day may in part be influenced by the number of black patients in the respective treatment groups (black patients were less responsive to losartan). There were more black patients in the losartan 50 mg group compared to the losartan 25 mg b.i.d. group. However, the argument against this being a factor is the observation that there is a consistently greater decline in siDBP with 25 mg b.i.d. compared to losartan 50 mg regardless of the subgroup.

Table 65.6. Mean Change In Trough Sitting Diastolic Blood Pressure (mmHg) at Week 12 By Race (All-Patients-Treated Approach)

<u>RACE</u>	<u>TREATMENT</u>	<u>N</u>	<u>BASELINE Mean</u>	<u>TREATMENT Mean</u>	<u>CHANGE Mean</u>	<u>95% Confidence Interval for Mean Change</u>
BLACK	Placebo	21	104.7	102.2	-2.5	(-6.2, 1.1)
	LOS 25 qd	21	101.9	97.9	-4.0	(-7.3, -0.7)
	LOS 50 qd	16	104.3	102.8	-1.5	(-4.7, 1.7)
	LOS 25 bid	10	103.6	100.8	-2.8	(-6.9, 1.3)
NON-BLACK	Placebo	81	100.4	98.5	-1.9	(-3.7, -0.1)
	LOS 25 qd	84	101.8	95.5	-6.3	(-7.7, -4.9)
	LOS 50 qd	85	101.9	94.7	-7.2	(-8.8, -5.7)
	LOS 25 bid	91	101.8	93.2	-8.6	(-10.2, -7.0)

Table 65.7. Mean Change in Trough Sitting Diastolic Blood Pressure (mmHg) at Week 12 by Degree of Hypertension at Baseline (All-Patients-Treated Approach)

<u>BASELINE TROUGH siDBP</u>	<u>TREATMENT</u>	<u>N</u>	<u>BASELINE Mean</u>	<u>TREATMENT Mean</u>	<u>CHANGE Mean</u>	<u>95% Confidence Interval for Mean Change</u>
MILD (≤ 105 mmHg)	Placebo	72	98.5	96.9	-1.6	(-3.5, 0.3)
	LOS 25 qd	77	98.9	93.1	-5.8	(-7.2, -4.4)
	LOS 50 qd	67	98.4	92.7	-5.6	(-7.3, -4.0)
	LOS 25 bid	72	99.1	92.0	-7.2	(-8.8, -5.5)
MODERATE (> 105 mmHg)	Placebo	30	108.2	105.1	-3.1	(-6.2, 0.0)
	LOS 25 qd	28	109.6	103.8	-5.9	(-8.7, -3.1)
	LOS 50 qd	34	110.1	102.4	-7.7	(-10.4, -4.9)
	LOS 25 bid	29	109.1	98.9	-10.2	(-13.5, -7.0)

Table 65.8. Mean Change in Trough Sitting Diastolic Blood Pressure (mmHg) at Week 12 by Age Category (All-Patients-Treated Approach)

<u>AGE CATEGORY</u>	<u>TREATMENT</u>	<u>N</u>	<u>BASELINE Mean</u>	<u>TREATMENT Mean</u>	<u>CHANGE Mean</u>	<u>95% Confidence Interval for Mean Change</u>
<65 YEARS	Placebo	80	101.4	99.1	-2.4	(-4.2, -0.6)
	LOS 25 qd	89	101.7	95.7	-6.0	(-7.4, -4.6)
	LOS 50 qd	85	102.4	96.0	-6.4	(-8.0, -4.8)
	LOS 25 bid	90	101.8	93.9	-7.9	(-9.6, -6.3)
≥ 65 YEARS	Placebo	22	100.9	100.1	-0.8	(-4.6, 3.1)
	LOS 25 qd	16	102.1	97.3	-4.8	(-8.0, -1.5)
	LOS 50 qd	16	101.7	95.9	-5.8	(-9.1, -2.5)
	LOS 25 bid	11	103.9	94.8	-9.1	(-13.7, -4.5)

Table 65.9. Mean Change In Trough Sitting Diastolic Blood Pressure (mmHg) At Week 12 By Sex (All-Patients-Treated Approach)

<u>PATIENT SEX</u>	<u>TREATMENT</u>	<u>N</u>	<u>BASELINE Mean</u>	<u>TREATMENT Mean</u>	<u>CHANGE Mean</u>	<u>95% Confidence Interval for Mean Change</u>
FEMALE	Placebo	34	100.2	97.8	-2.4	(-5.4, 0.5)
	LOS 25 qd	40	102.2	96.2	-6.0	(-8.0, -4.0)
	LOS 50 qd	33	102.2	96.1	-6.2	(-8.5, -3.8)
	LOS 25 bid	34	100.7	93.4	-7.3	(-9.9, -4.7)
MALE	Placebo	68	101.7	100.0	-1.8	(-3.8, 0.1)
	LOS 25 qd	65	101.5	95.8	-5.7	(-7.4, -4.0)
	LOS 50 qd	68	102.3	95.0	-6.4	(-8.2, -4.6)
	LOS 25 bid	67	102.6	94.2	-8.4	(-10.3, -6.5)

Table 65.10 lists the response rate for each treatment group at week 12. A positive response to therapy was defined as trough siDBP < 90 mmHg (category I) or a reduction of trough siDBP ≥ 10 mmHg in patients with trough siDBP ≥ 90 mmHg (category II). The response rate in the placebo group was significantly different from the losartan 50 mg and losartan 25 mg bid. Twenty-two percent of the placebo patients, 40% of the losartan 50 mg patients and 48% of the losartan 25 mg b.i.d. dose were responders.

Table 65.10. Categories Of Antihypertensive Response (Trough SiDBP) at Week 12 (All-Patients-Treated Approach)

TREATMENT	ANTIHYPERTENSIVE RESPONSE CATEGORY				COMPARISON		
	I	II	III	TOTAL	VS. B	VS. C	VS. D
PLACEBO (A)	12 (11.8%)	10 (9.8%)	80 (78.4%)	102 (100%)	NS	*	**
LOS 25 qd (B)	23 (21.9%)	14 (13.3%)	68 (64.8%)	105 (100%)	--	NS	NS
LOS 50 qd (C)	26 (25.7%)	14 (13.9%)	61 (60.4%)	101 (100%)	--	--	NS
LOS 25 bid (D)	33 (32.7%)	15 (14.9%)	53 (52.5%)	101 (100%)	--	--	--

NS - NOT STATISTICALLY SIGNIFICANT
 * - TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, P<0.05
 ** - TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, P<0.01
 CATEGORY I - TROUGH SiDBP <90 mmHg
 CATEGORY II - TROUGH SiDBP ≥90, REDUCTION ≥10 mmHg
 CATEGORY III - NEITHER I NOR II

Response rates for subgroups based on gender and race (only black and Caucasian included) are listed in table 65.11. Caucasians and blacks were the only racial subgroups that had sufficient numbers to derive meaningful information. The response rate in black patients suggests that blacks do not respond to losartan.

Table 65.11. Trough Response Rate in Subgroups. (carry forward data)

Subgroup	losartan 25 mg	losartan 50 mg	losartan 25 mg bid	placebo
Male	37.3% (25/67)	35.7% (25/70)	45.7% (32/70)	20.0% (14/70)
Female	31.7% (13/41)	47.2% (17/36)	50.0% (18/36)	21.1% (8/38)
Caucasian	40.5% (32/79)	45.1% (37/82)	49.4% (44/89)	17.9% (15/84)
Black	18.2% (4/22)	11.8% (2/17)	20.0% (2/10)	28.6% (6/21)

Tables 65.12 and 65.13 lists the changes in peak siDBP and peak siSBP at week 12. All treatment groups had significantly greater decreases in blood pressure compared to placebo.

Table 65.12 Mean Change in Peak Sitting Diastolic Blood Pressure (mmHg) at Week 12 (All-Patients-Treated Approach).

TREATMENT	N	Baseline			Treatment			Change			Comparison			
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	Adj. Mean	vs. B	vs. C	vs. D
Placebo (A)	92	98.8	99.0	7.5	95.7	95.0	9.8	-3	-4.0	9.7	-2.8	**	**	**
LOS 25 qd (B)	95	98.2	99.0	7.7	90.5	90.0	8.9	-7.7	-8.0	8.5	-8.0	--	NS	NS
LOS 50 qd (C)	94	98.8	97.5	7.1	90.1	90.0	10.2	-8.7	-8.0	8.1	-9.0	--	--	NS
LOS 25 bid (D)	94	100.5	99.5	5.9	90.6	89.0	9.4	-9.9	-10.0	9.5	-9.3	--	--	--

NS - NOT STATISTICALLY SIGNIFICANT
 ** - Treatment Difference statistically significant, p<0.01.

Table 65.13. Mean Change in Peak Sitting Systolic Blood Pressure (mmHg) at Week 12 (All-Patients-Treated Approach).

TREATMENT	N	Baseline			Treatment			Change			Comparison			
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	Adj. Mean	vs. B	vs. C	vs. D
Placebo (A)	92	154.2	151.0	19.8	153.1	150.0	19.7	-1.0	-2.5	15.9	0.5	**	**	**
losartan 25 qd (B)	95	151.1	149.0	18.4	141.8	139.0	17.7	-9.3	-8	16.3	-9.2	--	NS	*
losartan 50 qd (C)	94	153.1	151.0	16.6	141.9	139.0	17.8	-11.2	-11	13	-10.7	--	--	NS
losartan 25 bid (D)	94	151.3	149.0	16.0	137.7	137.5	17.0	-13.6	-12.5	15	-13.8	--	--	--

NS - NOT STATISTICALLY SIGNIFICANT
 * - TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, P≤0.05
 ** - TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, P≤0.01

Table 65.14 lists the response rates for peak week 12 siDBP measurements. The response rate at peak for losartan treatment groups ranged from 62.2% to 53.2%. The placebo group response rate was 39.1%.

Table 65.14. Categories of Antihypertensive Response (Peak siDBP) at Week 12 (All-Patients-Treated Approach)

TREATMENT	ANTIHYPERTENSIVE RESPONSE CATEGORY				COMPARISON		
	I	II	III	TOTAL	VS. B	VS. C	VS. D
PLACEBO (A)	25 (27.2%)	11 (12.0%)	56 (60.9%)	92 (100%)	**	*	**
LOS 25 qd (B)	47 (49.5%)	13 (13.7%)	35 (36.8%)	95 (100%)		NS	NS
LOS 50 qd (C)	43 (45.7%)	7 (7.4%)	44 (46.8%)	94 (100%)			NS
LOS 25 bid (D)	48 (51.1%)	11 (11.7%)	35 (37.2%)	94 (100%)			

NS -- NOT STATISTICALLY SIGNIFICANT

* -- TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, $P \leq 0.05$ ** -- TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, $P \leq 0.01$ I -- PEAK siDBP < 90 mmHgII -- PEAK siDBP ≥ 90 , REDUCTION ≥ 10 mmHg

III -- NEITHER I NOR II

The trough to peak ratios at week 12 for siDBP are listed in table 65.15.

Table 65.15. Trough-to-Peak Ratios for Sitting Diastolic Blood Pressure at Week 12.

N	TREATMENT GROUP	MEAN CHANGE (mmHg)		T:P RATIO	T:P RATIO (PBO ADJUSTED)
		TROUGH	PEAK		
91	Placebo	-2.2	-3.2	69%	--
95	LOS 25 qd	-6.0	-7.7	78%	85%
93	LOS 50 qd	-7.0	-8.7	80%	87%
94	LOS 25 bid	-8.2	-9.9	83%	90%

NOTE: Only patients with both trough and peak measurements were included in this table.

An analysis which included only trough siDBP measurements collected at week 12 (not carry forward, protocol violators included) yielded results similar to the all patients treated analysis. The changes in trough siDBP at week 12 based on a per protocol data analysis showed similar results as the carry forward analysis. The mean change from baseline at week 12 for trough siDBP using the per protocol data was -3.1, -6.5, -6.7 and -8.2 mmHg for placebo, losartan 25 mg qd, losartan 50 mg qd and losartan 25 bid respectively. Mean changes in trough siDBP were also generally similar for the two approaches at Week 12. The only difference between the approaches with respect to statistical significance ($p \leq 0.05$) was that losartan 50 mg q.d. was significantly different (smaller reduction) than losartan 25 mg b.i.d. using the "per-protocol" approach. In multifactor analysis of covariance, investigators who had less than two patients in any treatment group were combined for the purpose of a formal statistical test; there was no interaction observed utilizing this approach ($p=0.9102$). Except for race there were no statistically significant interactions observed between treatment and any of the other factors (age and sex). Race had a significant interaction with treatment ($p \leq 0.05$).

Safety

The percentage of patients with at least one adverse experience in the double blind period ranged from 55% to 61%. Three patients died during the study. Patient # 1330 (placebo) was a 58-year-old male hypertensive patient who had been treated for 85 days with placebo when a hydraulic lift fell on him and he died immediately. Patient # 1596 (losartan 25 bid) was a 78-year-old hypertensive male patient had a blood pressure reading of 211/143 and numbness and tingling of the right leg on Day 41 of treatment with losartan 25 mg b.i.d. He was hospitalized and diagnosed with a cerebral vascular accident secondary to malignant hypertension (Blood Pressure Measurements: 177/111, 157/110, 170/113, 176/118, 174/105 mmHg readings). Therapy was discontinued. Seven days later he had a cardiac arrest and was resuscitated. Eighteen days later he developed an arrhythmia, respiratory failure, and seizures. On Study Day 68 he had a second cardiac arrest and died. Patient # 1373 (placebo) was a 53-year-old hypertensive male patient who was hospitalized for myocardial infarction and cerebral vascular accident on Day 4 of treatment with placebo. The patient died on Day 39.

A total of 14 patients were discontinued because of clinical adverse experiences. Table 65.16. lists the adverse events associated for these patients. Of these, 10 patients were in the placebo group, 1 patient was in losartan 50 mg q.d. and 3 were in losartan 25 mg b.i.d. group.

Table 65.16. Patients Discontinued Due To Clinical Adverse Experiences

Patient #	Sex	Age	Treatment	Day Discontinued	Adverse Event	AE Start Day	AE Duration days
1145	M	61	Placebo	10	PALPITATION	5	10
					PHOTOPHOBIA	5	10
1153	F	51	Placebo	39	PAIN, BACK	14	2
					MYALGIA	27	2
					RASH	37	15
1246	M	69	Placebo	84	HEART FAILURE	81	4
1272	M	48	Placebo	33	EDEMA/SWELLING	1	34
					EDEMA/SWELLING	15	20
					STRAIN, BACK	30	4
1301	F	38	Losartan 50 mg	4	TACHYCARDIA	3	5
					HYPERGLYCEMIA	4	1
					LYMPHOCYTES DECREASED	4	1
					NEUTROPHILS INCREASED	4	1
1308	F	43	Placebo	5	DYSPNEA	4	2
1330	M	58	Placebo	85	DEATH	85	1
					TRAUMA	85	1
1373	M	53	Placebo	4	CVA	4	36
					MI	4	36
1415	F	61	Losartan 25 mg BID	16	DIZZINESS	1	28
1421	M	66	Placebo	43	DIARRHEA	22	22
					NEOPLASM, INTESTINAL, METASTATIC	43	1
1560	M	65	Placebo	52	HEMORRHAGE, RETINAL	48	5
1596	M	78	Losartan 25 mg BID	41	HEADACHE	7	4 hours
					CVA	41	28
					HYPERTENSION	41	28
1607	M	40	Losartan 25 mg BID	16	PAIN, ARM	16	1
					PAIN, CHEST	16	1
1623	M	63	Placebo	27	ARTHRALGIA	1	27

Two patients had laboratory adverse experiences that prompted withdrawal. Information pertaining to these patients are listed in table 65.17.

Table 65.17.

Patients Discontinued Due To Laboratory Adverse Experiences.

PL #	Sex/ Age	Drug/ Total Daily Dosage (mg) Frequency	Rel. Day of Onset	Adverse Experience	Laboratory Value and Unit	Normal Range	Rel. Day of Discontinue.	Serious
1599	F/44	50 mg q d	84	AST Increased	73 u/L	9-34 U/L	84	No
			84	ALT Increased	56 u/L	6-34 U/L	84	No
1750	M/45	50 mg q d	90	Hyperglycemia	326/mg/dl.	70-115 mg/dl.	90	No

Table 65.18 lists the patients who had adverse experiences that were considered to be serious. Five of the nine patients with serious adverse events required discontinuation. Narrative summaries for these patients are provided following table 65.18.

Table 65.18. Serious Clinical Adverse Experiences

Patient	Sex	Age	Treatment Group	Rel Day of Onset	Adverse Experience(s)	Duration (Days)	Outcome	
1173	F	74	Placebo	77	Phlebitis/Thrombophlebitis	16	Recovered	
1330*	M	58	Placebo	85	Trauma	1	Death	
1373*	M	53	Placebo	4	Myocardial Infarction	36	Not Recovered	
				4	Cerebral Vascular Accident	36	Not Recovered	
				39			Death	
1421*	M	66	Placebo	43	Metastatic CA Bowel	1	Not recovered	
1314	M	43	25 mg qd	68	Fracture Rt Patella	16	Recovered	
1110	M	45	50 mg qd	34	Chest and Abdominal pain	1	Recovered	
1194	M	64	25 mg bid	15	Squamous Cell Ca Forehead	13	Recovered	
				41	Malign Hypertension	28	Not recovered	
				41	CVA	28	Not recovered	
				Off drug	48	Cardiac Arrest	<1	Recovered
				Off drug	66	Resp Failure, Seizures	3	Not recovered
				Off drug	66	Arrhythmia	3	Not recovered
Off drug	68	Cardiac Arrest	<1	Death				
1607*	M	40	25 mg bid	16	Chest Pain, Arm Pain	1	Recovered	

* Discontinued the study.

Patient # 1421 - Metastatic CA Bowel (Placebo)

This 66-year-old hypertensive male patient with a history of mild to moderate diarrhea was hospitalized on Day 43 of treatment with placebo and surgically diagnosed with a malignant distal rectal tumor with metastasis to the peritoneum and liver. Therapy was discontinued.

Patient # 1173 - Phlebitis (Placebo)

This 74-year-old female hypertensive patient was hospitalized for phlebitis on Day 77 of treatment with placebo. She was medically treated and discharged on Day 88. Therapy was not interrupted.

Patient # 1330 - Trauma, Death (Placebo)

This 58-year-old male hypertensive patient had been treated for 85 days with placebo when a hydraulic lift fell on him and he died immediately. The investigator considered this event to be definitely not related to study drug.

Patient # 1373 - Myocardial Infarction, Cerebral Vascular Accident, Death (Placebo)

This 53-year-old hypertensive male patient was hospitalized for myocardial infarction and cerebral vascular accident on Day 4 of treatment with placebo. The patient died on Day 39.

Patient # 1314 - Broken Knee Cap (25 mg q.d.)

This 43-year-old hypertensive male patient was hospitalized for a broken knee cap on Day 68 of treatment with losartan 25 mg q.d. The patient had a surgical repair on Day 69 and recovered. Therapy was interrupted for surgery only. The investigator considered the event to be definitely not related to study drug.

Patient # 1110 - Chest and Abdominal Pain (50 mg q.d.)

This 45-year-old hypertensive male patient was admitted to the hospital on Day 34 of treatment with losartan 50 mg q.d. for lower abdominal pain and chest pain. His condition resolved without surgical or medical intervention and he was discharged on Day 37. Therapy was interrupted for three days.

Patient # 1607 - Chest Pain (25 mg b.i.d.)

This 40-year-old hypertensive male patient with a history of myocardial infarction was hospitalized for chest pain and pain in left arm on Day 16 of treatment with losartan 25 mg b.i.d. He was diagnosed with a possible myocardial infarction. Therapy was discontinued.

Patient # 1596 Study 065-011 - Malignant Hypertension, Cerebral Vascular Accident, Cardiac Arrest, Respiratory Failure, Seizures, Arrhythmia, Death (25 mg b.i.d.)

This 78-year-old hypertensive male patient had a blood pressure reading of 211/143 and numbness and tingling of the right leg on Day 41 of treatment with losartan 25 mg b.i.d. He was hospitalized and diagnosed with a cerebral vascular accident secondary to malignant (177/111, 157/110, 170/113, 176/118, 174/105 mmHg readings) hypertension. Therapy was discontinued. Seven days later he had a cardiac arrest and was resuscitated. Eighteen days later he developed an arrhythmia, respiratory failure, and seizures. On Study Day 68 he had a second cardiac arrest and died.

Patient # 1194 - Squamous Cell Carcinoma Forehead (25 mg b.i.d.)

This 64-year-old hypertensive male patient with a history of an excised squamous cell carcinoma of the forehead had a biopsy of the scar and was diagnosed with recurrent squamous cell carcinoma of the forehead on Day 15 of treatment with losartan 25 mg b.i.d. Therapy was not interrupted.

The number of patients in each treatment group with at least one adverse experience is listed in table 65.19. There is no difference between treatments.

Table 65.19. Adverse Experience Incidence

	PLACEBO (N=108)	LOS 25 QD (N=108)	LOS 50 QD (N=106)	LOS 25 BID (N=106)
Number (%) of Patients	n (%)	n (%)	n (%)	n (%)
With One Or More Adverse Experiences	66 (61)	60 (56)	61 (58)	60 (56.6)

Table 65.19a lists the adverse events with a reported incidence greater than 1%. This information was obtained from the CANDA by querying study 65 for adverse events during the acute period. Note that only 1 death is listed whereas three deaths occurred. Two deaths are listed as occurring in the post-acute drug treatment period. Impotence occurred only in losartan treated patients. Dizziness was not a dose related adverse event. Hemoglobinuria occurred in 3 losartan treated patients. Additional patient information is needed to determine whether hemoglobinuria is due to hemolytic anemia.

Table 65.19a. Adverse Event Incidence [Includes adverse events that have a total incidence > 1%, have potential serious clinical implications, are characteristic in ACE Inhibitors or may have clinical relevance based on the mechanism of action of losartan.]

Adverse Experience	losartan 25 mg	losartan 50 mg	losartan 25 mg bid	placebo	Total
ALT INCREASED	4	4			8
ASTHENA/FATIGUE	2	2	6	2	12
ARRHYTHMIA			1		1
AST INCREASED	2	3		1	6
BRONCHITIS	3		2		5
CONGESTION, NASAL	1		3	2	6
COUGH	5	4	3	3	15
DEATH				1	1
DIARRHEA	4	4	2	4	14
DIZZINESS	7	5	4	3	19
DYSPEPSIA	2	1	2	1	6
EDEMA/SWELLING	2	2		4	8
FEVER	1		1	3	5
GOUT		1	1	1	3
HEADACHE	17	19	18	23	77
HEART FAILURE		1		1	2
HEMOGLOBINURIA	2		1		3
HYPERGLYCEMIA		2	3		5
IMPOTENCE		3	2		5
URI	9	7	11	8	35
INSOMNIA	1	2	1	1	5
MYALGIA		1	2	2	5
NAUSEA	3	3		3	9
PAIN, CHEST	2	2	2		6
PAIN, KNEE	4	1		1	6
PARESTHESIA	2	2		1	5
PTT INCREASED	1			1	2
PERVERSION, TASTE			1		1
PHARYNGITIS	3	5		4	12
PROTEINURIA	1			2	3
PROTHROMBIN TIME INCREASED	1			1	2
RHINITIS	1	2	1	1	5
SINUS DISORDER	2	3	1	4	10
SINUSITIS	1	2	1	1	5
SWELLING, JOINT	3			2	5
URTICARIA			1	1	2

Patients had laboratory blood tests performed at baseline and week 12. Table 65.20 shows the incidence of laboratory adverse experience in all treatment groups.

Table 65.20. Laboratory Adverse Experience Summary

	Placebo (N*=104)	Losartan 25 qd (N*=105)	Losartan 50 qd (N*=103)	Losartan 25 bid (N*=104)
Number (%) of Patients With one or more Adverse Experiences	7 (6.7)	7 (6.7)	7 ** (6.8)	4 (3.8)

** The CANDA lists only six patients with laboratory Ab.

Patients # 1127 (losartan 25 mg), # 1479 (losartan 25 mg), and #1582 (losartan 25 mg bid) had hemoglobiuria. None of these patients had decreases in hemoglobin. Urine blood results are not available in the CANADA for this study. Nine patients (8 losartan, 1 placebo) had elevations of either ALT or AST. None of these patients had a simultaneous increase in both ALT or AST to double the upper limit of normal. Patients #1274 (losartan 25 mg bid) had a serum potassium of 2.7 mEq/L on day 30, 3.0 mEq/L on day 63 and 2.4 mEq/L on day 100 (baseline potassium = 3.3 mEq/L; day (-29) = 2.5 mEq/L). Patient #1744 (losartan 50 mg) had a serum potassium of 3.0 mEq/L on day 98 (baseline = 3.8 mEq/L). Patient # 1245 (losartan 25 mg) had a serum potassium of 5.6 mEq/L on day 85 (baseline = 4.4 mEq/L). Patient #1632 (losartan 50 mg) had a serum potassium of 5.5 mEq/L on day 92 (baseline = 4.1 mEq/L).

The mean changes in laboratory tests were unremarkable except for the parameters listed in table 65.21. Uric acid decreased with losartan treatment whereas potassium increased slightly. It is not clear that these changes are clinically relevant.

Table 65.21. Mean Changes from Baseline for Labs

LABORATORY TEST	UNIT	WEEK	TREATMENT	N	BASELINE		TREATMENT		CHANGE	
					Mean	S.D.	Mean	S.D.	Mean	S.D.
SERUM CREATININE	mg/dl	12	Placebo	100	1.13	0.19	1.12	0.19	-0.01	0.11
			Losartan 25 mg qd	102	1.12	0.17	1.08	0.18	-0.04	0.10 ^a
			Losartan 50 mg qd	99	1.08	0.15	1.08	0.18	0	0.11
			Losartan 25 mg bid	102	1.11	0.2	1.09	0.19	-0.02	0.1
SERUM URIC ACID ⁺	mg/dl	12	Placebo	100	5.91	1.33	5.75	1.28	-0.16	0.83
			Losartan 25 mg qd	102	5.93	1.27	5.62	1.34	-0.31	0.7
			Losartan 50 mg qd	99	5.83	1.34	5.59	1.34	-0.24	0.7
			Losartan 25 mg bid	102	5.81	1.44	5.46	1.35	-0.35	0.86 ^b
SERUM POTASSIUM ⁺	mEq/L	12	Placebo	100	4.3	0.39 ^c	4.27	0.4	-0.03	0.42
			Losartan 25 mg qd	102	4.31	0.39	4.32	0.39	0	0.39
			Losartan 50 mg qd	98	4.19	0.37	4.32	0.42	0.13	0.42 ^c
			Losartan 25 mg bid	101	4.26	0.38	4.32	0.42	0.06	0.39

⁺ These laboratory tests were statistically analyzed due to special interest

^a Statistically significantly different from losartan 50 mg q d, p=0.003

^b Statistically significantly different from placebo, p=0.050

^c Statistically significantly different from placebo and losartan 25 mg q d, p=0.007 and p=0.011, respectively

Study 021. A Double-Blind, Randomized, Parallel-Group, Placebo-Controlled Pilot Study to Investigate the Magnitude and Duration of Response and the Safety of MK-954 (50 mg Given Once or Twice Daily, or 100 mg Given Once Daily) Compared to Placebo Using Ambulatory Blood Pressure Monitoring [The open label extension portion of this study is reviewed separately]

Protocol

This is a randomized, double-blind, placebo controlled, parallel-group study to obtain a preliminary evaluation of the magnitude and duration of the antihypertensive efficacy and safety of three different dose regimens of losartan compared to placebo. The trial consisted of a 4 week placebo baseline period at the end of which patients were randomized to either placebo, losartan 50 mg, losartan 100 mg or losartan 50 mg bid for 6 weeks of therapy. Ambulatory blood pressure monitoring (ABPM) was performed twice during the study, once at the end of the placebo washout period and again at the end of four (4) weeks of double-blind monotherapy treatment. After 4 weeks of treatment, patients with siDBP $\geq$ 85 mmHg could have HCTZ added to the double blind treatment.

The trial enrolled only non-black patients, > 21 years of age and within 30% of ideal body weight. Mean 24 hour ambulatory monitoring blood pressure had to be $\geq$ 85 mmHg. Conventional siDBP by the mercury sphygmomanometer at screening had to be $\geq$ 90 mmHg and $\geq$ 95 mmHg at the week 2 and 4 baseline visits. The difference between the measurements taken at these 2 visits had to be no more than 7 mmHg. Table 21.1 outlines the procedures performed during the study

Table 21.1 Clinical and Laboratory Assessments Performed During the Double-Blind Study

	Prestudy	Baseline		Double-Blind Monotherapy Treatment			Concomitant HCTZ	
		Week -3	Week -1	Week 1	Week 2	Week 4	Week 5	Week 6
Days of Treatment:		14	28	35	42	56	63	70
Procedure								
Sign informed Consent	x							
Discontinue Anti-hypertensive Medications	x							
Physical Examination Electrocardiogram (ECG)	x					x		x
Medical History	x							
Laboratory Evaluation ¹		x				x		x
Trough Sitting and Standing Blood Pressure and Heart Rate	x	x	x	x	x	x	x	x
Adverse Experience Assessment		x	x	x	x	x	x	x
Ambulatory BP Monitoring			x			x		x ²
Review Inclusion and Exclusion Criteria	x	x	x					
Body Weight and Pill Count		x	x	x	x	x	x	x
Assign Baseline Number	x							
Assign Allocation Number			x					
Dispense Medications	x		x			x		

¹ Fasting, Hematology, blood chemistry and urinalysis ² Optional

Blood pressure measurements were performed simultaneously with the ABP monitor and the mercury sphygmomanometer using a "T" tube. The purpose was to verify that the ABP monitor was measuring blood pressure consistent with the mercury sphygmomanometer (the "gold standard").

The type of statistical analysis to be performed on the data was not pre-specified in the protocol. The primary efficacy variable specified in the protocol was baseline versus week 4 ABPM mean results.

Results

Demographics

One hundred twenty-two (122) patients were randomized into four treatment groups (~30 per treatment group) at nine treatment centers. Table 21.2 provides demographic information on the treatment groups. For the most part, demographic variables were similar among treatment groups. The number of patients on ACE inhibitor therapy prior to enrolling in the trial is provided in table 21.3. Interestingly, none of the patients were on beta pill.

Table 21.2. Baseline Patient Demographic Characteristics

	Placebo (N=32)	Losartan 50 qd (N=29)	Losartan 100 qd (N=30)	Losartan 50 bid (N=31)	Total (N=122)
Sex					
Female	7 (22%)	10 (34%)	9 (30%)	13 (42%)	39 (32%)
Male	25 (78%)	19 (66%)	21 (70%)	18 (58%)	83 (68%)
Age (years)					
Mean	52.3	56.8*	51.2	54.1	53.5
S.D.	12	12.1	9.6	7	10.8
Range	28 - 76	34 - 75	34 - 73	35 - 69	28 - 76
Racial Origin					
Caucasian	30 (94%)	29 (100%)	30 (100%)	30 (97%)	119 (98%)
Oriental	0	0	0	1 (3%)	1 (1%)
Filipino	1 (3%)	0	0	0	1 (1%)
Indian	1 (3%)	0	0	0	1 (1%)
Duration of Hypertension (years)					
Mean	9.8	9.4	11.2	13.7	11.1
S.D.	10.1	7.6	7.7	10.8	9.2
Median	5.5	8	10	12	9
Range	0.08 - 46	0.25 - 28	1 - 31	0.33 - 49	0.08 - 49
SiDBP (Clinic)					
Mean	100.7	100	101.5	101.2	100.9
S.D.	4	4.6	5.1	4.8	4.6
DBP 24-Hour Mean ABPM					
N	26	28	28	30	112
Mean	94.8	94	93.8	94.4	94.2
S.D.	5.9	6.9	6	6.9	6.4

*Statistically significantly different from Los 100 qd, p<0.05. [Statistical Analysis: Categorical Variables = Fisher's Exact test, Continuous = ANOVA (treatment is independent variable)]

Table 21.3. ACE Inhibitor Use Prior to Enrollment

	Placebo (N=32)	Los 50 qd (N=29)	Los 100 qd (N=30)	Los 50 bid (N=31)
	n (%)	n (%)	n (%)	n (%)
Enalapril Maleate	2 (6.3)	6 (20.7)	4 (13.3)	5 (16.1)
Lisinopril	2 (6.3)	3 (10.3)	3 (10.0)	2 (6.5)

Disposition

Table 21.4. lists the number of patients randomized to each treatment group. Eight patients withdrew during the six week double-blind treatment period.

Table 21.4. Patient Accounting

	Placebo	Losartan 50 QD	Losartan 100 QD	Losartan 50 BID
Total Entering Monotherapy Period	32	29	30	31
Total Completing Period	30	28	29	29
Continuing Into Combination Period (siDBP > 85)	28	21	21	23
Not Continuing Into Combination Period (siDBP < 85)	2	4	7	5
Not Continuing Into Combination Period (siDBP > 85)	0	3	1	1
Total Discontinued Period	2	1*	1	2
Clinical Adverse Experience	1	1*	1	1
Protocol Deviation	0	0	0	1
Patient Withdrew	1	0	0	0
Total Entering Combination Therapy Period	28	21	21	23
Total Completing Period	28	21	19	23
Total Discontinued Period	0	0	2	0
Clinical Adverse Experience	0	0	1**	0
Protocol Deviation	0	0	1	0

* Did not adhere to protocol.

* This patient (AN 81) had an adverse experience during placebo baseline that continued (without change) into double-blind. He discontinued after having Week 4 efficacy measurements obtained.

** This patient (AN 88) discontinued HCTZ (on his own) after 5 days due to a loss of equilibrium (ataxia). The patient continued the double-blind medication (losartan) for the remaining 7 days of the "combination" phase.

Table 21.4a lists the patients withdrawn and the reason for withdrawal.

Table 21.4a. Patients Withdrawn

Patient Number	Treatment Regimen	Reason Discontinued	Day Discontinued
11	Losartan 50 mg BID	CLINICAL AE	3
35	Placebo	CLINICAL AE	11
160	Losartan 100 mg	CLINICAL AE	20
81	Losartan 50 mg	CLINICAL AE	29
88	Losartan 100 mg	CLINICAL AE	39
46	Losartan 50 mg BID	Protocol Deviation	29
62	Losartan 100 mg	Protocol Deviation	32
99	Placebo	Patient Withdrew	8

Efficacy

According to the ABPM design specifications, the total number of readings that were to be taken during the 26-hour monitoring was 72. Less than 10% of the patients had fewer than 60 readings over 24 hours. Table 21.5 and 21.5a displays the mean baseline, Week 4 and change in diastolic and systolic 24-hour mean ABPM by treatment group. [Adjusted means are provided in this table since baseline was included as a covariate in the model and the pairwise comparisons were based upon these adjusted means.] Ten patients were not included in the analysis for various reasons (6 placebo, 1 losartan 50 mg, 2 losartan 100 mg, 1 losartan 50 mg bid). For all losartan groups, the change in ambulatory DBP was significantly different from placebo. The losartan 50 mg b.i.d. group had a greater decline (non-significant) in ambulatory DBP than the losartan 100 mg group. Ambulatory SBP change was significantly different in all losartan groups compared to placebo.

Table 21.5. Diastolic 24-Hour Mean ABPM

Treatment	N	Baseline		Week 4		Change		Change Adj Mean	Comparison		
		Mean	S.D.	Mean	S.D.	Mean	S.D.		vs. B	vs. C	vs. D
Placebo (A)	26	94.8	5.9	94.6	7.0	-0.2	4.8	-0.8	**	**	**
Los 50 qd (B)	28	94.0	6.9	88.8	9.9	-5.2	5.1	-5.6	--	NS	*
Los 100 qd (C)	28	93.8	6.0	87.4	6.8	-6.4	5.5	-7.1	--	--	NS
Los 50 bid (D)	30	94.4	6.9	86.0	6.9	-8.5	6.7	-9.0	--	--	--

Table 21.5a. Systolic 24-Hour Mean ABPM

Treatment	N	Baseline		Week 4		Change		Change Adj Mean	Comparison		
		Mean	S.D.	Mean	S.D.	Mean	S.D.		vs. B	vs. C	vs. D
Placebo (A)	26	147.4	13.3	147.4	12.8	0.0	7.8	-1.2	**	**	**
Los 50 qd (B)	28	150.9	15.4	141.7	17.3	-9.2	9.9	-9.4	--	NS	*
Los 100 qd (C)	28	147.7	12.2	137.9	13.5	-9.9	7.6	-10.9	--	--	NS
Los 50 bid (D)	30	148.7	12.2	135.5	12.4	-13.2	10.6	-14.2	--	--	--

NS - Not Statistically Significant

* - Treatment Difference Statistically Significant, $P < 0.05$

** - Treatment Difference Statistically Significant, $P < 0.01$

Pair-wise comparisons are based upon adjusted means.

The hourly mean DBP throughout the 24 hours of monitoring at baseline and week 4 is depicted in figure 21.2. The hourly mean change in DBP from baseline throughout the 24 hours of monitoring at week 4 is depicted in figure 21.3. For all losartan treatment groups, the hourly ambulatory DBP is below baseline values.

Figure 21.2. Diastolic Hourly Mean ABPM

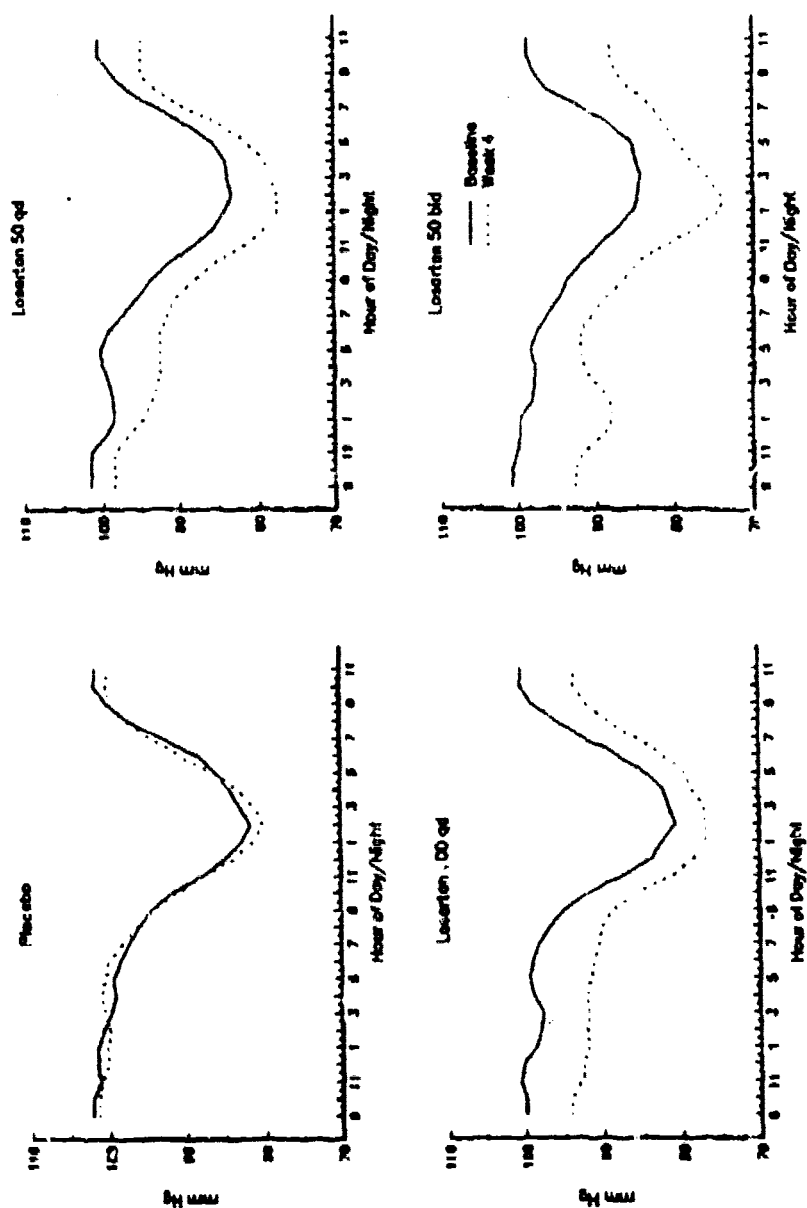


Figure 21.3. Diastolic Hourly Mean ABPM Change From Baseline

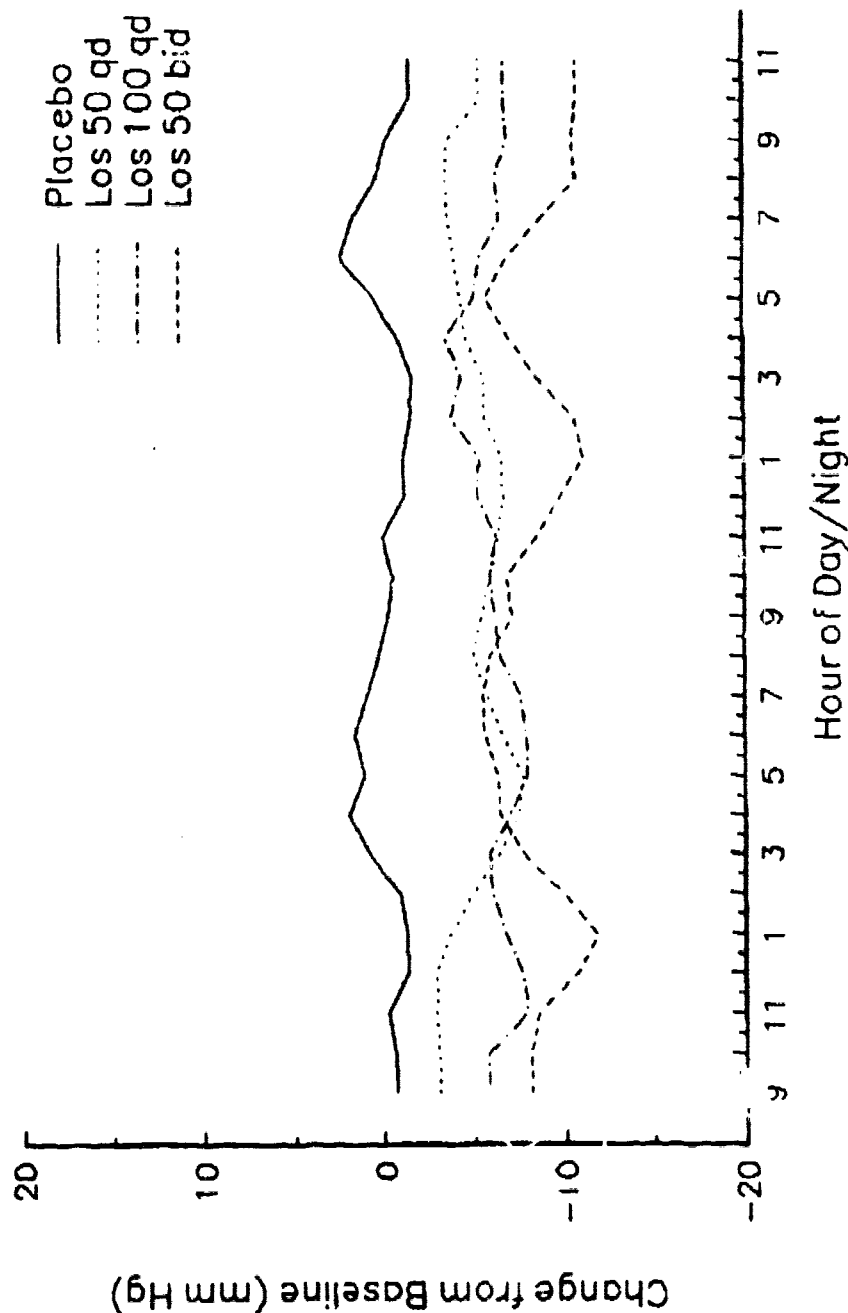


Table 21.6 and table 21.7 lists the mean change in trough siDP^o and siSBP at week 4 for sphygmomanometer measurements. The results are similar to ABPM measured 24 hour means except that the changes in all groups are numerically greater with sphygmomanometer measurements and the losartan 100 mg effect on siDBP is now numerically greater than the losartan 50 mg bid effect.

Table 21.6. Mean Changes in Sitting Diastolic Blood Pressure (mmHg) at Week 4 (sphygmomanometer measurements)

Treatment	N	Baseline		Week 4		Change		Change	Comparison		
		Mean	S.D.	Mean	S.D.	Mean	S.D.		vs. B	vs. C	vs. D
Placebo (A)	30	100.3	3.6	98.2	7.5	-2.1	6.9	-2.1	*	**	**
Los 50 QD (B)	29	100.0	4.6	93.3	9.0	-6.7	7.8	-6.7	-	NS	NS
Los 100 QD (C)	28	101.1	4.8	91.5	8.8	-9.6	6.5	-9.7	-	-	NS
Los 50 BID (D)	30	101.4	4.7	92.6	8.2	-8.8	7.8	-8.6	-	-	-

NS - Not Statistically Significant; * - Treatment Difference Statistically Significant, $P < 0.05$

** - Treatment Difference Statistically Significant, $P < 0.01$; Pairwise comparisons are based upon adjusted mean.

NDA 020386

FIRM:

MERCK

3 OF 10

TRADE NAME:

COZAAR (LOSARTAN POTASSIUM) 25/50 MG TAB

GENERIC NAME:

LOSARTAN POTASSIUM

Table 21.7 Mean Changes in Sitting Systolic Blood Pressure (mmHg) at Week 4 (sphygmomanometer measurements)

Treatment	N	Baseline		Week 4		Change		Change Adj Mean	Comparison		
		Mean	S.D.	Mean	S.D.	Mean	S.D.		vs. B	vs. C	vs. D
Placebo (A)	30	149.3	14.9	149.7	13.2	0.3	12.2	-2.3	*	**	**
Los 50 QD (B)	29	148.2	17.7	146.5	17.5	-11.7	14.2	-10.3	-	NS	NS
Los 100 QD (C)	28	149.4	12.5	138.9	15.9	-10.5	13.6	-12.9	-	-	NS
Los 50 BID (D)	30	155.5	14.8	141	14.1	-14.5	15.1	-14.4	-	-	-

NS – Not Statistically Significant; * – Treatment Difference Statistically Significant, P<0.05

** – Treatment Difference Statistically Significant, P<0.01; Pairwise comparisons are based upon adjusted means

For those patients who received HCTZ after week 4, there was an additional reduction in sBP of 4.8 mmHg to 6.5 mmHg. This result in itself is unimpressive since this phase was essentially not blinded for the investigator.

Safety

One patient from each treatment group withdrew from monotherapy due to adverse events. One additional patient in the losartan 100 mg group withdrew after HCTZ was added. Table 21.7a lists the patients withdrawn for adverse events.

Table 21.7a. Withdrawals for Adverse Events

Patient #	Treatment	Day Withdrawn	Reason for Withdrawal
35	placebo	10	Myocardial Infarction
160	losartan 100 mg	20	tinnitus and headache
81	losartan 50 mg	completed 4 weeks	sexual dysfunction*
11	losartan 50 mg bid	3	diarrhea and nausea
88	losartan 100 mg + HCTZ 12.5 mg	39	ataxia

* present during baseline period also

The incidence of patients experiencing adverse events was 46.9%, 37.9%, 29% and 33.3% in the placebo, losartan 50 mg, losartan 50 mg bid and losartan 100 mg groups respectively (monotherapy). Table 21.8 lists all adverse experiences with an incidence of greater than 4% in any one treatment group. Four percent was chosen as the cutoff because this would require at least 2 patients within a treatment group experience the adverse event.

Table 21.8 Most Common Clinical Adverse Experiences (Patient Incidence > 4% in Any One Treatment Group)

	Placebo (N=32)	Losartan 50 QD (N=29)	Losartan 100 QD (N=30)	Losartan 50 BID (N=31)
Monotherapy	n (%)	n (%)	n (%)	n (%)
Dyspepsia	1 (3.1)	2 (6.9)	0	0
Headache	3 (9.4)	1 (3.4)	4 (13.3)	2 (6.5)
URI	2 (6.3)	0	1 (3.3)	3 (9.7)
Pharyngitis	1 (3.1)	2 (6.9)	0	0
Congestion, Nasal	0	0	2 (6.7)	1 (3.2)
Monotherapy + Combination therapy				
Headache	4 (12.5)	1 (3.4)	5 (16.7)	6 (19.4)
Dizziness	0	2 (6.9)	1 (3.3)	1 (3.2)
URI	2 (6.3)	1 (3.4)	1 (3.3)	5 (16.1)
Pharyngitis	1 (3.1)	2 (6.9)	0	1 (3.2)
Congestion, Nasal	0	0	2 (6.7)	2 (6.5)
Asthenia/Fatigue	1 (3.1)	1 (3.4)	0	2 (6.5)
Edema	2 (6.3)	0	0	0
Pain, Chest	2 (6.3)	0	0	0
Dyspepsia	1 (3.1)	2 (6.9)	0	0
Pain, Back	0	0	2 (6.7)	0

Two losartan 50 mg bid patients (82 and 103) had mildly elevated ALT and AST. Both patients were receiving lovastatin. Mean uric acid levels tended to decrease with therapy.

Mean pulse did not differ significantly from baseline with losartan treatment.

Clinical Pharmacology Trials						
Study #	Design/ Patient Population	Treatment Groups	N	Primary Endpoints	Other Measures	Page
001	- ol, single dose (multiple single oral doses separated by approximately 1 week) - healthy male subjects	- placebo - losartan 2.5 mg - losartan 5.0 mg - losartan 10 mg - losartan 20 mg - losartan 40 mg Total Enrolled	6 2 2 6 8 7 8	- blunting of angiotensin I pressor response	- neurohormones - losartan levels	78
002	- ol, single dosing, 8 day dosing, pc - healthy male subjects	- placebo - losartan 5.0 mg - losartan 10 mg - losartan 20 mg - losartan 40 mg Total Enrolled	6 6 6 5 6 29	- blunting of angiotensin II pressor response	- neurohormones - losartan levels	78
003	- single dose, pc, db, single center (each subject received 3 active and 1 placebo dose) - healthy male Caucasians or Hispanics	- placebo - losartan 10 mg - losartan 20 mg - losartan 40 mg - losartan 80 mg - losartan 120 mg - losartan 150 mg - losartan 200 mg - losartan 250 mg - losartan 300 mg Total Enrolled	7 7 7 15 8 15 8 8 15 7 34	- pharmacokinetics and pharmacodynamics	- urinary Na and K baseline renin	79
004	- r, db, single center, pc, escalating single dose (each subject received 4 active and 1 placebo dose separated by 1 week) - hypertensive caucasian or hispanic males or females	- placebo - losartan 5 mg - losartan 10 mg - losartan 20 mg - losartan 40 mg - losartan 60 mg - losartan 80 mg - losartan 100 mg - losartan 120 mg Total Enrolled	18 10 8 10 8 10 8 10 8 18	- change in blood pressure	- pharmacokinetics	84
006	- ol, single dose - healthy males	- placebo - losartan 40 mg - losartan 80 mg - losartan 120 mg Total Enrolled	7 6 7 6 7	- blunting of angiotensin II pressor response	- neurohormones - losartan levels	87
007	- db, single center, pc, 7 days treatment - healthy males	- placebo - losartan 100 mg Total Enrolled	4 10 14	- compare pharmacokinetics on day 9 versus day 1	- neurohormones - urinary excretion of Na ⁺ and K ⁺	88
013	- db, pc, single dose 20 minute intravenous infusion - healthy males	- placebo - losartan 1 mg - losartan 10 mg - losartan 20 mg - losartan 40 mg Total Enrolled	9 6 6 6 6 18	- pharmacokinetics		91
015	- ol, r, 2-period co, single dose - healthy males	- losartan 100 mg	8	- change in pharmacokinetics with food	- neurohormone levels	94
017	- db, pc, r, rising single dose infusion of E-3174 - healthy males	- placebo - E-3174 1 mg i.v. - E-3174 5 mg i.v. - E-3174 1 mg i.v. - E-3174 5 mg i.v. - E-3174 10 mg i.v. - E-3174 20 mg i.v. - E-3174 40 mg i.v. - E-3174 80 mg i.v. Total Enrolled	17 6 7 6 6 6 6 6 6 6 19	- pharmacokinetics		96

Clinical Pharmacology Trials (continued)						
Study #	Design/ Patient Population	Treatment Groups	N	Primary Endpoint	Other Measures	Page
019	- r, db, pc, 4 period co, single dose - healthy, non-black males on sodium restricted (40 mmole/day) and furosemide	- placebo - losartan 5 mg - losartan 10 mg - losartan 25 mg - losartan 50 mg - losartan 100 mg Total Enrolled	12 4 5 7 9 8 14	- change in supine SBP	- change in supine and standing blood pressure - neurohormones	99
022	- 3 period co, single dose, losartan 100 mg tablets, capsules and losartan 30 mg i.v. - healthy male	- losartan 100 mg tablets - losartan 100 mg capsules - losartan 30 mg i.v. Total Enrolled	8 8 8 8	- bioequivalence		97
023	- r, db, pc, single dose, 2 - period co (crossover based on high and low salt diet) - healthy, non-black males	- placebo - losartan 100 mg	8 16	- renal hemodynamics and tubular function		101
024	- 2 period co cimetidine interaction study - healthy male subjects	- losartan 100 mg - losartan 100 mg + cimetidine 400 mg q6 hr. Total Enrolled	8 8 16	- pharmacokinetics		100
031	- r, db, pc, 4-period co, single dose - healthy male	- losartan 100 mg - losartan 20 mg - enalapril 10 mg - placebo Total Enrolled	8 8 8 8 8	- inhibition of the pressor response of angiotensin I and II in the dorsal hand vein		105
034	- r, db, pc, 4-period co single dose - healthy non-black males - low salt diet (40 mmol/day) + furosemide 40 mg bid and replete salt diet (100 mmol salt/day + 40mmol salt diet)	- losartan 100 mg - placebo Total Enrolled	12 12 12	- autonomic function 4 hours post dose	- 24 hour urine excretion - plasma renin activity, All, aldosterone, NE, Epi, drug concentrations	108
035	- r, db, pc, 4 period co single dose - healthy males	- placebo - losartan 20 mg - losartan 100 mg - enalapril 20 mg Total Enrolled	9 9 9 9 9	- forearm blood flow response to intraarterial infusions of angiotensin I, angiotensin II and bradykinin		112
043	- r, db, pc, ac, 6 wk Rx period - non-black hypertensives	- losartan 25 mg od - losartan 100 mg od - placebo - enalapril 20 mg od	11 14 12 14	- plasma renin - plasma angiotensin II	- losartan levels - E-3174 levels - plasma and urine aldosterone - plasma and urine NE and Epi - supine DBP and SBP - rebound hypertension	128
060	- o, 3 period co - healthy males - losartan doses labeled with ¹⁴ C	- losartan 100 mg oral - losartan 30 mg i.v. - E-3174 20 mg i.v. Total Enrolled	6 6 6 6	- pharmacokinetics		114
067	- o, 3 period co - patients with hepatic insufficiency	- losartan 50 mg oral - losartan 10 mg i.v. - E-3174 10 mg i.v. Total Enrolled	9 9 9 9	- pharmacokinetics		115

Clinical Pharmacology Trials (continued)						
Study #	Design/ Patient Population	Treatment Groups	N	Primary Endpoint	Other Measures	Page
070	- db, pc, 2-period co, 14 day treatment period - healthy males - 30 mg warfarin on day 7 of each period	- losartan 100 mg - placebo Total Enrolled	10 10 10	- warfarin enantiomer pharmacokinetics	- change in prothrombin time	119
072	- sb, 2 period, ad, phenobarbital interaction study - healthy males - Rx included single dose of losartan then 14 day of phenobarbital followed by single dose of losartan or placebo	- losartan 100 mg - placebo	10 5	- pharmacokinetics		117
074	Refer to Biopharm Review					
075	Refer to Biopharm Review					
079	- db, r, pc, 2-period co, 15 day treatment - healthy male subjects - digoxin 5 mg i.v. on day 4 and digoxin 5 mg orally on day 11	- losartan 50 mg - placebo Total Enrolled	13 13 13	- digoxin pharmacokinetics		127
012	- ol, no, 2 center, 7 day Rx period - hypertensives with renal insufficiency - includes hemodialysis patients	- losartan 100 mg daily		pharmacokinetic parameters (losartan and E-3174)	- plasma renin - plasma aldosterone - urine creatinine clearance - urine sodium, urea nitrogen - hemodynamics	165
018	- sb, 4 wk Rx period - female hypertensives	- losartan 50 mg	16	- change in prostaglandin excretion (PGE ₂ , prostacyclin, thromboxane A ₂)	- renin - aldosterone	132
069	- r, db, pc, single i.v. dose of E-3174 - non-black hypertensives	- placebo - E-3174 i.v.	8 12	Relationship between blood pressure changes and plasma levels of E-3174	- plasma renin - creatinine clearance	136
357	NO DATA PROVIDED					
065	- o, 2-period co, single center - elderly hypertensives (≥ 65 years)	- losartan 50 mg oral - losartan 10 mg i.v. Total Enrolled	10 10 10	- pharmacokinetics	- change in blood pressure	122

wk = week, db = double-blind, ol = open label, od = once a day, bid = twice a day, r = randomized, ac = active control, pc = placebo control, n = no control, p = parallel, c = crossover, hx = history, HTN = hypertension, ACEI = angiotensin converting enzyme inhibitor, NE = norepinephrine, Epi = epinephrine, PRA = plasma renin activity Rx = treatment

Study 001.

This open label trial of 8 healthy male subjects attempted to show that single doses of losartan blunt the pressor response of angiotensin I infusions. This trial was reviewed in the original IND application. Patients received multiple intravenous infusions of angiotensin I until a dose that increased supine systolic blood pressure by 20 - 30 mmHg was determined. Single doses of placebo and losartan were administered and angiotensin I infusions were repeatedly administered over time. The change in blood pressure was measured with each infusion. Each patient was to receive a single dose of placebo and 3 single doses of either losartan 2.5 mg, 5.0 mg, 10 mg, 20 mg or 40 mg (oral solution lot # 88 RM 018). Each dose was separated by 1 week. There were some deviations from the protocol by the investigator that do not impact the outcome of the trial. The following results were obtained.

- 1) Losartan doses of 10 mg or greater blunted the angiotensin I pressor response.
- 2) Pre-angiotensin I challenge systolic blood pressure increased after losartan dosing. It is unclear whether this is due to a losartan agonist effect.
- 3) Immunoreactive angiotensin II increased with losartan treatment.

Study 002.

This was an open label trial in 29 healthy male subjects (24 Caucasians, 3 blacks, 1 Asian, 1 Arab) that attempted to show that losartan (multiple doses) blunts the pressor response of angiotensin II infusions. The amount of angiotensin II infusion required to increase systolic blood pressure by 20 - 30 mmHg was determined during the week prior to treatment. Subjects received a single dose of either placebo or losartan (5 mg, 10 mg, 20 mg, 40 mg). This was followed by multiple infusions of angiotensin II on day 1, 4 and 8 [pre-dose, 6, 12 (except day 4) and 24 hours post-dose] of treatment during which blood pressure changes were measured. The following results were obtained.

- 1) Losartan blunted the pressor response of angiotensin II predominately at 6 and 12 hours with some effect apparent at 24 hours.
- 2) Plasma renin and immunoreactive angiotensin II increased post losartan dosing (table 2.1. and table 2.2.)

Table 2.1. PLASMA RENIN ACTIVITY (ng/ml/h)

		Time Relative to Dosing			
		Day 1		Day 8	
		0 hrs	6 hrs	0 hrs	6 hrs
Dose (mg)	N				
Placebo	N	6	6	6	6
	MEAN	0.79	1.09	0.96	1.16
	STDERR	0.28	0.23	0.19	0.25
5	N	6	6	6	6
	MEAN	0.99	2.00	1.29	2.57
	STDERR	0.37	0.59	0.33	0.62
10	N	6	6	6	6
	MEAN	1.18	3.31	1.75	3.80
	STDERR	0.24	0.88	0.36	0.95
20	N	5	5	5	5
	MEAN	1.00	4.24	2.02	6.78
	STDERR	0.16	0.91	0.47	2.06
40	N	6	6	6	6
	MEAN	0.77	4.18	2.30	8.93
	STDERR	0.12	1.17	0.29	1.00

Table 2.2. Immunoreactive-ANGIOTENSIN II (pg/ml)

Dose (mg)		Time Relative to Dosing			
		Day 1		Day 8	
		0 hrs	6 hrs	0 hrs	6 hrs
Placebo	N	6	6	6	6
	MEAN	4.08	6.72	4.73	6.63
	STDERR	1.07	1.53	1.11	1.42
5	N	6	6	6	6
	MEAN	6.45	13.95	7.47	18.02
	STDERR	2.33	5.09	2.19	5.15
10	N	6	6	6	6
	MEAN	9.30	18.98	9.36	18.90
	STDERR	1.77	5.01	1.77	5.01
20	N	5	5	5	5
	MEAN	5.62	20.82	11.44	35.24
	STDERR	0.78	4.10	2.59	9.80
40	N	6	6	6	6
	MEAN	4.38	21.47	13.55	49.50
	STDERR	0.73	4.84	1.88	7.05

3) Aldosterone and epinephrine remained unchanged compared to placebo.

4) No serious adverse events were reported.

5) Losartan levels were essentially non-detectable for doses less than 40 mg. For losartan 40 mg, levels were detectable at 3 and 6 hours post dose. E-3174 levels were detectable up to 12 hours post-dose. (see table 2.3)

Table 2.3. Losartan and E-3174 Concentrations

	Losartan concentrations (ng/ml)							E-3174 concentrations (ng/ml)							
	Hour	Losartan 20 mg			Losartan 40 mg			Hour	Losartan 20 mg			Losartan 40 mg			
		Mean	S.D.	Range	Mean	S.D.	Range		Mean	S.D.	Range	Mean	S.D.	Range	
Day 1	0	0	0	bql	0	0	bql	Day 1	0	0	0	bql	0	0	bql
	3	22.4	13.2	bql - 35.2	31.2	8.1	22.1 - 45.3	3	68.3	23.7	31.9 - 91.7	181	88.3	75.5 - 292.1	
	6	5.1	11.5	bql - 25.6	6	14.6	bql - 35.8	6	93	63.6	37.7 - 195.5	151.3	60.7	86.1 - 249.5	
	12	0	0	bql	0	0	bql	12	22.8	16.5	bql - 38.3	56	10.9	42 - 70.1	
	24*	0	0	bql	0	0	bql	24*	0	0	bql	0	0	bql	
Day 4	72*	0	0	bql	0	0	bql	Day 4	72*	0	0	bql	0	0	bql
	75	13	17.7	bql - 32.5	38.9	14.9	24.1 - 64.3	75	90.2	63.7	36.1 - 200.8	182.7	84.6	86.1 - 320.7	
	78	0	0	bql	0	0	bql	78	73.9	22.4	44.8 - 95.1	131.3	34.6	85.9 - 167	
	84	0	0	bql	0	0	bql	84	18.9	17.3	bql - 32.5	48.2	11.2	37.4 - 64.6	
Day 8	168*	0	0	bql	0	0	bql	Day 8	168*	0	0	bql	3.5	8.7	bql - 21.2
	171	0	0	bql	29.2	19.9	bql - 55.5	171	94.2	32.6	56.5 - 137.8	186	97.1	92.3 - 326.5	
	174	0	0	bql	5.3	12.9	bql - 31.6	174	81.4	18.8	65.3 - 111.8	160.3	54.3	118.1 - 237	
	180	0	0	bql	0	0	bql	180	27.3	15.9	bql - 39.9	56.3	25	33.7 - 96.6	
Day 9	192	0	0	bql	0	0	bql	Day 9	192	0	0	bql	0	0	bql
	198	0	0	bql	0	0	bql	198	0	0	bql	0	0	bql	
	204	0	0	bql	0	0	bql	204	0	0	bql	0	0	bql	

bql = below quantifiable limit, * = pre-dose (trough)

Study 003.

Protocol

The study was conducted in a single center employing a double-blind, placebo-controlled design. The study enrolled healthy male subjects. Each subject received four single-dose treatments of study drug (three active, one placebo) in rising dose order with respect to active drug and placebo inserted into the sequence according to a random allocation schedule. A one-week washout period was maintained between treatments, resulting in a per subject study duration of five weeks. There were four treatment groups with Group 1 receiving single doses of 10 mg, 20 mg, and 40 mg; Group 2 receiving doses of 40 mg, 80 mg, and 120 mg; Group 3 receiving 120 mg, 150 mg, and 200 mg; and Group 4 receiving 200 mg, 250 mg, and 300 mg. Prior to the start of the active treatment periods, each subject received a single dose of placebo (open-label) and blood pressure and ECG recording were measured for a 24 hour period. These measurements were treated as baseline values.

Table 3.1 outlines the clinical procedures and laboratory measurements performed during the study.

Table 3.1. Procedures

EVALUATION	Days	PLACEBO PHASE***									TREATMENT GROUP 1-4							Post
		-9	-8	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	
	Screen										7	8	9	10	11	12	13	
											14	15	16	17	18	19	20	
											21	22	23	24	25	26	27	
Medical History	X																	
Physical Exam	X																	
12-Lead ECG	X		X	X								X	X					
BP Measure	X		X	X								X	X					
Vital Signs	X		X	X								X	X					
Lab Tests	X											X	X					
Drug Screens	X	X								X								
Plasma Samples												X	X					
Urine Samples												X	X					
Drug Administration			P									X						

P = Placebo only.

*** = Placebo phase occurs one week prior to the start of each treatment group, respectively. BP and vital signs measured only through 24 hours post-dose.

12-Lead ECG: Prior to each dose administration and at 3, 6, 12, and 24 hours post-dose.

BP and Vital Signs: 1, 0.75, 0.5, 0.25 hours, and immediately prior to each dose administration and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, 23, 24, 28, 32 and 36 hours post-dose.

Clinical Labs: Prior to each dose administration and prior to discharge from clinic after plasma samples and BP measurements completed.

Losartan PK profile: At 0 (pre-dose), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 30 hours post-dose.

Urine collection intervals: Pre-dose, 0-2, 2-4, 4-12, 12-24 and 24-36 hours post-dose.

Effect of Losartan dose on urinary excretion of sodium (Na), potassium (K) and creatinine (Cr) was explored. Excretion per hour was calculated for each parameter and displayed for each subject by collection interval and by total excreted over 24 hours. Glomerular filtration rate (GFR) was estimated from total Cr excreted in 24 hours divided by plasma creatinine concentration post-dose.

Descriptive pharmacokinetic parameters were determined based on the plasma concentration-time data. Pharmacokinetic parameters and their methods of estimation are presented in table 3.1a.

Table 3.1a. Pharmacokinetic Parameters Definitions

Parameter	Definition
C _{max}	observed maximum plasma concentration
T _{max}	time C _{max} is observed
AUC	area under the plasma concentration-time curve from time zero to infinity. The AUC from time zero to the last quantifiable concentration time point was calculated by the linear trapezoidal rule. The residual area was estimated from the calculated concentration (linear regression) at the last quantifiable concentration time divided by λ . If the calculated concentration was not available (i.e. subject failed the criteria for half-life determination), the observed concentration was used.
Half-life ($t_{1/2}$)	the 'apparent' disposition or terminal $t_{1/2}$. It is calculated as $\ln 2/\lambda$, where λ is the absolute value of the terminal slope from linear regression of natural logarithm of plasma concentrations versus time. The number of concentration-time points used for regression analysis was based on the goodness of fit and on the coefficient of determination (r^2) which had to be equal to or exceeding 0.90. If these criteria were not met and a terminal slope was required in a subsequent calculation (i.e. estimating AUC), then the mean of the terminal slopes from other doses of the same subject was used as the best estimate.

Data are expressed as arithmetic mean $\pm$ standard deviation (S.D.) unless otherwise indicated. The harmonic mean was calculated for $t_{1/2}$ along with a pseudo S.D. based on the jackknife variance technique.^[3] The median and range were calculated for T_{max}. When calculating mean and S.D., bql (below quantifiable limit for the assay) was treated as zero. If all values were bql, the mean concentration was reported as zero. The bql for Losartan was 20 ng/mL and for E-3174 the bql was 17 ng/mL.

Results

The study was conducted with a total of 34 enrolled subjects. All subjects were male caucasian. The subjects ranged in age from 19 to 47 years with a median age of 32.5 years. Five subjects discontinued the study prematurely. Table 3.2 lists the reasons for discontinuation.

Table 3.2. Patients Discontinued Prematurely

Subject #	Last Treatment	Reason Discontinued
#17	open label placebo	Adverse Event - cellulitis
#30	open label placebo	Positive hepatitis A IgM
#10	not provided	protocol violation - erroneous report of alcohol use
#5	20 mg	adverse event - persistent headache (negative rechallenge)
#115	200 mg	adverse event - severe orthostatic hypotension 8 hours post dosing

Table 3.3 lists the pharmacokinetic results for losartan and E-3174. The harmonic mean elimination half-life for losartan ranged between .9 and 1.6 hours. Increases in mean C_{max} were slightly greater than expected for the percentage increase in dose. AUC increased dose proportionally. The harmonic mean elimination half-life for E-3174 ranged between 3.9 and 5.5 hours (excluding the 10 mg dose group - only one patients values could be measured). As with losartan, increases in mean C_{max} were slightly greater than expected for the percentage increase in dose. AUC increased dose proportionally.

Table 3.3. Pharmacokinetic Parameters

Dose (mg)		Losartan					E-3174				
		C _{max} (ng/mL)	T _{max} (hr)	AUC (ng·hr/mL)	λ(n) (hr ⁻¹)	t _{1/2} ^a (hr)	C _{max} (ng/mL)	T _{max} (hr)	AUC (ng·hr/mL)	λ(n) (hr ⁻¹)	t _{1/2} ^b (hr)
10	Mean	21.1	1.00	94.1	0.4418	1.6	30.3	6.00	434.3	0.0393	17.6
	S.D.	15.9	(0.25-1.50)	NA	NA	NA	15.8	(4.0-8.0)	178.0	NA	NA
	n	7	5	2	2	2	7	6	6	1	1
20	Mean	71.6	0.50	137.8	0.7437	0.9	66.4	4.00	777.9	0.1266	5.5
	S.D.	35.2	(0.5-2.0)	57.9	0.5327	0.7	35.4	(3.0-6.0)	122.8	0.0182	0.8
	n	7	7	7	4	4	7	6	6	6	6
40 ^c	Mean	214.8	0.75	391.5	0.4539	1.5	186.7	4.00	1720.8	0.1607	4.3
	S.D.	123.4	(0.5-1.5)	225.5	0.2062	0.7	80.9	(3.0-4.0)	509.2	0.0460	1.3
	n	15	15	15	14	14	15	14	14	14	14
80	Mean	537.5	0.75	932.7	0.5262	1.3	480.6	3.00	3639.3	0.1669	4.1
	S.D.	226.1	(0.5-1.5)	519.2	0.2269	0.6	181.5	(2.0-4.0)	1451.7	0.0390	1.0
	n	8	8	8	7	7	8	8	8	8	8
120 ^c	Mean	600.5	1.00	1277.7	0.6111	1.2	907.7	2.00	5333.7	0.1781	3.9
	S.D.	371.3	(0.5-1.5)	572.7	0.2974	0.6	206.2	(1.5-3.0)	1664.1	0.0715	1.6
	n	15	15	15	15	15	15	15	15	15	15
150	Mean	1141.1	1.00	1678.0	0.4029	1.7	1241.6	1.75	6806.9	0.1610	4.3
	S.D.	364.3	(0.5-2.0)	296.6	0.1194	0.5	236.2	(1.5-3.0)	1735.2	0.0672	1.9
	n	8	8	8	8	8	8	8	8	8	8
200 ^c	Mean	2177.3	0.75	2371.6	0.4636	1.5	1718.5	1.50	8118.6	0.1454	4.8
	S.D.	826.8	(0.5-1.5)	704.1	0.2471	0.8	452.5	(1.0-3.0)	2110.3	0.0445	1.5
	n	15	15	15	15	15	15	15	15	15	15
250	Mean	2118.7	1.00	2567.3	0.5410	1.3	2039.9	2.00	9057.8	0.1693	4.1
	S.D.	1442.6	(0.5-2.0)	1062.1	0.3758	1.1	639.3	(1.5-2.0)	2910.9	0.0647	1.6
	n	7	7	7	7	7	7	7	7	7	7
300	Mean	2870.3	0.50	3492.4	0.5471	1.3	2327.1	2.00	10546.6	0.1426	4.8
	S.D.	1659.8	(0.5-1.0)	1593.8	0.3696	0.9	669.5	(1.5-3.0)	3219.1	0.0233	0.8
	n	7	7	7	7	7	7	7	7	7	7

a - Median and range

b - Harmonic mean and pseudo standard deviation based on the jackknife variance

c - Mean and S.D. of all subjects in two groups for this dose

NA - Not applicable

Figures 3.1 and 3.2 show the concentration versus time plots for losartan (DuP 753) and the metabolite E-3174.

Figure 3.1.

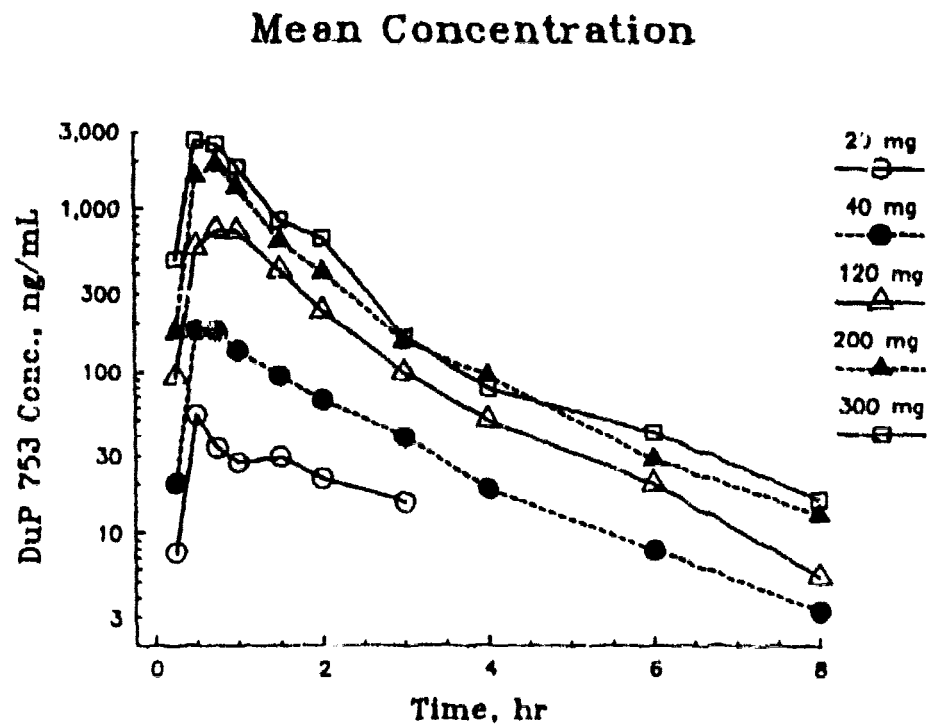


Figure 3.2.

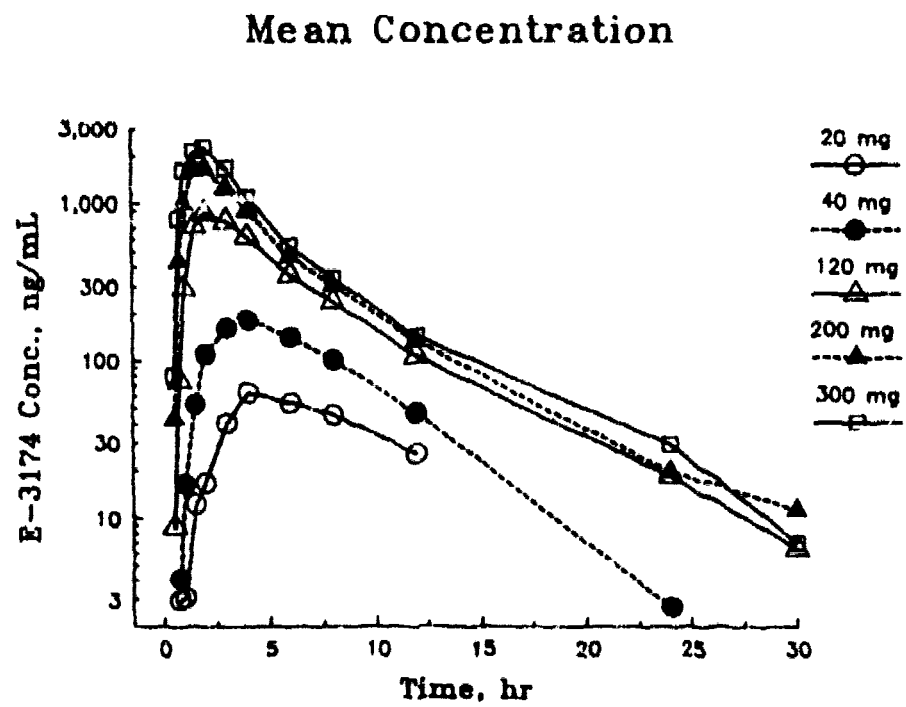


Figure 3.3 and 3.4 show the individual C_{max} values for losartan and E-3174 concentrations at each dose.

Figure 3.3.

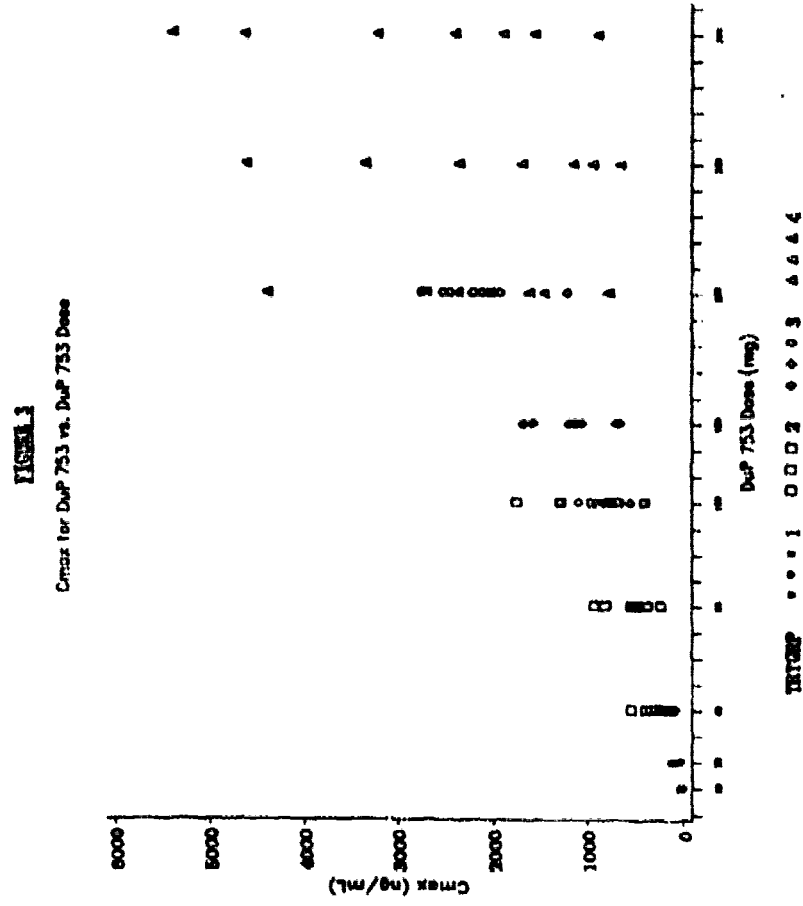
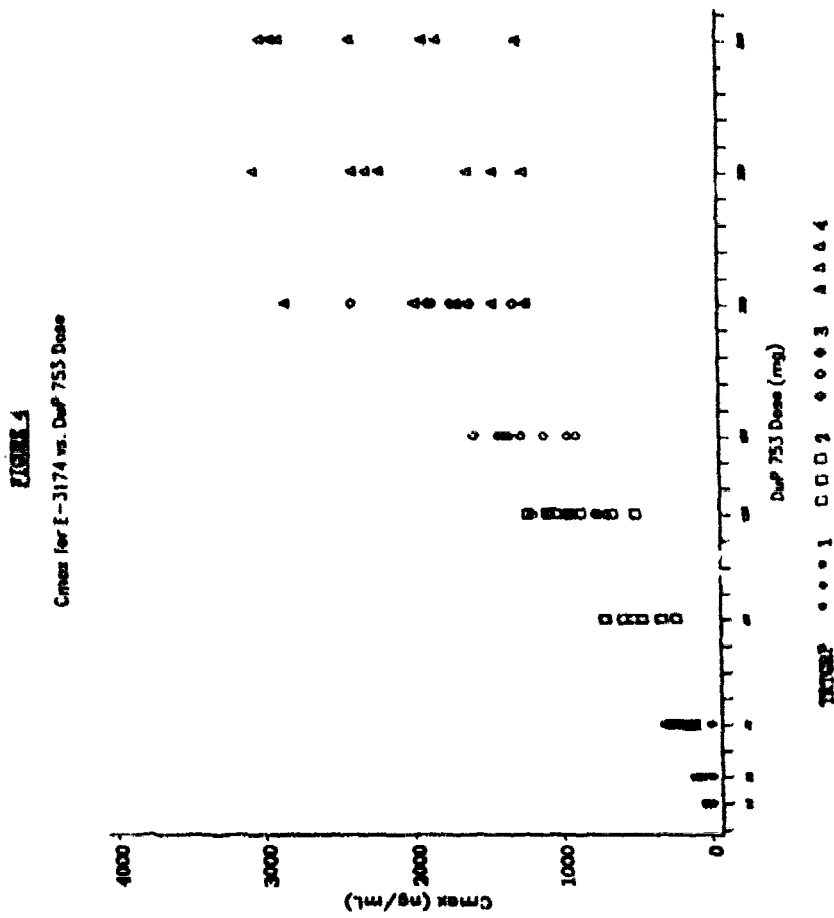


Figure 3.4.



For the most part, adverse events were unremarkable. Subject #2 had three instances of maculopapular rash on the palms; one instance occurred 3 days after dosing while the other 2 occurred 6 days after dosing. One subject (#15, Group 2) had a laboratory adverse experience. Hematuria was reported after the 0 mg dose which was mild.

There was no significant change in sodium excretion, potassium excretion or in creatinine clearance.

Study 004.

Protocol

This was a single center, randomized, double-blind, placebo controlled trial in 18 hypertensive patients. To be enrolled, patients had to have a supine DBP 95 - 115 mmHg on three consecutive screening visits. None of the screening DBP could be > 5 mmHg from the mean of the three screening measurements. There were two treatment groups with Group 1 receiving single doses of 5 mg, 20 mg, 60 mg and 100 mg and Group 2 receiving doses of 10 mg, 40 mg, 80 mg, and 120 mg. Group 1 and Group 2 patients were staggered in enrollment by three days so that preliminary safety and tolerance data on the lower doses were available before giving the next higher dose.

Table 4.1 summarizes the dosing sequence of the active phase of the study for Group 1 and Group 2, respectively.

Table 4.1. Treatment Allocations (dose expressed in mg)

Group 1

Dosing Sequence	Period				
	P1	P2	P3	P4	P5
S1	PLACEBO	5	20	60	100
S2	5	PLACEBO	20	60	100
S3	5	20	PLACEBO	60	100
S4	5	20	60	PLACEBO	100
S5	5	20	60	100	PLACEBO

Group 2

Dosing Sequence	Period				
	P1	P2	P3	P4	P5
S1	PLACEBO	10	40	80	120
S2	10	PLACEBO	40	80	120
S3	10	40	PLACEBO	80	120
S4	10	40	80	PLACEBO	120
S5	10	40	80	120	PLACEBO

Prior to the active phase, each patient received a single dose of placebo and their blood pressure and ECG recording was obtained for a 24 hour period. Patients advanced to the next higher dose if the previous dose was tolerated. Table 4.2 outlines the clinical procedures and laboratory measurements performed during the study.

Table 4.2. Procedures

12-Lead ECG	Prior to each dose administration and at 3, 6, 12 and 24 hours post-dose
Vital Signs	At -60, -45, -30, -15 and 0 minutes and at 15, 30, 45, 60, 90 minutes post dose and at 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, 23, 24, 28, 32, 36 and 48 hours post-dose.
Clinical Labs	Prior to each dose administration and at approximately 24 hours post-dose
DuP 753 PK Profile	Pre-dose, and at 30 minutes, 1, 2, 4, 8, 12, 24, 36 and 48 hours post-dose
Urine Collection Intervals	Pre-dose and each void for 24 hours post-dose

Results

Eighteen patients enrolled in the active treatment periods. An additional patient had been enrolled in the placebo phase of the study, but this patient was discontinued prior to the start of the active treatment periods. Group 1 consisted of 5 males (4 Hispanic, 1 Caucasian) and 5 females (all Hispanic) and Group 2 consisted of 8 males (5 Hispanic, 3 Caucasian). The patients ranged in age from 32 to 65 years with a median age of 51.5 years. The demographic data is summarized in table 4.3.

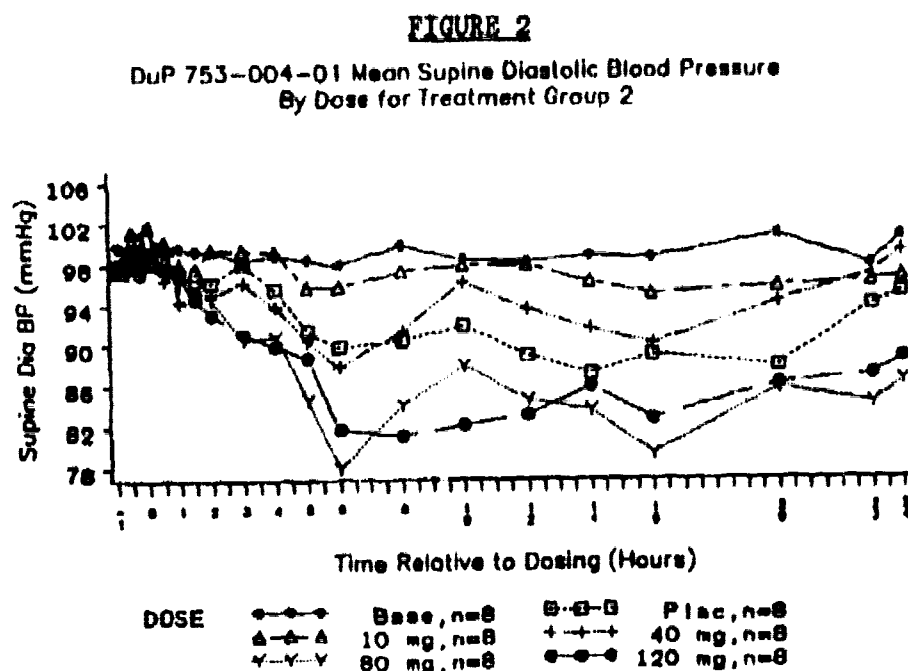
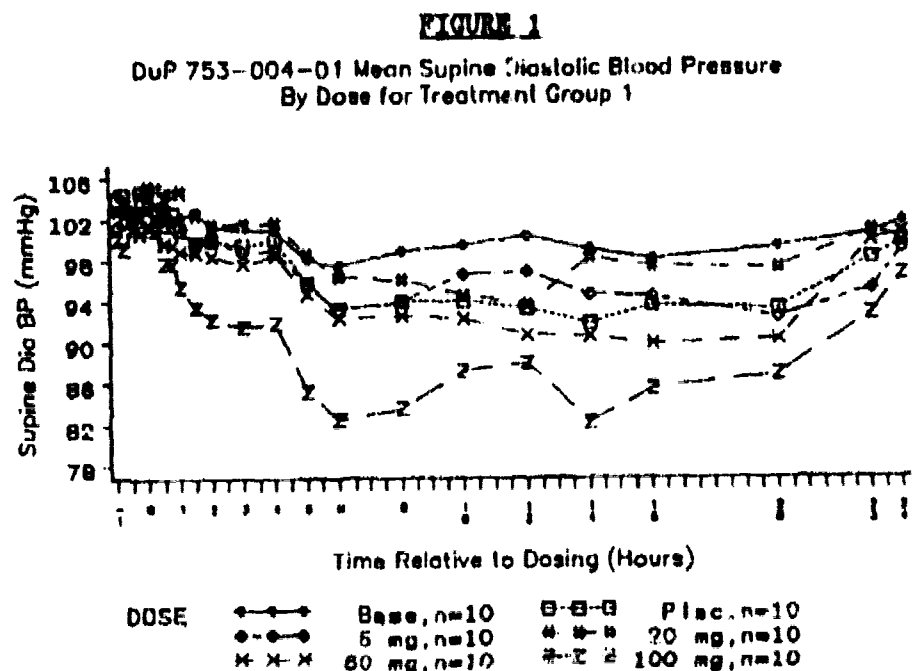
Table 4.3. Demographic Data

	Mean (S.D.)	Median (Min-Max)
Group 1 (n=10)		
Age (Yrs)	49.4 (6.1)	48.6 (37-58)
Weight (kg)	78.0 (15.3)	78.5 (61-99)
Hypertension (Yrs)	9.8 (8.2)	7.7 (1-30)
Group 2 (n=8)		
Age (Yrs)	56.6 (11.2)	61.2 (32-65)
Weight (kg)	85.8 (9.5)	85.7 (69-98)
Hypertension (Yrs)	9.2 (5.1)	8.2 (3-16)

Several models were used to test whether there was a sequence effect that could influence blood pressure outcome. The effect of sequence on pre-dose mean blood pressures was significant for supine DBP and standing SBP in group 2 patients.

The effect of sequence on the change in placebo response was significant for supine and standing DBP and supine SBP. Thus, there appears to be some sequence effect. Since lower doses are given in the early sequences in the escalating dose design, a sequence effect would influence the higher doses more than the lower with placebo somewhere in between. However, keeping in mind the limitations of this design, it is worthwhile to review the effect of dose on blood pressure over time. Figures 4.1 and 4.2 show the change in mean supine DBP over time. There appears to be a larger decrease in DBP with increases in dose.

Figures 4.1 and 4.2. Mean Supine DBP



The effect of dose on SBP are less distinguishable but still tend to be greater with higher doses.

Table 4.4 lists the pharmacokinetic parameters for losartan by dose. The mean (harmonic) elimination half life is approximately 1 hour. There is a linear relationship between C_{max} and dose but the relationship is not proportional. There is a linear relationship between AUC and dose that is proportional (e.g. a doubling of dose results in a doubling of the AUC).

Table 4.4. Pharmacokinetic Parameters for Losartan

Dose (mg)		C _{max} ^a (ng/mL)	T _{max} ^a (hr)	AUC ^a (ng·hr/mL)	Cl _o ^a (L/min)	λ(n) ^b (hr ⁻¹)	t _{1/2} ^b (hr)
5	Mean	12.5	0.75	NA	NA	NA	NA
	S.D.	17.1	(0.5-2.0)	NA	NA	NA	NA
	n	10	4	NA	NA	NA	NA
10	Mean	36.7	0.5	116.3	1.594	NA	NA
	S.D.	24.1	(0.5-1.0)	41.6	0.576	NA	NA
	n	8	7	5	5	NA	NA
20	Mean	124.5	0.5	381.2	1.229	0.500	1.4
	S.D.	63.8	(0.5-2.0)	245.8	0.786	0.273	0.9
	n	10	10	7	7	5	5
40	Mean	206.5	0.5	403.4	1.792	0.498	1.4
	S.D.	130.3	(0.5-1.0)	143.0	0.472	0.244	0.8
	n	8	8	8	8	6	6
60	Mean	521.1	0.5	876.8	1.287	0.677	1.0
	S.D.	225.1	(0.5-1.0)	280.4	0.563	0.411	0.7
	n	10	10	10	10	9	9
80	Mean	471.8	1.0	882.4	1.609	0.558	1.2
	S.D.	257.8	(0.5-1.0)	212.0	0.476	0.405	0.5
	n	8	8	8	8	8	8
100	Mean	863.0	0.75	1533.9	1.367	0.664	1.0
	S.D.	466.8	(0.5-2.0)	789.4	0.739	0.311	0.5
	n	10	10	10	10	10	10
120	Mean	811.0	0.75	1409.1	1.420	0.684	1.0
	S.D.	398.3	(0.5-1.0)	322.1	0.363	0.253	0.4
	n	8	8	8	8	8	8

a Median and Range, b Harmonic mean and pseudo standard deviation based on jackknife variance
c Not available

Table 4.5 list the pharmacokinetic parameters for E-3174. C_{max} increases linearly with dose but not proportionally. AUC increases linearly with dose.

Table 4.5. Pharmacokinetic Parameters for E-3174

Dose (mg)		C _{max} ^a (ng/mL)	T _{max} ^a (hr)	AUC ^a (ng·hr/mL)	Cl _o ^a (L/min)	λ(n) ^b (hr ⁻¹)	t _{1/2} ^b (hr)
5	Mean	7.2	8.0	288.4	NA	NA	NA
	S.D.	11.8	(4.0-12.0)	107.4	NA	NA	NA
	n	10	3	2	NA	NA	NA
10	Mean	39.5	8.0	526.1	NA	NA	NA
	S.D.	12.0	(8.0)	123.1	NA	NA	NA
	n	8	8	7	NA	NA	NA
20	Mean	89.9	4.0	955.7	0.125	5.5	5.5
	S.D.	44.6	(4.0-8.0)	413.5	0.056	2.8	2.8
	n	10	10	10	6	6	6
40	Mean	198.6	4.0	2113.4	0.132	5.2	5.2
	S.D.	50.0	(4.0)	698.0	0.027	1.1	1.1
	n	8	8	8	7	7	7
60	Mean	486.5	4.0	3563.0	0.200	3.5	3.5
	S.D.	234.2	(1.0-8.0)	1075.9	0.060	1.0	1.0
	n	10	10	10	8	8	8
80	Mean	385.7	4.0	4536.1	0.176	3.9	3.9
	S.D.	237.7	(2.0-4.0)	1360.1	0.047	1.2	1.2
	n	8	8	8	8	8	8
100	Mean	839.0	2.0	3056.6	0.209	3.3	3.3
	S.D.	352.3	(1.0-4.0)	1170.0	0.070	1.1	1.1
	n	10	10	10	10	10	10
120	Mean	1046.7	2.0	6774.4	0.169	4.1	4.1
	S.D.	374.8	(2.0-4.0)	2116.5	0.034	0.8	0.8
	n	8	8	8	8	8	8

a Median and Range
b Harmonic mean and pseudo standard deviation based on jackknife variance
c Not available

T_{max} results were not dose dependent for plasma losartan. For plasma E-3174, T_{max} decreased with increasing dose.

There were no serious adverse events reported. The most common laboratory AE was hematuria with 7 occurrences in three patients.

Twenty-four hour urinary excretion of Na, K, and Cr, and of glomerular filtration (creatinine clearance) rate were measured. There was no significant treatment effect.

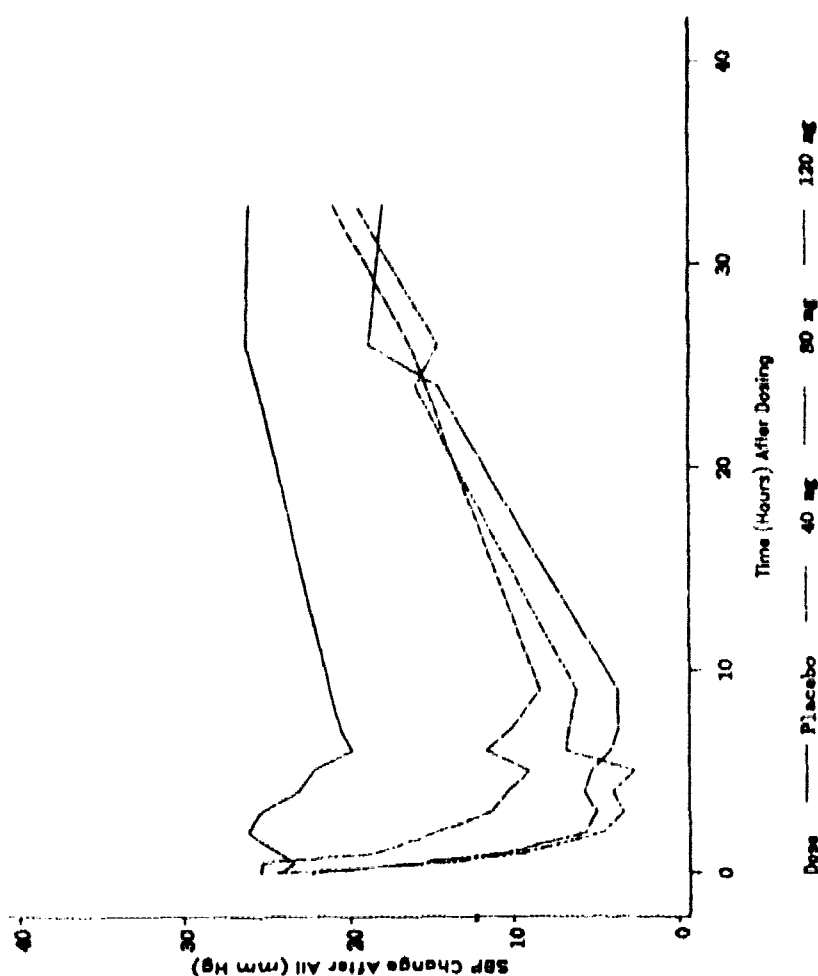
Study 006.

This was an open label trial that attempted to evaluate the ability of losartan 40 mg, 80 mg and 120 mg to suppress the pressor response of infusions of angiotensin II. The methodology is similar to that previously described in study 001 and 002. Subjects received a single dose of placebo, losartan 40 mg, losartan 80 mg and losartan 120 mg. After each dose, infusions of angiotensin II that increased the SBP by 20 - 30 mmHg on no therapy was administered on numerous occasions post dosing. Seven healthy males (5 caucasian, 2 arab) enrolled. The mean age was 24 years. One subject withdrew prematurely due to abdominal cramps.

In study 001, there was data to suggest that the SBP increased post dosing compared to baseline (measured prior to angiotensin I infusion). The concern was that this may suggest losartan has agonist activity (similar to saralasin). In this study, at 30 and 60 minutes post dosing, there was no evidence of an increase in SBP prior to angiotensin II infusion.

Figure 6.1 shows the mean responses to angiotensin II challenges. The suppression of the angiotensin II pressor effect persists for up to 30 hours. A similar response was seen with DBP. Heart rate generally decreases with angiotensin II infusion. After losartan, the decline in heart rate after angiotensin II infusion was less pronounced.

Figure 6.1. Mean Change in SBP in Response to Angiotensin II



Repeated measures analysis of variance showed that plasma renin activity, ir-angiotensin II, and aldosterone levels were significantly affected by dose ($p < 0.05$). Mean plasma renin, ir-angiotensin II and aldosterone are listed in tables 6.1 - 6.3.

Table 6.1. Plasma renin (ng/ml/h) after Losartan administration

TIME	PLACEBO	Losartan DOSE (mg)		
		40	80	120
PRE-DOSE	0.82	0.73	0.61	0.88
4 hours	1.28	3.23	4.15	10.82
9 hours	1.13	3.50	4.78	10.80
24 hours	1.19	2.09	2.41	3.10
33 hours	0.77	1.83	1.55	1.89

Post-tests showed that plasma renin levels after the 80 mg and 120 mg doses were larger than levels after placebo ($p < 0.05$), and that plasma renin levels after the 120 mg dose were larger than the 40 mg and 80 mg doses ($p < 0.05$). There was no significant difference between plasma renin levels after the 40 mg and 80 mg doses.

Post-tests least square difference (LSD) showed that ir-angiotensin II levels after the 120 mg dose were statistically significantly larger than levels observed after the other doses of Losartan or placebo ($p < 0.05$).

Table 6.2. Plasma ir-angiotensin II (pm) after Losartan administration

TIME	PLACEBO	Losartan DOSE (mg)		
		40	80	120
PRE-DOSE	6.00	7.23	3.43	4.38
4 hours	8.52	22.78	31.13	46.02
9 hours	12.10	21.42	19.02	50.00
24 hours	9.44	12.48	15.93	13.77
33 hours	11.53	10.75	8.73	9.24

Table 6.3. Plasma aldosterone (pg/ml) after Losartan administration

DOSE (MG)	PLACEBO	Losartan DOSE (mg)		
		40	80	120
TIME				
PRE-DOSE	71.83	52.67	68.33	83.83
4 hours	45.00	21.20	21.83	26.00
9 hours	46.00	25.33	26.83	26.00
24 hours	48.83	46.50	48.50	47.67
33 hours	47.17	41.83	41.33	29.67

For aldosterone, LSD showed that plasma concentrations after all doses of Losartan were significantly lower than concentrations after placebo ($p < 0.05$). Also, levels after 120 mg of Losartan were larger than levels after 40 mg of Losartan ($p < 0.05$).

Patient #1 experienced syncope after losartan 120 mg which was attributed to a vasovagal reaction. Scant information on this patient was provided in the study report.

Study 007.

Investigator: Thorir D. Bjornsson, M.D.
Jefferson Medical College

Protocol

This is a double-blind, parallel, placebo-controlled, three-phase study in fourteen healthy male volunteers between the ages of 18 and 40 years and within 20% of ideal body weight. The primary objectives of the study were as follows: (1) To determine whether the pharmacokinetics of losartan change with multiple dosing. (2) To determine the safety, tolerability, and hemodynamic effects in normotensive volunteers. (3) To investigate the effects of losartan on renin, angiotensin II, and aldosterone. For 3 days prior to the initiation of study drug, all subjects received a diet with 135 - 165 mEq of sodium and 70 - 90 mEq of potassium. The study was divided into 3 phases. During phase 1, subjects received a single dose of placebo (day 0). During phase 2, subjects received a single dose of either losartan 100 mg or placebo on day 1. During phase 3, subjects received 7 days of losartan 100 mg or placebo on days 3 through 9. Procedures performed during the study are outlined in table 7.1.

Table 7.1. Study Flow Chart

Procedure	Pre-study	Days -3, -2, -1	Phase 1		Phase 2		Phase 3							Post-Study		
			Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10			
Physical Examination	X															X
ECG	X		X	X						X			X			X
Laboratory Safety	X			X			X			X					X	X
Diet*		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dosing with Placebo Q.D.			X													
Dosing with losartan or Placebo Q.D.				X			X	X	X	X	X	X	X			
Blood Pressure/Heart Rate Monitoring			X**	X**			X	X	X	X	X	X	X**	X		
Plasma Collection for Drug Concentration				X	X				X†		X†	X†	X	X		
Urine Collection for Drug Concentration				X									X			
RAAS Profile a			X	X									X			
Norepinephrine/Epinephrine			X	X									X			
24-Hour Urine			X	X									X			
Overnight Stay at CRU		X	X	X									X	X		

* Diet - 135-165 mEq Na⁺, 70-90 mEq K⁺ to be started Day -3 a - -1, 6, 24 hours (supine 60 minutes prior to sample) and 6.5 hours (upright 30 minutes prior to sample)

**Frequent monitoring for 24 hours postdose.

† Trough Drug

The angiotensin II assay utilized in this study was highly specific for angiotensin II octapeptide combining HPLC separation of a plasma extract with radioimmunoassay of defined fractions utilizing an antibody with low crossover activity of angiotensin I.

Results

Fourteen male volunteers ranging in age from 18 to 31 years were enrolled in the study. Table 7.2 lists the demographic characteristics of the volunteers who entered and completed the study.

Table 7.2. Subject Characteristics

Subject	Race	Age (Years)	Weight (lb.)	Height (in.)
1	Caucasian	24	137	66
2	Caucasian	25	183	69.5
3	Caucasian	22	214	70
4	Caucasian	21	175.5	72
5	Caucasian	22	175	70
6	Caucasian	24	158	72
7	Negr	18	137	69
8	Caucasian	28	147.5	69.5
9	Caucasian	31	168	66
10	Caucasian	25	134.5	65
11	Caucasian	24	149.5	71
12	Caucasian	27	151.5	67
13	Caucasian	23	165	69
14	Caucasian	26	157.5	76
Mean		24.3	160.9	69.4
S.D.		3.15	21.6	2.89

Pharmacokinetic variables were evaluated for both losartan and E-3174. E-3174 is the active metabolite of MK-954. For losartan, the respective AUC_{24} and AUC_{∞} values were corrected for renal clearance prior to statistical evaluation. Table 7.3 lists mean pharmacokinetic data for day 1 and day 9. The mean C_{max} was 38% greater at day 9 compared to day 1. Renal clearance of losartan accounted for less than 4% of the dose. Table 7.4 lists the pharmacokinetic parameters of the active metabolite E-3174.

Table 7.3. Mean Changes From Day 1 on Day 9 In Pharmacokinetic Variables for losartan (N=10)
Difference Analyses

Variable	Day 1	Day 9	Difference (Day 9-Day 1)	P-Value
C _{max} (ng/ml)	315.5 ± 126.4	436.9 ± 311.6	121.4 ± 304.4	0.24
T _{max} (Hours)	1.5 ± 0.9	0.9 ± 0.5	(-) 0.6 ± 0.9	0.066
Elimination Rate (Hours ⁻¹)	0.352 ± 0.127	0.312 ± 0.111	(-) 0.040 ± 0.104	0.26
t _{1/2} (hours)	2.0 ± .7	2.2 ± .8		
Renal Clearance	74.3 ± 17.7	91.9 ± 24.2	17.7 ± 20.9	0.026
Urine % Dose	3.42 ± 1.08(c)	3.60 ± 1.67(c)	0.18 ± 1.19(c)	0.67

(c) N=9; Data excluded for Subject #1 due to possible incomplete urine collection on Day 9

Table 7.4. Mean Changes From Day 1 on Day 9 In Pharmacokinetic Variables for E-3174 (N=10)
Difference Analyses

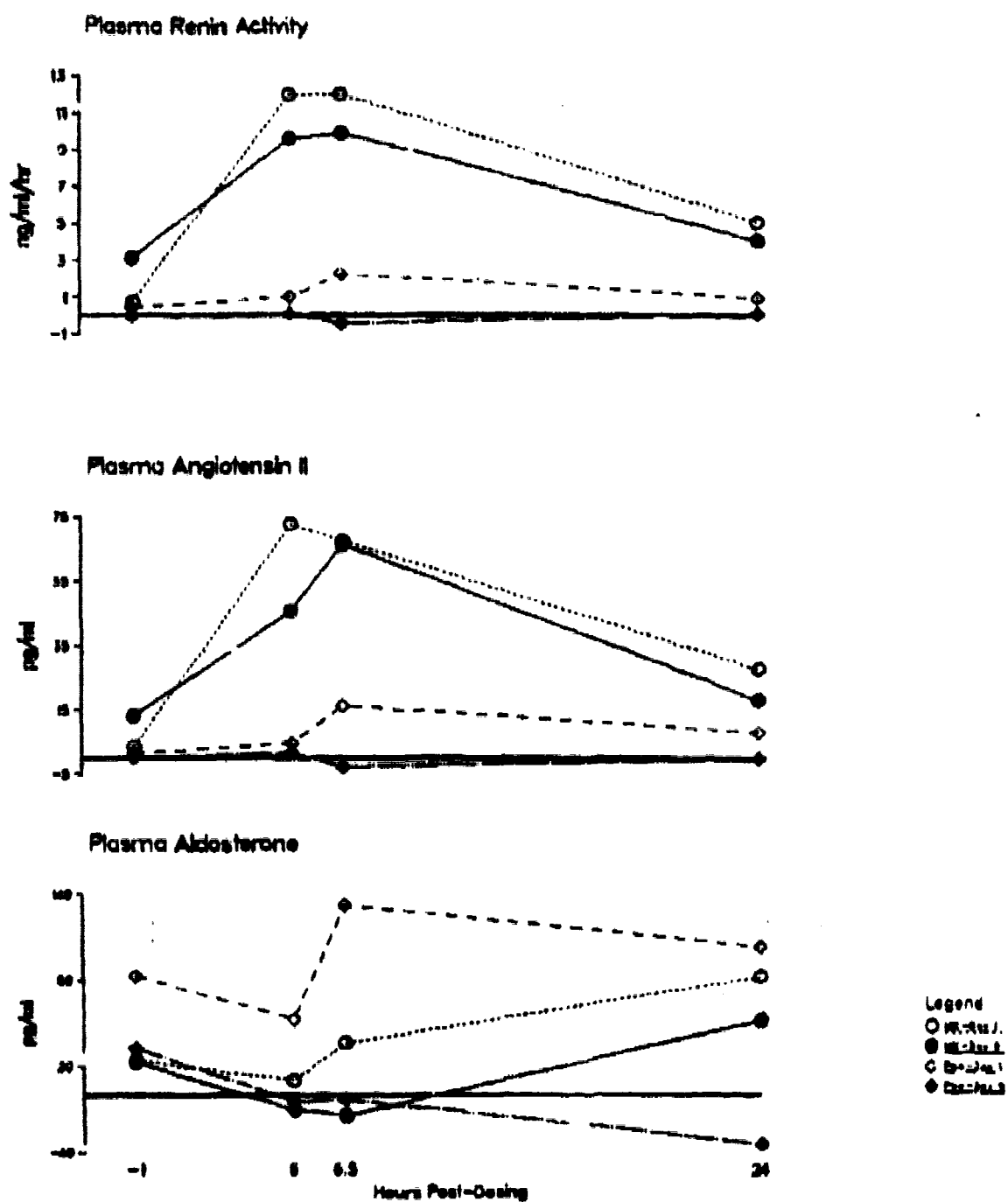
Variable	Day 1	Day 9	Difference (Day 9-Day 1)	P-Value
C _{max} (ng/ml)	568.4 ± 205.4	547.2 ± 179.2	(-)21.2 ± 131.7	0.62
T _{max} (Hours)	3.4 ± 0.9	2.7 ± 0.9	(-)0.7 ± 1.4	0.11
Elimination Rate (Hours ⁻¹)	0.077 ± 0.015	0.077 ± 0.014	(-)0.0004 ± 0.0189	0.95
t _{1/2} (hours)	9.0 ± 1.7	9.1 ± 1.6		
Renal Clearance (ml/min)	25.1 ± 5.0	26.6 ± 5.9	1.5 ± 7.1	0.51
Urine % Dose	5.7 ± 1.8(a)	5.8 ± 2.1(a)	0.1 ± 1.3(a)	0.84

(a) N=9; Data excluded for Subject #1 due to possible incomplete urine collection on Day 9.

The clinical summary report only includes the AUC corrected for clearance and expressed as the geometric mean of the ratio of day 9/day 1. The actual numerical values for AUC are not provided.

As illustrated in figure 7.1, plasma renin and angiotensin II levels increase with losartan treatment. Plasma aldosterone does not appear much different between treatments.

Figure 7.1. Renin, angiotensin II and aldosterone activity.



Urine excretion of sodium and potassium was not affected by losartan in subjects on a restricted sodium and potassium diet.

Adverse Experience

Table 7.5 lists the patients who experienced adverse events during the clinical trial.

Table 7.5. Clinical Adverse Experiences

Patient #	Day	Symptoms	Treatment	Intensity	Serious	Duration
1	-1	Headache	Placebo Run-In	Mild	No	3 hours
	1	Orthostatic BP	100 mg	Mild	No	6 hours
	off drug	Orthostatic BP	off drug	Moderate	No	30 min
	3	Orthostatic BP	100 mg	Mild	No	30 min
	10	Diarrhea	off drug	Mild	No	1 day
2	1	Esophageal Spasm	100 mg	Moderate	No	1.8 hours
	3	Orthostatic BP	100 mg	Moderate	No	8.7 hours
	10	Esophageal Spasm	off drug	Moderate	No	70 min
3	-1	Vasovagal Reaction	Placebo Run-In	Mild	No	1 day
	9	Vasovagal Reaction	100 mg	Mild	No	1 day
	15	Upper Respiratory	off drug	Mild	No	5 days
		Infection				
4	15	URI	off drug	Moderate	No	5 days
5	-1	Abdominal Cramps	Placebo Run-In	Mild	No	55 min
	1	Orthostatic BP	100 mg	Moderate	No	11 hours
	2	Listlessness	off drug	Mild	No	1.3 hours
	7	Change in Bowel Habit	100 mg	Mild	No	5 days
	16	Staph. Infection	off drug	Mild	No	10 days
	24	Head Trauma	off drug	Mild	No	2 days
12	6	Eyelid Disorder	100 mg	Mild	No	200 min
13	1	Orthostatic BP	100 mg	Moderate	No	30 min
	3	Palmar Inflammation	100 mg	Mild	No	68 days

Subject AN 013 had several peripheral smears which showed evidence of hemolysis, and an increase of serum creatinine level (within the normal range), both related to study drug. The hemolysis was noted during the study, while the rise in serum creatinine was noted poststudy. Events on this subject, who also had a dermatological reaction are summarized as follows. On October 3, 1990 (Day 8 of study), subject #13 reported that his palms were peeling. Upon examination he was noted to have had mild palmar desquamation with mild inflammation. There were no findings on the soles of his feet, and he reported no other symptoms. The subject had first noted the peeling Day 3 of the study (2 days after the initiation of dosing). He denied any change in soap, detergent or activities of daily living that might have accounted for his findings. He was evaluated by _____ who felt that his physical findings were consistent with a resolving inflammatory process.

On October 5, 1990, his peripheral smear, prepared from a heparinized specimen, revealed schistocytes and crenated red blood cells. His hemoglobin and hematocrit were 14.2 g/dl and 41.4%, respectively. At the time of his prestudy evaluation, on September 22, 1990, his hemoglobin was 16.3 with a hematocrit of 49.3. His hemoglobin and hematocrit continued to decrease and were 13.9 and 38.9 at the time of his poststudy physical exam; these were the lowest levels noted throughout his course.

On October 5, 1990, the subject was referred to _____ for further evaluation. After a thorough exam, including evaluation of a fresh peripheral smear, _____ concluded that the subject had experienced a transient hemolytic episode. A haptoglobin done at this time was within normal limits. An LDH was also normal at all timepoints. At the time of this visit, blood was sent for a serum creatinine and it was noted that the creatinine was elevated from a baseline of 1.2 mg/dl to a value of 1.5 thus suggesting that this episode might also be associated with mild alteration in renal function. Table 7.6 lists relevant laboratory values.

On October 18, 1990, the subject had an ESR of 2, a negative RPR, a negative Monospot, negative titers for cytomegalovirus, Lyme disease, and herpes simplex viruses type 1 and 2. His titers to Epstein-Barr virus on the same day revealed a negative IgM titer and a positive IgG titer suggesting a history of exposure to this virus at an unknown time in the past.

By October 20, 1990, the subject's hemoglobin had returned to 14.6 with a hematocrit of 44.0. His serum creatinine had also returned to baseline. All other laboratory safety screens including liver function tests, electrolytes, blood glucose, blood urea nitrogen, and urinalysis remained stable throughout his course. Follow-up with _____ on December 4, 1990,

revealed complete resolution of his physical and laboratory findings. At this time he was discharged from the study. Pertinent laboratory results for subject #13 are listed in table 7.6.

Table 7.6. Laboratory Values for Patient 013

Date	Phase	Hgb.	Hct.	Creatinine	Comments
8/23/90	Prestudy	15.9	46.6	1.2	
9/20/90	Prestudy	15.3	45.5		
9/22/90	Prestudy	16.3	49.3	1.4	
9/25/90	Run-In Placebo				
9/26/90	Single Dose-DuP	14.8	42.5	1.2	
9/27/90	No Dose				
9/28/90	Multiple Dose-DuP	15	44.1	1.3	
10/1/90		14.2	39.1	1.2	
10/3/90	Day 8 - AE				
10/5/90	Day 10	14.2	41.4	1.3	
10/9/90	Poststudy	13.9	38.9	1.4	
10/16/90	Dr. Martinez			1.5	
10/18/90				1.2	Hgb/Hct Hemolysis
10/20/90		14.6	44		

10/18/90: Monospot-Negative; CMV - Negative; HSV 1 & 2 - Negative; EBV - Positive IgG; Lyme - Negative; ESR-2

Study 013.

Protocol

This was a double-blind, randomized, rising-dose, placebo-controlled study in two alternating panels of 9 healthy male subjects per panel to evaluate the safety and tolerability of IV losartan infused over a 20-minute period. On each study day, 6 subjects in each panel received losartan and 3 received placebo, according to a randomized allocation schedule. Panel I (also referred to as Panel A) received 1, 10 and 40 mg of losartan or placebo and Panel II (also referred to as Panel B) received 5 and 20 mg of losartan or placebo. Panel II was to receive a maximal dose of 80 mg. However, adverse events and preliminary data suggesting changes in vital signs at 40 mg resulted in a decision to stop dose advancement at this dose.

Subjects reported to the clinic on the morning of each study day after an overnight fast. Predosing blood and urine samples were collected from each subject. Subjects then received the designated IV losartan or placebo infusion over a 20-minute period, according to a randomized allocation schedule. At specified doses, blood was to be collected for measurement of losartan concentration at the following time intervals: 0, 5, 10, 15, 20, 25, 30, 45, 60, 80, 100 and 120 minutes, 3, 4, 5, 6, 8, 10, 12, 16, 24, 30 and 36 hours post-initiation of infusion of losartan.

Urine samples for losartan concentration were collected at the following time intervals: 0-6, 6-12, 12-24, 24-36 and 36-48 hours postinitiation of infusion of losartan. Dose escalation occurred after a 7-day washout.

Results

Eighteen healthy male (15 caucasian, 2 black, 1 hispanic) subjects were enrolled. The mean age of subjects was 23.8 years (range: 19 - 40). Table 13.1 lists the mean pharmacokinetic parameters for losartan and E-3174. Figure 13.1 plots the concentration versus time curve for losartan and E-3174.

Table 13.1. Losartan (MK-954) Intravenous Safety Study. Summary of Pharmacokinetic Analysis

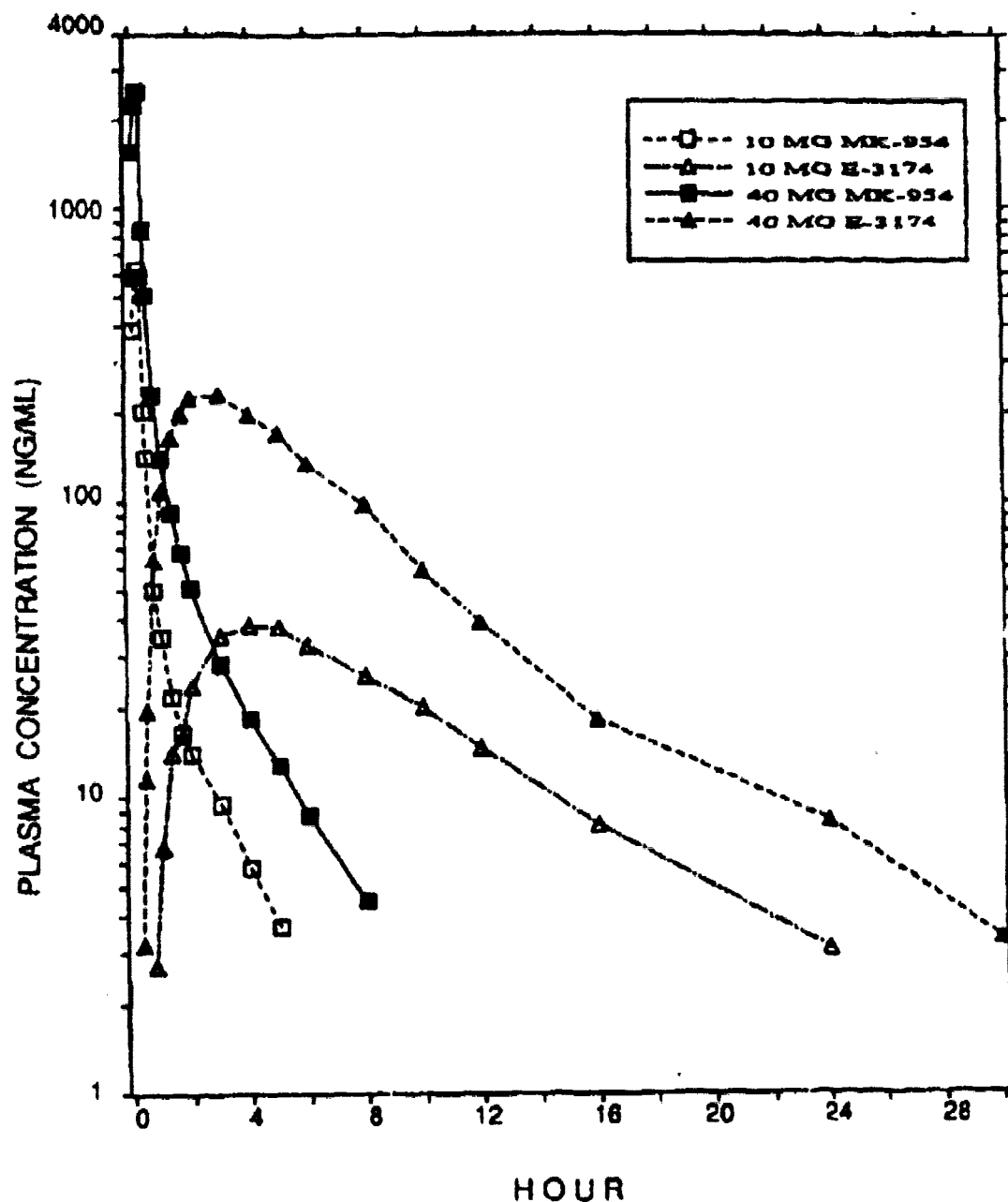
	Losartan				E-3174			
	10 mg		40 mg		10 mg		40 mg	
	mean	s.d.	mean	s.d.	mean	s.d.	mean	s.d.
C ₂₀ (ng/mL)	594	+/- 131	2501	+/- 564				
C _{max} (ng/mL)					40	+/- 14	241	+/- 63
t _{max} (hr)					4	+/- 0.9	2.6	+/- 0.9
AUC _(0-∞) (ng*hr/mL)	307	+/- 56	1187	+/- 254	433	+/- 122	1786	+/- 369
t _{1/2} (hr)	2.1	+/- 0.7	2.2	+/- 0.7	6.2	+/- 2.3	6.7	+/- 1.6
V _{dss} (L)	33	+/- 11	26	+/- 10				
Cl (mL/min)	563	+/- 93	585	+/- 102				
Cl _r (mL/min)	87	+/- 26	80	+/- 31	25	+/- 12	25	+/- 6
% Dose	15	+/- 2	16	+/- 4	5	+/- 1	7	+/- 1

*Values are mean (SD) except for t_{1/2} (harmonic mean [pseudo standard deviation])

C₂₀ = Concentration at end of infusion; Cl = Systemic clearance; Cl_r = Renal clearance

% dose = Percent of dose found in urine (0-48 hours)

Figure 13.1. Mean Plasma Concentrations of Losartan and L-158,641 (E-3174) Following 10 mg and 40 mg Losartan (n=6)



Blood pressures were measured frequently after dosing. There was no evidence of agonist activity (exemplified by no increase in blood pressure immediately after infusion). The maximum effect on DBP seemed to occur at 5 - 8 hours post dosing. Since these were non-hypertensive subjects, it is not clear if this can be extrapolated to the hypertensive population.

The original protocol planned for subjects to receive up to 80 mg of losartan. However, dosing was stopped after the 40 mg dose because five of six subjects receiving 40 mg experienced adverse events and heart rates increased after 40 mg. The adverse events included dizziness, headache and tachycardia.

Study 015.

At an early stage of the losartan program, preliminary data from the Japanese development program showed a significant delay in absorption of losartan and reduction in the apparent bioavailability of losartan formed when the dose was given with a standard Japanese meal (see table 15.1). In addition to the apparent reduction in bioavailability, the biochemical response to losartan, as measured by the 6-hour postdose increase in plasma renin activity (PRA) and immunoreactive angiotensin II, was also attenuated (see table 15.2).

Table 15.1 Losartan and L-158,641 Pharmacokinetic Parameters in Food* Interaction Study

Losartan 100 mg	C _{max} (ng/mL)	T _{max} (hr)	AUC (ng·hr/mL)	t½ (hr)
Losartan Fasted	801 ± 331	0.7 ± 0.3	1069 ± 393	1.5 ± 0.4
	282 ± 98	2.8 ± 1.2	855 ± 239	1.6 ± 0.2
E-3174 Fasted	1211 ± 271	2.0 ± 0.6	5958 ± 1192	4.2 ± 0.5
	775 ± 157	4.5 ± 1.2	5116 ± 702	4.2 ± 0.4
Mean ± S.D., n=6				

*The meal consisted of rice, miso soup (soybean soup), fried vegetables, boiled beans and grilled dried fish (710 Kcal, 36 g protein, 2.1 g salt)

Table 15.2. Influence of Feeding on RAAS Response to Losartan 100 mg

		Predose	6 hr	Postdose
PRA	Fasted	1.0 ± 0.1	18.5 ± 3.5	4.5 ± 3.0
	Fed	1.1 ± 0.1	6.0 ± 3.0	1.0 ± 0.2
All	Fasted	2.0 ± 0.5	9.0 ± 3.5	3.0 ± 1.0
	Fed	1.0 ± 0.5	2.8 ± 0.8	1.0 ± 0.5

This study was performed to verify the data in the Japanese trial. It is an open label, 2 period crossover study in healthy male subjects designed to evaluate the effect of food on the absorption of a single 100 mg losartan tablet as compared to administration in the fasting state. The natural log transformed area under the plasma concentration curve (ln AUC), natural log transformed maximum plasma concentration (ln C_{max}), the maximum plasma concentration (C_{max}), and the time of maximum plasma concentration (T_{max}), were used to evaluate the equivalence of losartan administered in the fed and fasted states. Plasma renin activity (PRA) and plasma angiotensin II (A II) levels were collected at -1 Hour predose and 2, 4, 6, 8, 12, and 24 hours postdose.

Results

For losartan, there were statistically significant ($p \leq .05$) and/or graphical indications of carryover effects for the ln AUC, ln C_{max}, and C_{max} variables. Therefore, separate first period and second period analyses were performed comparing the fed and fasted states using a two-sample Student t-test. For the eight subjects in this study, this analysis compared the four subjects who were fasting in the first period with the four who were fed (see Table 3) and, for the second period, the converse comparison was made. Ninety percent confidence intervals for the ratio of geometric means were computed.

Eight healthy male volunteers between the ages of 19 and 29 were initially deemed acceptable for participation in the study. One subject (AN 004) discontinued from the study after the first period due to a scheduling conflict. A second subject (AN 005) discontinued due to a deviation from the protocol (proteinuria present prior to the first dose of losartan and increased SGOT, SGPT and LDH) during Period I. Two replacement subjects entered the study and completed the study after the 6 original subjects. The average age was 23.9 years. Four black and 6 caucasians entered the study.

The data from the 8 subjects who completed the study are included in the bioequivalence and pharmacodynamic analysis. Table 15.3 and 15.3a lists the pharmacokinetic parameters for losartan. The AUC for losartan decreases approximately 20%. C_{max} decreases by approximately 52%. There is a decrease in C_{max} and AUC for E-3174 as listed in table 15.3b and 15.3c.

Table 15.3. Equivalence Analyses: Losartan Summary of Ratio Analyses

Variable	Geometric Means		Fed/Fasted	90% C.I.	Carryover	ANOVA P-Values		
	Fed	Fasted	Ratio			Treatments	Periods	MSE
			Geometric Means			For Ratio		
AUC (ng·hr/mL)	662.1	808.9	.82	(.71, .94)	.19	.024*	.97	.0178
1st Period Only ^(*)	596.2	900.6	.66	(.47, .93)	-	.054 ^Δ	-	.0593
2nd Period Only ^(*)	735.2	726.7	1.02	(.75, 1.36)	-	.94	-	.0444
C _{max} (ng/mL)	232.5	483.8	.48	(.32, .72)	.025*	.011*	.70	.1646
1st Period Only ^(*)	169.9	611.4	.28	(.16, .48)	-	.0035*	-	.1522
2nd Period Only ^(*)	318.2	382.8	.83	(.48, 1.42)	-	.52	-	.1491

Δ = .05 < p ≤ .10; * = p ≤ .05; ** = p ≤ .01

Table 15.3a. Equivalence Analyses: Losartan
Summary of Difference Analyses

Variable	Arithmetic Means		Fed Minus Fasted	90% C.I. for Difference	ANOVA P-Values			
	Fed	Fasted	Arithmetic Means		Carryover	Treatments	Periods	MSE
C _{max} (ng/mL)	267.3	514.0	-246.7	(-420.6, -72.8)	.021*	.033*	.67	32,026.4
1st Period Only ^(a)	184.8	635.6	-450.8	(-673.7, -227.9)	-	.0077**	-	26,306.6
2nd Period Only ^(a)	349.7	392.5	-42.8	(-251.7, +166.1)	-	.70	-	23,118.4
T _{max} (Hours)	2.95	1.29	+1.66	(+0.46, +2.86)	.20	.035*	.97	1,516.7

Δ = .05 < p ≤ .10, * = p ≤ .05, ** = p ≤ .01

MSE = Mean Squared Error (6 d.f.) (a) = Evaluated using two-sample pooled variance student t-test with N=4 per fed or fasted treatment group.

Table 15.3b. Equivalence Analyses: E-3174
Summary of Ratio Analyses (N=8)

Variable	Geometric Means		Fed/Fasted	90% C.I. For Ratio	Crossover ANOVA P-Values			
	Fed	Fasted	Geometric Means		Carryover	Treatments	Periods	MSE
AUC (ng·hr/mL)	2,637.7	3,042.3	0.87	(0.76, 0.99)	.28	.078 ^Δ	.99	.0181
C _{max} (ng/mL)	373.9	489.2	0.76	(0.58, 1.00)	.93	.094 ^Δ	.97	.0731

Δ = .05 < p ≤ .10

MSE = Mean Squared Error (6 d.f.)

Table 15.3c. Equivalence Analyses: E-3174
Summary of Difference Analyses (N=8)

Variable	Arithmetic Means		Fed Minus Fasted	90% C.I. for Difference	Crossover ANOVA P-Values			
	Fed	Fasted	Arithmetic Means		Carryover	Treatments	Periods	MSE
C _{max} (ng/mL)	414.6	502.3	-87.7	(-193.5, +18.1)	.84	.15	.96	11,845.2
T _{max} (Hours)	4.75	3.07	+1.68	(+0.26, +3.10)	.23	.060 ^Δ	.68	2,130.3

Δ = .05 < p ≤ .10

MSE = Mean Squared Error (6 d.f.)

Study 017.

This was a randomized, double blind, placebo controlled, rising single dose study to evaluate the pharmacokinetics of intravenous doses of E-3174 infused over 20 minutes. The study subjects were divided into 2 panels of eight. Panel 1 received single i.v. doses of placebo and/or E-3174 .1 mg, 1 mg, 10 mg or 40 mg. Panel 2 received placebo and/or E-3174 .5 mg, 5 mg, 20 or 80 mg. Each subject received 4 infusions.

Results

Nineteen healthy males (14 caucasians, 2 blacks, 1 asian, 1 mulatto, 1 hispanic) were enrolled in the study. The mean age of subjects was 24.2 years. Three subjects (#5, #9, #14) discontinued prematurely and were replaced. Patient #9 was discontinued due to elevated SGPT. This subject did not receive E-3174. The reason for discontinuation of the other subjects is not provided. Patient #5 did not experience any adverse events. Patient #14 experienced headache after E-3174 5 mg on day 16, pharyngitis on day 18 and an elevated WBC on day 21. No additional doses of E-3174 were received by this patient.

Table 17.1 lists the pharmacokinetic parameters for E-3174 10, 40 and 80 mg. There appears to be a dose proportional increase in AUC and C_{max}. The harmonic mean elimination half-life was similar for all doses. Approximately half of the E-3174 was eliminated in the urine.

Table 17.1. Pharmacokinetic Parameters of E-3174.

	10 mg	40 mg	80 mg
$C_{20 \text{ min}}$ (ng/mL)	1818 ± 132	7814 ± 1129	14,307 ± 2676
AUC_{∞} (ng·hr/mL)	2897 ± 407	12,808 ± 2688	24,310 ± 4147
$t_{1/2}$ (hr*)	6.9 ± 5.0	6.5 ± 1.2	6.6 ± 1.2
Vd_{ss} (L)	16.4 ± 5.6	10.3 ± 2.4	9.8 ± 1.3
CL (ml/min.)	53.0 ± 7.4	48.8 ± 9.5	51.4 ± 11.9
CL _{renal} (ml/min.)	27.5 ± 6.1	23.8 ± 4.7	27.9 ± 5.4
% Dose in urine	52.6 ± 2.7	49.2 ± 6.6	54.9 ± 9.7

*Harmonic mean and pseudo standard deviation.

There were no serious adverse events attributable to E-3174 therapy.

Study 022.

This was a 3 period, crossover study in healthy males to assess the following:

1. the bioequivalence of 100 mg losartan tablets as compared to 100 mg losartan capsules;
2. the absolute bioavailability of oral losartan,
3. the plasma concentration profile of the metabolite E-3174 following administration of 100 mg losartan tablet as compared to 100 mg losartan capsule;
4. the plasma concentration profile of the metabolite E-3174 following administration of losartan, 100 mg orally and 30 mg intravenously.

The primary hypotheses of this study was that the geometric mean ratio of $AUC_{0-\infty}$ for losartan of 100 mg losartan tablets as compared to 100 mg losartan capsules will be between 0.8 and 1.25. The formulations used in this study are outlined in table 22.1.

Table 22.1. Formulations Used in Study 022.

Dose	Batch #	Formulation #
Losartan Capsule (100 mg)	C-W737	0954DFC001D003
Losartan Tablet (100 mg)	C-W738	0954FCT004D001
Losartan Solution (30 mg)	C-W739	0954HSS001A001

Results

Eight healthy male subjects (6 caucasian, 1 black, 1 other) were enrolled in and completed the trial. The mean age of subjects was 26 years.

Table 22.2 lists the losartan and E-3174 AUC and C_{max} data for the tablet and capsule. The estimated bioequivalence AUC ratio of tablets relative to capsules based upon back transformation of the natural log transformed data was 0.93 with a corresponding 90% confidence interval of (0.68, 1.25). The estimated 90% interval (back transformed from natural log data) for the tablet relative to the capsule C_{max} ratio was (0.53, 1.38) with a geometric mean estimate of the ratio as 0.86. Since the confidence intervals of the geometric mean ratios for losartan are outside of the .80 - 1.25 interval, the tablet and capsule can not be considered to be bioequivalent. The geometric mean ratios for E-3174 are within the interval .80 - 1.25.

Table 22.2. AUC and C_{max} for Tablet and Capsule

Compound	Variable	Geometric Means			90% C.I. for ratio	Crossover ANOVA p-values			
		Tablet	Capsule	Tablet/Capsule Geometric Mean Ratio		Carryover	Treatment	Period	M.S.E.
Losartan	AUC (ng·hr/ml)	660.3	711.9	0.93	(.68, 1.25)	0.59	0.64	0.35	0.0937
	C_{max} (ng/ml)	430.4	502.6	0.86	(.53, 1.38)	0.2	0.54	0.63	0.2369
E-3174	AUC (ng·hr/ml)	3,501.2	3,423.3	1.03	(.95, 1.10)	0.29	0.55	0.77	0.0053
	C_{max} (ng/ml)	572.7	537.3	1.07	(.92, 1.23)	0.23	0.41	0.29	0.0217

Each individuals AUC and C_{max} ratio is plotted in figures 1 and 2.

Figure 22.1. Individual AUC Ratios (Tablet/Capsule) and 90% Confidence Interval About Geometric Mean Ratio (●)

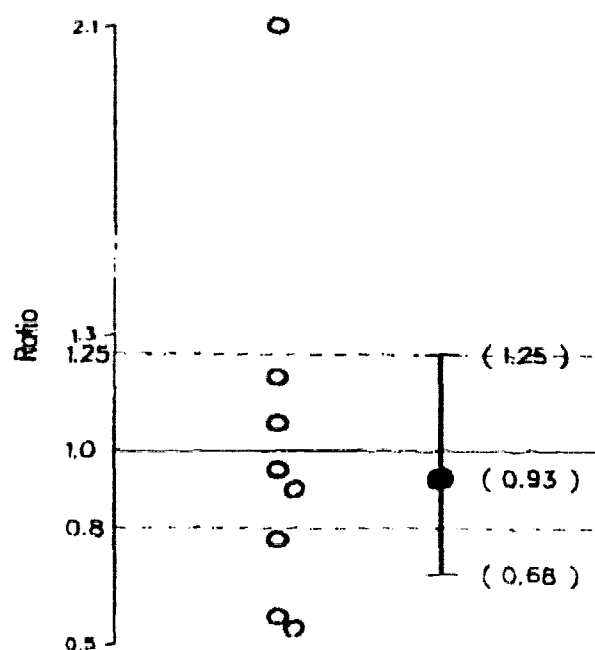


Figure 22.2. Individual C_{max} Ratios (Tablet/Capsule) and 90% Confidence Interval About Geometric Mean Ratio (●)

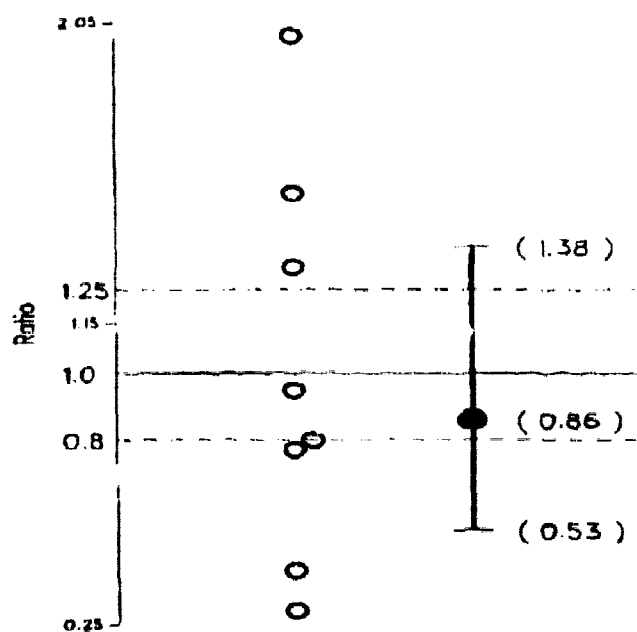


Table 22.3 lists the pharmacokinetic parameters for the tablet and i.v. formulation. The absolute bioavailability of losartan tablet is 23%.

Table 22.3 Summary of Pharmacokinetics of Losartan and E-3174 Following Oral (100 mg Tablet) and Intravenous (30 mg) Losartan

Parameter ¹	Losartan		E-3174	
	Oral Tablet	i.v.	Oral Tablet	i.v.
C _{max} (ng/ml)	486.2 (231.7)	--	584 (119.5)	112.5 (21.8)
T _{max} (hr)	1.4 (0.8)	--	3.1 (1.0)	3.8 (0.5)
Auc _∞ (ng·hr/ml)	722.4 (375.8)	925.6 (349.7)	3561 (686)	1066 (198)
K (hr ⁻¹)	0.36 (0.09)	0.31 (0.11)	0.084 (0.012)	0.090 (0.021)
t _{1/2} (hr)	1.9 (0.5)	2.3 (0.9)	8.3 (1.2)	7.7 (1.8)
V _{dss} (L)	--	40.2 (13.0)	--	--
Cl (ml/min)	--	618 (247)	--	--
Clr (ml/min)	90 (42)	76 (39)	22.5 (6.1)	24.2 (4.6)
Urinary Recovery (% dose)	3.7 (1.3)	11.6 (2.5)	5.0 (1.7)	5.3 (1.5)
F ²	0.23 (0.17, 0.30)			

1 Values are mean (SD). C_{max} and AUC values for losartan and E-3174 were normalized to nominal doses of 100 mg (oral) and 30 mg (i.v.) based on actual doses given.

t_{1/2} is harmonic mean and pseudo SD.

2 Geometric mean (90% Confidence Interval)

Study 019.

The aim of this study was to obtain information on the dose-response relationship with losartan in subjects whose renin system had been stimulated by sodium depletion. This study was a double-blind, randomized, placebo-controlled, four period, crossover study. Three separate dose panels were employed. Each panel was designed to allow 4 subjects to receive three different doses of losartan (5, 10, 25, 50 or 100 mg) and one dose of placebo. The time elapsed between each study period was 7 to 10 days. During the three days prior to each study day, subjects were maintained on a 40 mmol/day sodium diet and received oral furosemide 40 mg b.i.d. Subjects were normotensive as defined by a resting supine blood pressure less than 145/90 mmHg and a lack of a history of hypertension. Additional inclusion criteria included: heart rate of 45 to 100 beats/minute and body weight within 10% of ideal body weight for height and build. Furthermore, only non-black subjects were eligible to enter this study. Table 19.1 and 19.1a outline the testing performed in the trial.

Table 19.1. Procedures

Approx. Time	Hour																								
	-24	-1	-½	0	½	1	1 ½	2	2 ½	3	3 ½	4	4 ½	5	5 ½	6	6 ½	7	7 ½	8	8 ½	9	9 ½	10	24
Empty Bladder		X																							
Body Weight		X																							
Insert Venous Cannula			X																						
BP & HR (Supine and Standing)			X ¹	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Comparison of Semiautomated BP Device with Mercury Column				X												X									
RAAS Hormones & NE, Epinephrine & [Drug]				X		X		X				X				X				X				X	X
Hematology & Biochemistry																									X
Urine Collections		X ^a	X																						X
Urinalysis			X																						X
Standard Meal								X						X								X			
Test Drug Administration					X*																				
EKG			X																						

* Following Hour 0 evaluations: ¹ For purposes of acclimating subjects to procedure. NE = norepinephrine

^a 24-hour urine collection for determination of Na⁺ (to establish compliance with the restricted sodium/furosemide regimens)

Table 19.1a. Labs

Hematology	Biochemistry	Urinalysis	RAAS Hormones
Hemoglobin	Sodium	Protein	Plasma Renin Activity
Hematocrit	Calcium	Glucose	Plasma Renin Concentrations
WBC	Potassium	Uric Acid	Angiotensin Peptides
Platelet Count	Chloride	Ketones	Aldosterone
Ferritin	Bicarbonate	Blood	Angiotensin Converting Enzyme
	Urea		
	Globulin		
	Alkaline Phosphatase		
	Phosphate		
	AST		
	ALT		
	Glucose		

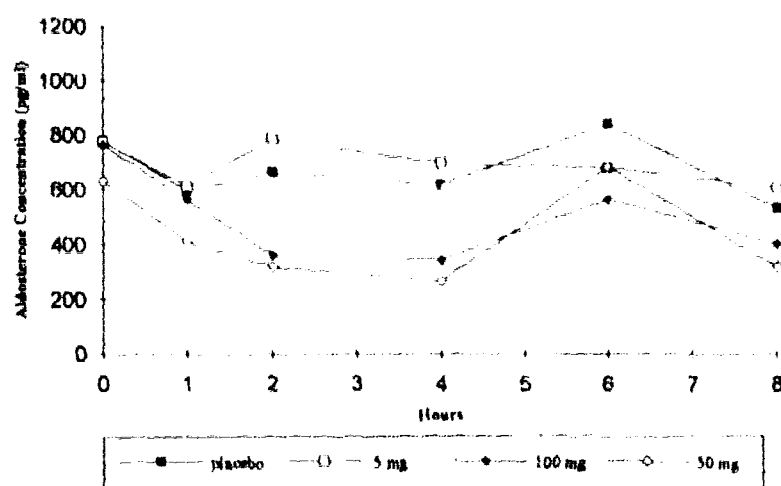
Results

Fourteen subjects entered the study. Subjects were healthy white males between the ages of 22 and 34. The median age was 24. Eleven subjects completed all four periods. Subject #1 developed a sore throat after the third period and withdrew. Subject #101 from the study after the second period due to alcohol consumption. Subject #12 withdrew from the study after the second period and was replaced by patient #112.

Plots of blood pressure versus time in the clinical summary report are uninterpretable because the different treatment groups can not be differentiated.

Plasma renin increased with losartan therapy. Plasma aldosterone levels were difficult to interpret from the graph provided. Figure 19.1 was produced from data in appendix 13. Plasma aldosterone levels versus time over the first 8 hours post-dosing are plotted. During the first 6 hours post dosing, losartan 50 mg and 100 mg tend to have lower aldosterone levels compared to placebo and 5 mg. The difference is less impressive by 8 hours.

Figure 19.1. Aldosterone Levels



Angiotensin converting enzyme activity appeared to be unchanged with losartan therapy.

Not unexpectedly, orthostatic hypotension and vasovagal reactions were common in patients treated with losartan (especially 100 mg). Subject #112 had an elevation of serum creatinine (baseline = 93 $\mu\text{mol/L}$; post-100 mg = 190 $\mu\text{mol/L}$) and blood urea nitrogen (baseline = 5.8 mmol/L ; post-100 mg = 10.1 mmol/L). These results suggest possible renal insufficiency related to losartan. Subject #6 had an elevation of SGPT to 74 IU/L (normal = 11 - 55 IU/L) without a significant increase in SGOT.

Study 024.

This was a 2 period crossover study to evaluate the effect of cimetidine on the pharmacokinetics of losartan. Patients received a single dose of losartan 100 mg alone and on day 6 of a 7 day course of cimetidine 400 mg every 6 hours. Eight healthy, caucasian males completed the study. The average age of subjects was 27.5 years. Table 2.1 lists the mean pharmacokinetic parameters for losartan and E-3174. The elimination half-life is the expressed as the harmonic mean. Cimetidine was associated with an 30% increase in losartan C_{max} and 23% increase in losartan AUC. There was no increase in E-3174 C_{max} or AUC.

Table 2.1. Geometric Mean Pharmacokinetic Parameters

Pharmacokinetics:	Losartan		E-3174	
	-Cimetidine	+Cimetidine	-Cimetidine	+Cimetidine
C_{max} , ng/mL	614 + 366	836 + 921	504 + 253	499 + 218
C_{max} Range	262.5 - 1391.3	166.3 - 3047.1	259.5 - 900.7	259.1 - 784.7
T_{max} , hr	0.7 + 0.2	1.2 + 1.2	2.6 + 0.8	2.8 + 1.1
AUC_{∞} , ng·hr/mL	849 + 383	1047 + 647	3359 + 1329	3430 + 1553
$AUC_{0-\infty}$ Range, ng·hr/mL	512.4 - 1712.7	533.2 - 2583.5	2112.1 - 5326.6	1701.2 - 6055.3
$t_{1/2}$, hr@	1.7 + 0.6	1.7 + 0.5	8.7 + 3.6	8.1 + 2.1
λ , hr ⁻¹	0.40 + 0.13	0.42 + 0.12	0.080 + 0.031	0.085 + 0.021

@Harmonic mean and pseudo standard deviation.

Study 023.**Protocol**

This was a randomized, double blind, placebo controlled, 2-period crossover, single center trial designed to study the effect of losartan on renal hemodynamics and mineral excretion in healthy, non black male subjects on high and low sodium diets. Sixteen patients received losartan 100 mg and eight patients received placebo during both treatment periods. Subjects were also randomized to receive a High-Salt (HS) [200 mmol/day] or Low-Salt (LS) [50 mmol/day] diet in the first period and the opposite diet in the second period.

Subjects were maintained on a low salt or high salt diet on days 1 - 6 (period I) and 12 - 17 (period II). Losartan 100 mg or placebo were administered as single doses on days 6 and 17. Patient did not cross over therapies. Diets were crossed over. Twenty-four-hour urine collections were obtained on days 2, 3, 4 and 5, as well as days 13, 14, 15, and 16. Sodium balance was assessed by measuring the 24-hour urinary sodium excretion. In order to receive therapy, subjects on a low sodium diet had to have a mean 24-hour urinary sodium excretion no greater than 70 mmol/day on days 4 and 5 or 15 and 16. Subjects on high sodium diets had to have a mean 24-hour urinary sodium excretion no less than 180 mmol/day on days 4 and 5 or 15 and 16 (individual daily urinary sodium excretion rate must have been > 165 mmol/day).

Studies which assessed the effects of the oral administration of 100 mg losartan and PBO on renal hemodynamic and tubular functions were performed at the day of drug administration.

Table 23.1 lists the procedures performed during the study.

Table 23.1. Procedures

Study Day	Period I						Washout Period					Period II						
	-14 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Clinical Evaluations																		
Hx/PE/ECG	X																	X
BP/PULSE	X						X											X
Height/Weight	X						X											
Laboratory Evaluations																		
Blood hematology	X						X											X
Blood Chemistry*	X						X											X
24 hr. Urine Chem.	X	X		X		X	X					X		X		X	X	X
Timed Urine Chem.							X											X
Renal Function Studies																		
Inulin							X											X
PAH							X											X
Lithium							X											X
Creatinine Clearance	X						X											X
PRA and AII						X	X										X	X
Pregnancy Test**							X											X

Hematology tests included: H₁, h, Hct, WBC, Diff, Platelet. Blood Chemistry tests included: Aldosterone, Calcium, Chloride, Amino Acids, Creatinine, Glucose, Bicarbonate, Magnesium, Osmolality, Phosphorus, Potassium, Sodium, Uric Acid. 24-Hour Urine Chemistries included: Creatinine, Potassium, Sodium, Uric Acid, Chloride, Glucose, Phosphorus.

**Timed Urine Collections included: Aldosterone, Calcium, Chloride, Creatinine, Glucose, Magnesium, Osmolality, pH, Phosphorus, Potassium, Sodium, Uric Acid, Bicarbonate, Amino Acids, Ammonium, Titratable Acids and fractional clearances of Amino Acids. Urine was collected at 30 minute intervals for 6 hours after dosing. PRA and AII results were sent directly to MSDRI. PRA and AII were measured on Day 6 at -3 hours, 0 hours, 4 hours and 6 hours.

* Samples were collected every 30 minutes during renal function studies.

** A pregnancy test had to be done and negative results had to be obtained 72 hours prior to administration of study medication.

Results

Twenty four healthy male volunteers, between the ages of 20 and 35, were entered into this study. Sixteen were randomized to losartan and 8 were randomized to PBO. Twenty two (91.7%) of the 24 subjects were caucasian. No black patients were enrolled. One placebo patient dropped out due to an arrhythmia. No other information is provided.

Because data collection was for the first six hours post-dosing, it is not clear how the results can be applied to long term therapy in assessing the effect of losartan on renal hemodynamics or excretion of electrolytes. The clinical summary report and appendices do not include the data from the 24 hour urine collections. The only data presented is for the six hours post dose. The extensive amount of information collected in this trial is outside the realm of this review to describe in its entirety. Only selected information is presented. Most of this will be presented in graphical form without emphasis on the p values. Many tables providing analysis with p values can be found in the sponsor's clinical summary report.

In figure 23.1 and 23.2, plasma renin and plasma angiotensin II activity increased after losartan therapy. The effect was more pronounced in patients on a low salt diet.

Figure 23.1. Plasma Renin Activity

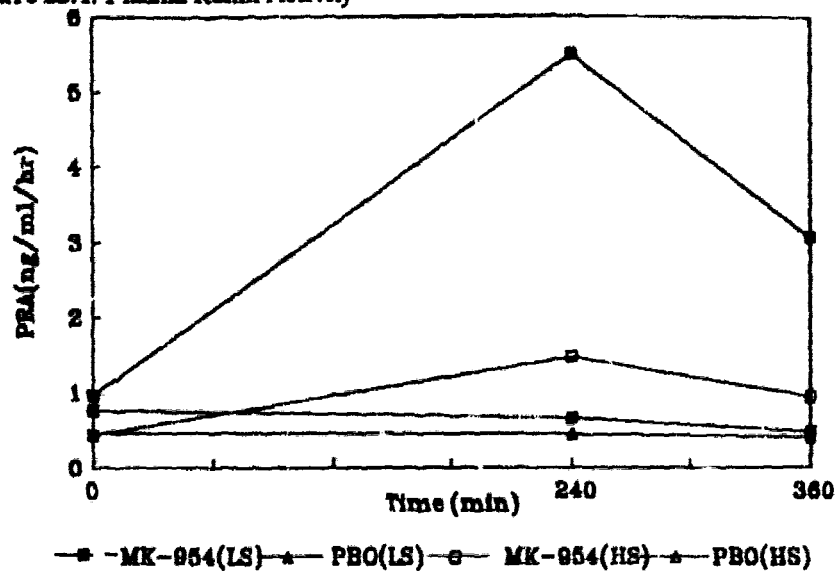
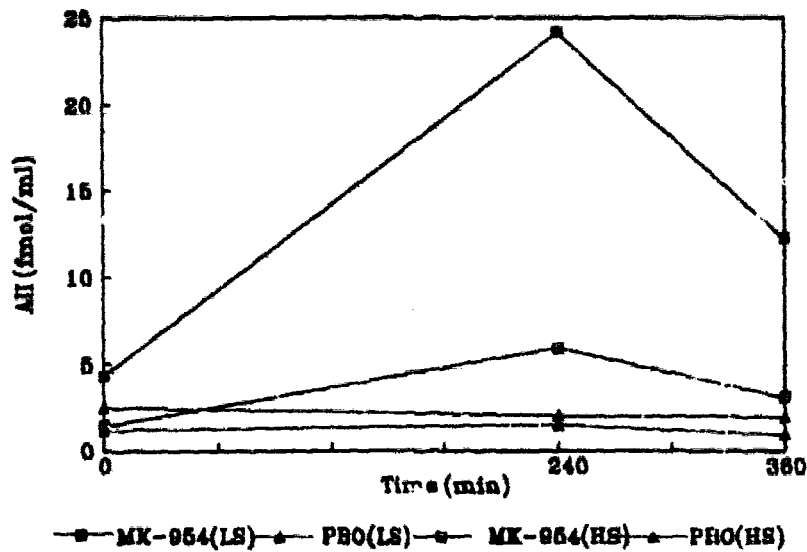


Figure 23.2. Angiotensin II Levels



As might be expected, baseline aldosterone levels were elevated with the low salt diet. Placebo and losartan had a similar effect on aldosterone levels regardless of diet.

Figure 23.3. Aldosterone Levels

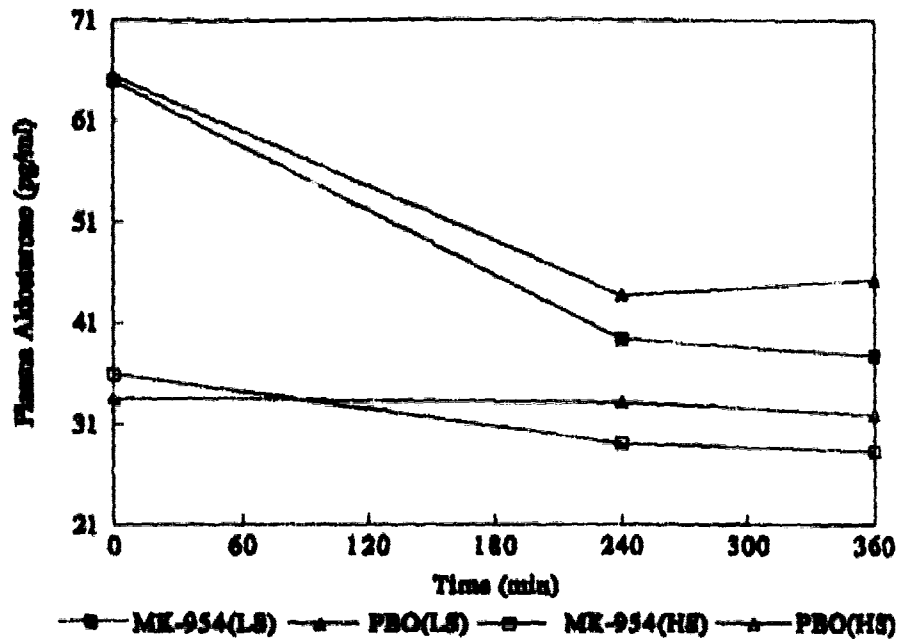
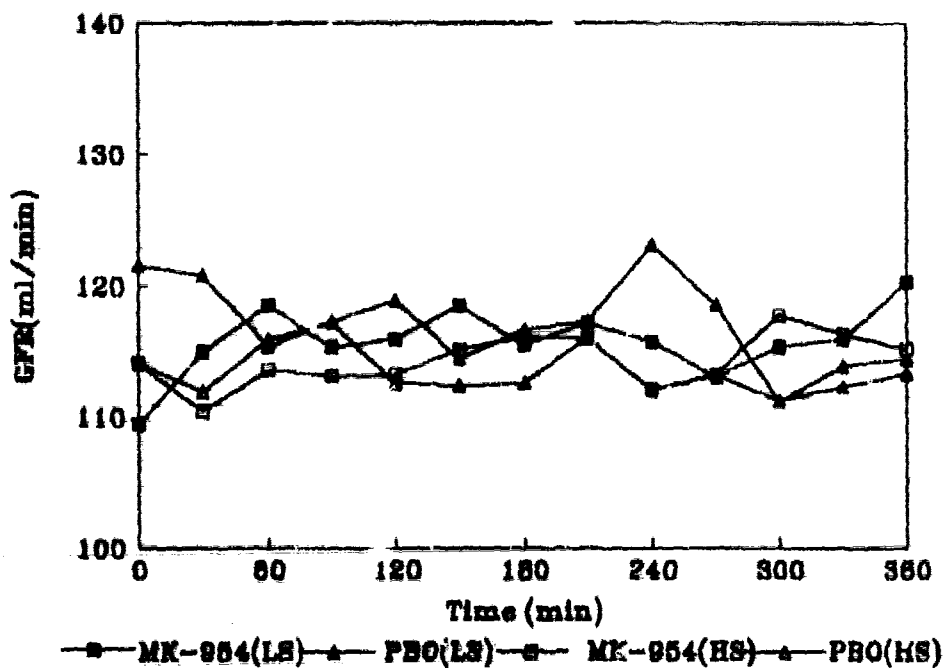


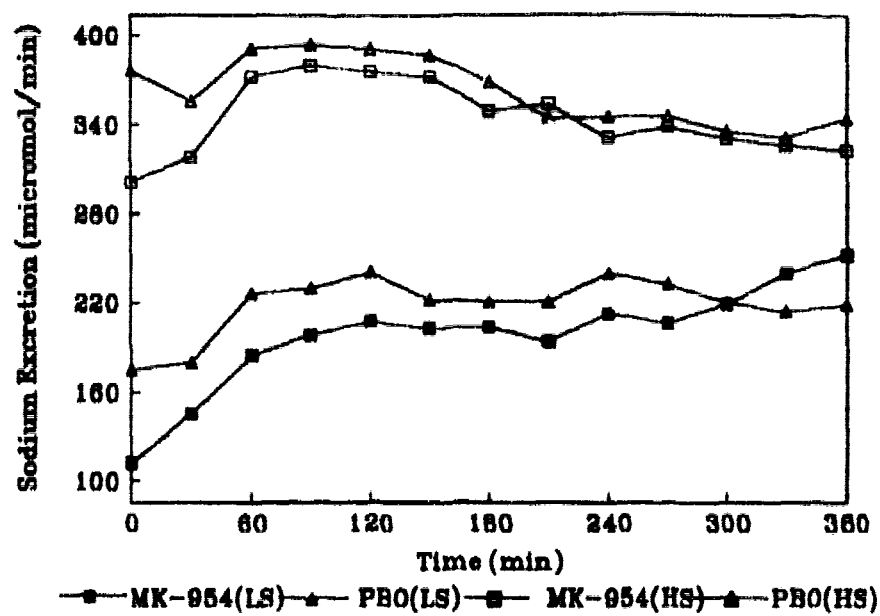
Figure 23.4 illustrates that there does not appear to be any trends in the change of GFR (presumably measured by inulin clearance) during the first 6 hours post treatment.

Figure 23.4. GFR Results



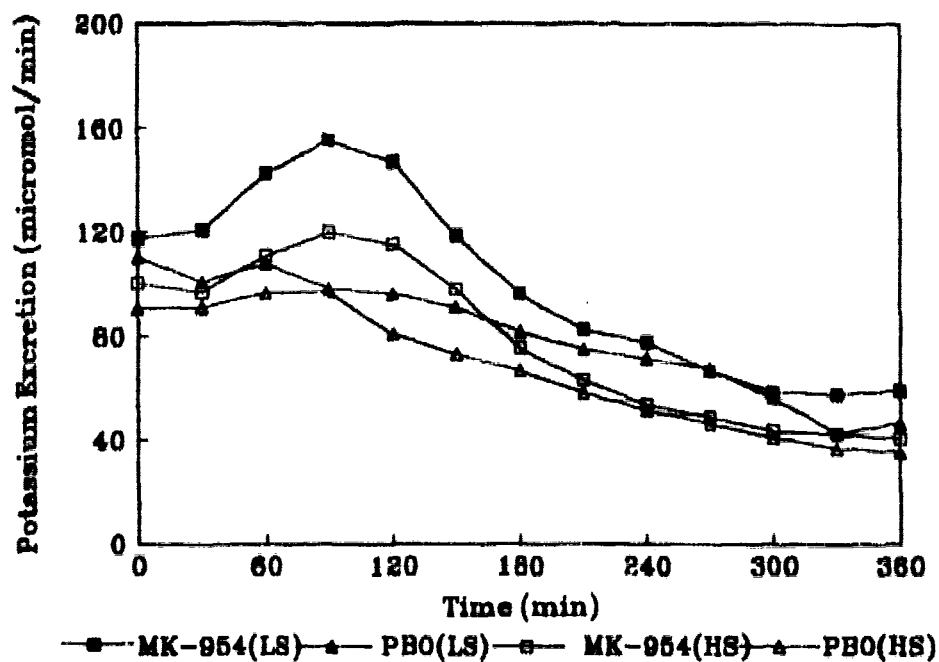
Effective renal plasma flow and filtration fraction do not appear to be affected much with losartan therapy. As illustrated in figure 23.5, sodium excretion was greater in subjects on high salt diets. Losartan does not change sodium excretion in the first 6 hours after dosing.

Figure 23.5. Urinary Sodium Excretion



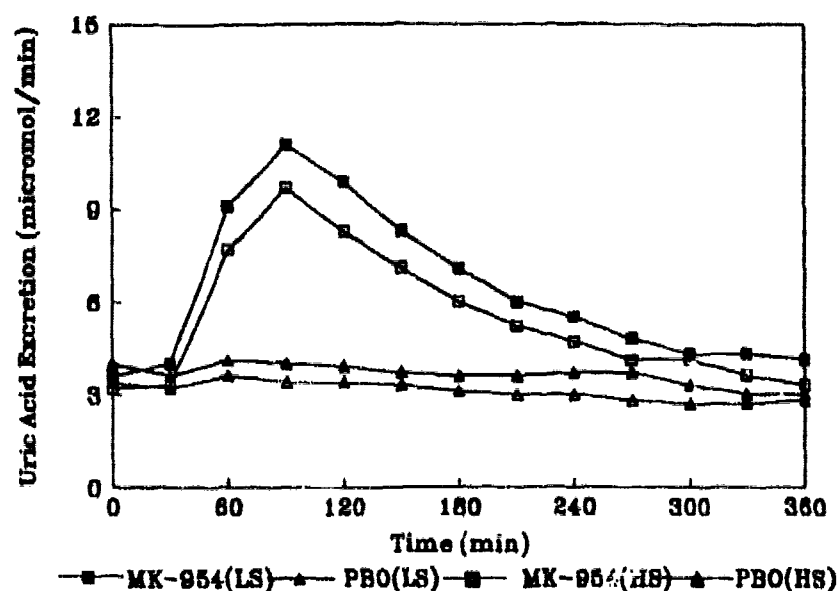
There may be an acute increase in urinary excretion of potassium with losartan as illustrated in figure 23.6. The effect, if present, is short lived.

Figure 23.6. Urinary Potassium Excretion



The urinary excretion of uric acid increases acutely with losartan regardless of salt intake but is short lived.

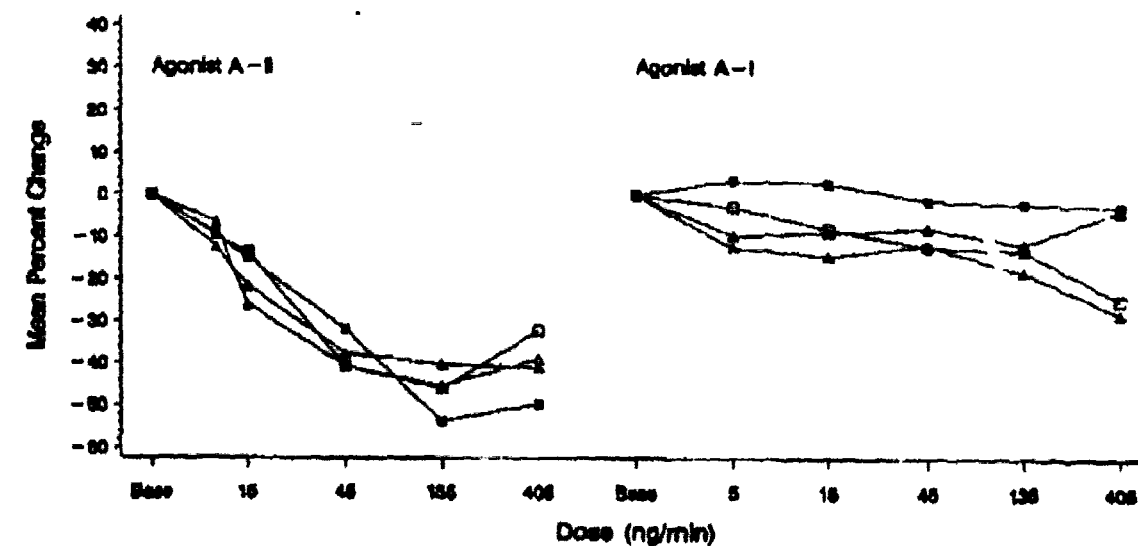
Figure 23.7. Urinary Uric Acid Excretion

**Study 033.**

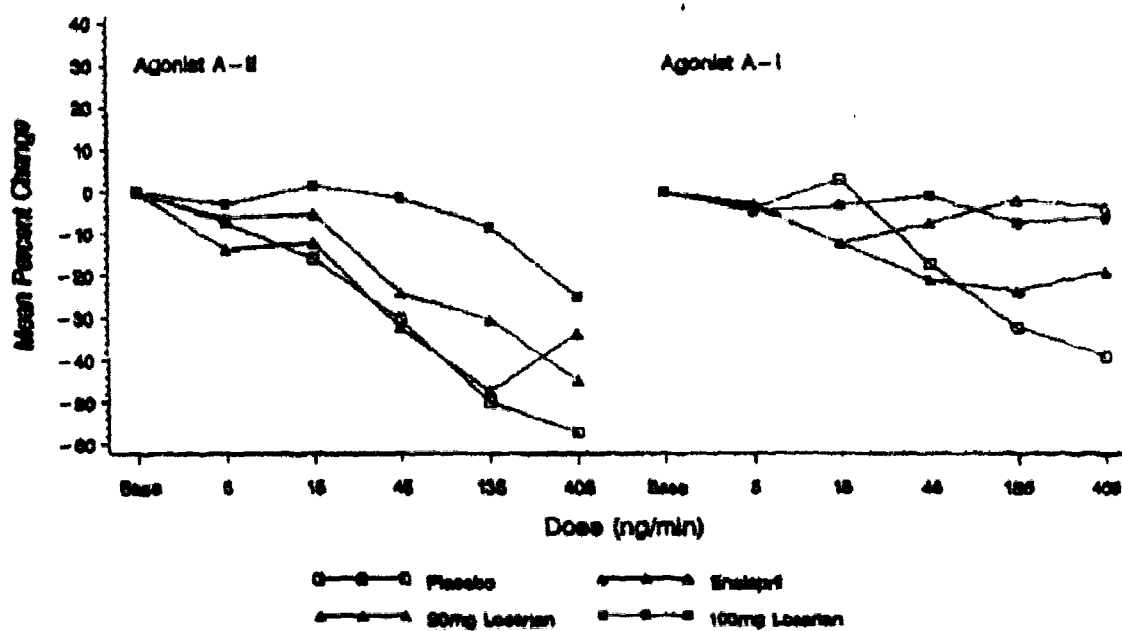
Angiotensin I and II have a vasoconstrictor effect on the dorsal hand vein of humans. This study attempted to show that losartan and enalapril could inhibit the pressor response to angiotensin I and losartan but not enalapril inhibited the pressor response to angiotensin II by measuring dorsal hand vein diameters. This study is a randomized, double-blind, placebo controlled 4 - period crossover study in which healthy male subjects received single doses of losartan 20 mg, losartan 100 mg, placebo and enalapril 10 mg. Five different doses of angiotensin I and II were infused over 4 minutes in 2 cycles at 1.0 and 3.5 hours after dosing of randomized therapy. A cycle started with saline baseline infusion, followed by angiotensin II infusion with stepwise increasing infusion rates, then a second saline baseline infusion followed by the angiotensin I infusion with stepwise increasing infusion rates.

Eight caucasian male subjects ranging in age from 23 to 31 years were enrolled in the study. Figure 33.1 shows the mean percent change in dorsal hand vein diameter from baseline. At 2 hours post dose (first cycle), there is little distinction between treatments. At 4 hours post dose, losartan attenuated the response to angiotensin II infusion. At the higher doses of angiotensin I infusion, enalapril and losartan 100 mg attenuated the pressor response.

Figure 33.1. Dorsal Hand Vein Response to Angiotensin II (Left Side) and Angiotensin I (Right Side)
Two Hours Post-Dose



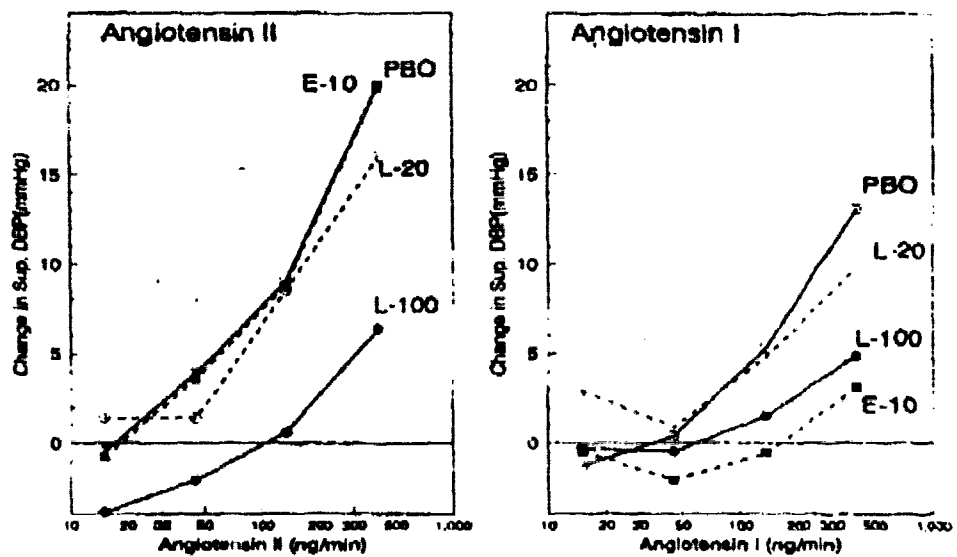
Four Hours Post-Dose



Figures 33.2 and 33.3 plot the change in DBP and SBP with each dose of angiotensin I and II. In general, losartan 100 mg and enalapril attenuated the increase in blood pressure with angiotensin I infusion. Enalapril and losartan 20 mg did not block the increase in blood pressure associated with angiotensin II infusion. Losartan 100 mg attenuated the increase in blood pressure associated with angiotensin II infusion.

Figure 33.2. Diastolic Pressor Responses to Angiotensin II

Two Hours Post-Dose



Four Hours Post-Dose

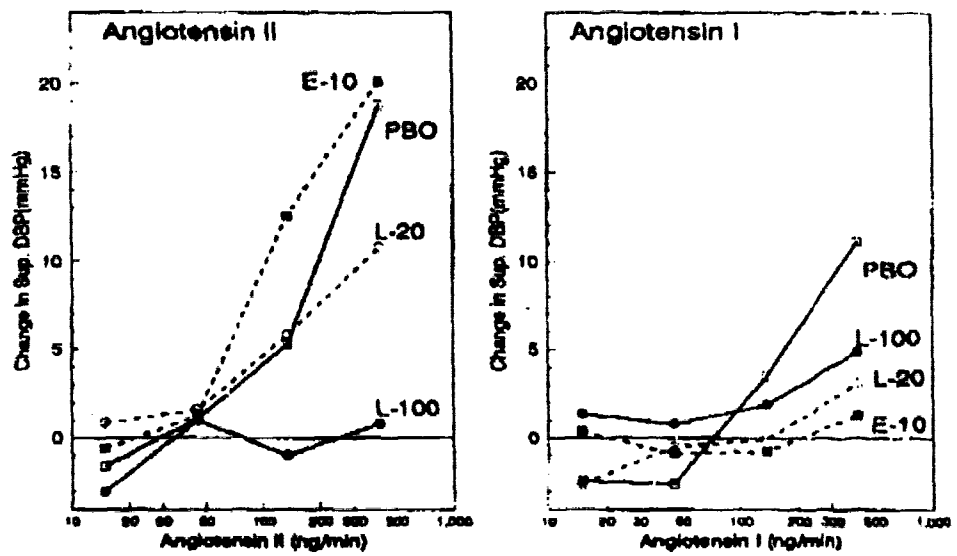
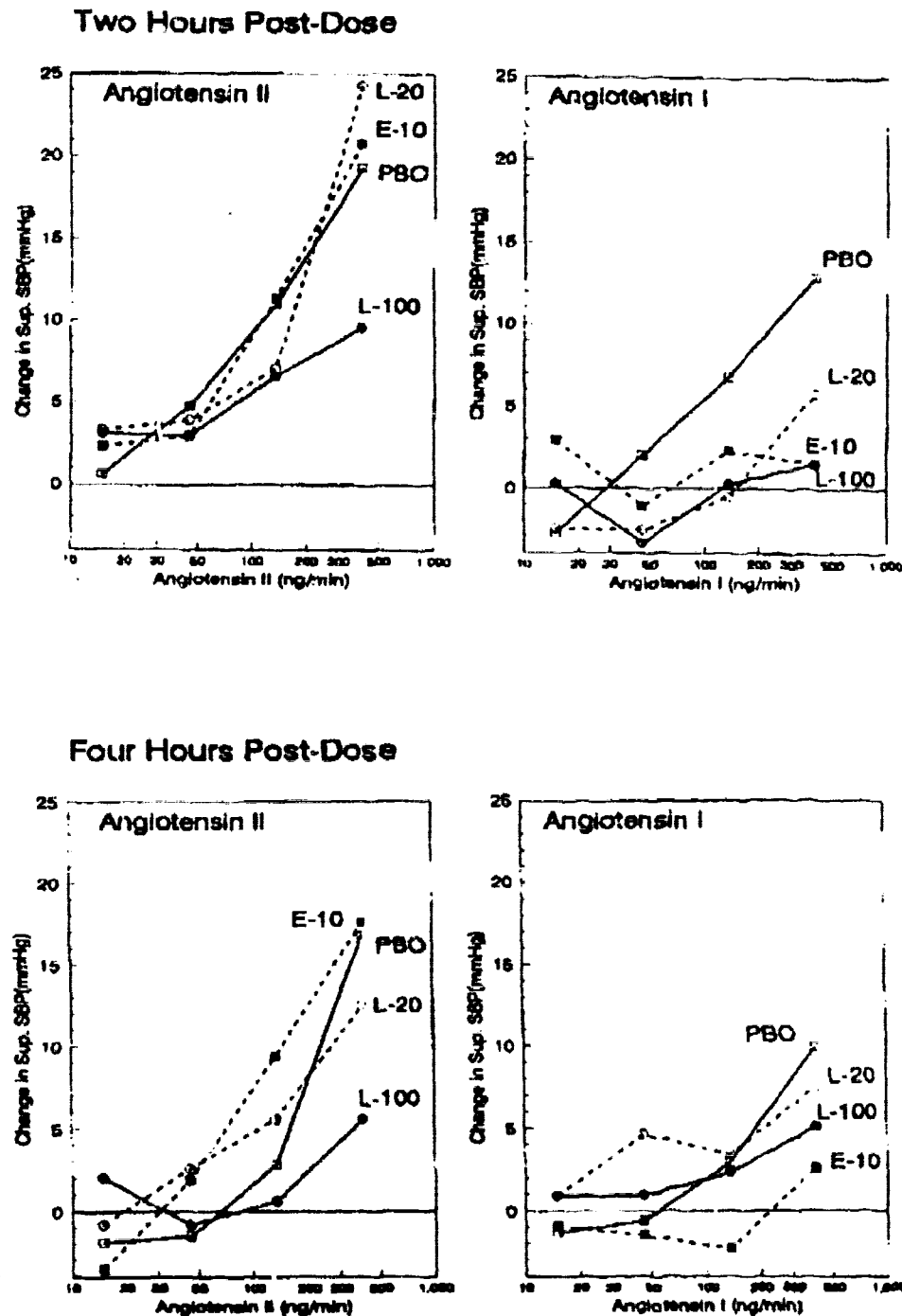


Figure 33.3. Systolic Pressor Responses to Angiotensin II

**Study 034.**

The purpose of this study was to evaluate the effect of losartan on the autonomic nervous system in subjects who were sodium deficient and sodium replete. This was a double-blind, randomized, placebo-controlled, four-period, crossover study in which a single oral dose of placebo or losartan (100 mg) was administered to healthy, non-black male subjects under sodium-depleted and sodium-replete conditions. Sodium depletion was produced by starting subjects on a 40 nmol/day sodium diet plus furosemide 40 mg twice a day for three days prior to dosing. Sodium repletion was produced by giving a subject a 40 nmol/day diet plus Slow Sodium® tablets (100 mmol/day) for three days prior to dosing. Each subject received a single dose of losartan and a dose of placebo on each sodium supplementation regimen. Approximately 14 days elapsed between dosing. The study was performed at a single center:

Prof. John L. Reid
 University Department of Medicine & Therapeutics
 Gardiner Institute, Western Infirmary
 Glasgow, Scotland

The procedures performed in the study are outlined in table 34.1.

Table 34.1. Flowchart of Clinical and Laboratory Procedures

Approximate Time		8:00					9:00					10:00													
Time Postdose: (Hours)	Pre-study	-24	-2	-1	-5	-25	Pre-dose	0.25	0.5	0.75	1	1.5	2	3	4	5	6	7	8	9	10	24	48	Post-study	
PE	X																							X	
Weight	X		X																						X
ECG	X																								X
Urine Electrolytes & Creatinine	X						X					X		X		X		X			X	X			
Urine Aldosterone & Osmolality							X					X		X		X		X			X	X			
Urinalysis	X						X																		X
Insert Venous Cannula			X																						
Hematology	X		X																						X
Biochemistry	X		X				X							X							X	X	X	X	X
PRA, ALI, Plasma Drug Conc.							X		X		X	X	X	X		X	X	X	X	X	X	X	X		
BP & HR: Supine	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BP & HR: Erect	X						X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Comparison of Semiautomatic BP Device with Hg Manometer							X									X									
Test Drug Administration							X ⁴																		
Meal			X																X						
Autonomic Function Tests															X--X										
Urine Void Collection	X		X ¹	-----X ² -----X ² -----X ² -----X ² -----X ² -----X ² -----X ² -----X ² -----X ³																					
Fluid Replacement			X ⁵	X ⁵			X ⁵																		

1 = 24-hour collection, 2 = 2-hour collection; 3 = 14-hour collection; 4 = Following all predose evaluations, 5 = 15 ml/kg of fluid will be given in 3 equal portions.

The tests outlined in table 34.2 were initiated beginning 4 hours after study drug administration. Descriptions of the testing procedures can be found in the clinical summary report of the sponsor.

Table 34.2. Test of Autonomic Function

Test	Rationale	Measure
Standing-to-Lying Test	Bradycardia following this maneuver is due to activation of the parasympathetic system.	Heart rate change. Standing-to-lying ratio was calculated as the ratio of the mean erect heart rate* period to the shortest heart rate period in the first 10 beats after starting to lie down.
Forearm Isometric Exercises	This maneuver assessed the sympathetic nervous system.	Blood pressure and heart rate change.
Valsalva's Maneuver	Blood pressure overshoot is sympathetically mediated and bradycardia following the maneuver is vagally mediated.	Heart rate change. Difference between pre- and post-Valsalva blood pressures and the ratio of the longest heart rate period after the maneuver to the shortest during the maneuver.
Diving Reflex	The profound bradycardia induced by the test is due to parasympathetic stimulation.	Heart rate change. Difference between the heart rate before the test and the minimum heart rate during the test.
Cold Pressor Test	Sympathetic efferent integrity was assessed.	Blood pressure and heart rate change. Maximum difference between inspiratory and expiratory heart rate in the final cycle of respiration. Plasma NE before and after dosing.
Heart Rate Variation With Deep Breathing	The variation in heart rate (an increase in inspiration and a decrease in expiration) is due to changes in vagal tone.	Heart rate change. Maximum difference between inspiratory and expiratory heart rate in the final cycle of respiration.

* Mean erect heart rate period is defined as the average time interval between heart beats before lying down.

The study enrolled twelve caucasian males between the ages of 18 and 38. Twenty-four hour sodium excretion prior to dosing was not available for two to four subjects depending on the diet and dosing regimen. No explanation for the missing data was provided. For both sodium-depleted regimens, the predose urinary sodium values were less than 100 mmol/24 hours in all subjects for which data were available with the exception of AN 1 and AN 6 (118 mmol/24 hours and 128 mmol/24 hours prior to losartan treatment, respectively). Data were not received for AN 1 and AN 4 prior to placebo administration or for AN 2, AN 7 and AN 8 prior to losartan administration. For the sodium-replete diet regimen, the urinary sodium values recorded were greater than 100 mmol/24 hours for all subjects for which data were available with the exception of 2 subjects prior to placebo dosing (AN 10: 11 mmol/24 hours; AN 12: 21 mmol/24 hours) and 2 subjects prior to losartan dosing (AN 10: 6 mmol/24 hours; AN 11: 56 mmol/24 hours). No data were available for AN 1, AN 2, AN 3 and AN 5 prior to placebo dosing or for AN 4 prior to losartan dosing. AN 8 in the sodium replete/placebo group did not have a postdose value.

All subjects completed each dosing period. Table 34.3 lists the results from the autonomic tests performed. Overall, reflexes following losartan administration, whether in the sodium-replete or sodium-deplete state, were not different from the reflexes following placebo with one exception. In the sodium-deplete state (but not the sodium-replete state), the Valsalva

ratio in the losartan group was significantly ($p \leq 0.050$) lower than that of the placebo group (2.0 vs. 2.2). In view of the many multiple comparisons, the lone significant result is unlikely to represent a true difference between treatments.

Table 34.3. Summary Of Autonomic Nervous System Tests

Test	Placebo/Deplete		Placebo/Replete		MK-954/Deplete		MK-954/Replete	
	N	Mean (SEM)	N	Mean (SEM)	N	Mean (SEM)	N	Mean (SEM)
Hand Grip SBP (mmHg)	12	19.8(2.9)	12	20.9(3.1)	12	19.7(2.8)	12	24.8(4.6)
Hand Grip DBP (mmHg)	12	15.3(1.7)	12	17.4(2.4)	12	16.8(3.0)	12	15.4(3.1)
Hand Grip HR (bpm)	12	5.7(1.6)	12	13.3(2.6)	12	9.2(1.9)	12	11.2(2.6)
Cold Pressor SBP (mmHg)	12	21.8(4.3)	12	27.9(4.1)	12	24.3(3.1)	11	27.9(3.8)
Cold Pressor DBP (mmHg)	12	15.0(2.6)	12	19.3(3.7)	12	20.8(3.5)	11	24.2(4.5)
Cold Pressor HR (bpm)	12	10.3(1.8)	12	11.9(2.5)	12	9.1(3.3)	11	9.5(2.1)
Valsalva Maneuver (ratio)	12	2.2(0.1)	12	2.3(0.1)	12	2.0(0.2) ⁺	12	2.2(0.1)
Diving Reflex (msec)	12	300.0(41.8)	12	485.0(125)	12	408.4(75.0)	12	504.6(61.6)
Deep Breathing (%)	12	26.2(2.5)	12	35.3(4.8)	12	25.2(2.3)	12	30.8(3.3)
Supine to Erect (ratio)	12	1.2(0.1)	12	1.1(0.0)	12	1.0(0.0)	12	1.1(0.0)

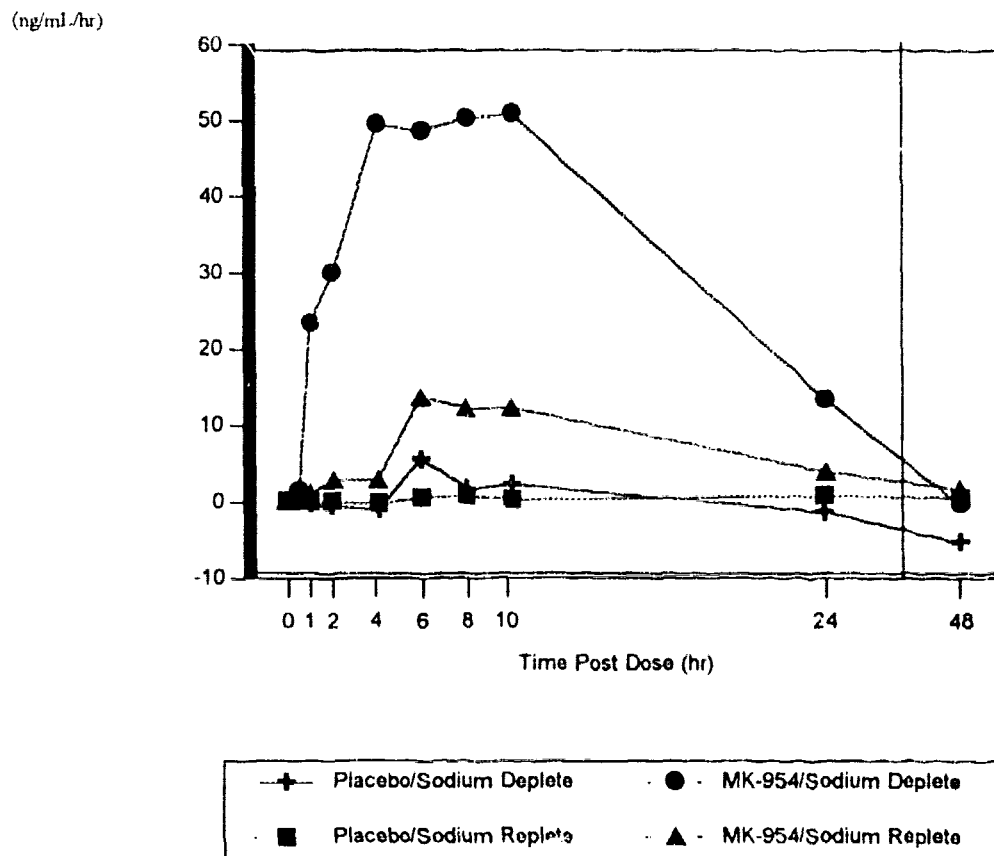
⁺ Significant difference between MK-954 and placebo within sodium deplete diet, $p \leq 0.05$.

There were no significant differences between MK-954 and placebo within sodium replete diet, $p > 0.05$.

There were no significant differences between treatments across diet regimens, $p > 0.05$.

Plasma renin activity was measured at baseline and at 0.5, 1, 2, 4, 6, 8, 10 and 24 hours postdose. All but the 0.5- and 1-hour evaluations postdose were analyzed. Clinically meaningful increases in baseline PRA were observed in both sodium-depleted treatment groups (losartan 11.6 ng/mL/hr, placebo 8.1 ng/mL/hr) compared to the sodium-replete groups (losartan 1.3 ng/mL/hr, placebo 1.8 ng/mL/hr) indicating an activation of the renin-angiotensin system in the sodium-depleted group. Figure 34.1 shows the change in renin activity with each treatment. Losartan caused an increase in renin activity regardless of treatment. The effect is most pronounced in the sodium deplete group.

Change From Baseline in Plasma Renin Activity (ng/mL/hr)



There was no difference in creatinine clearance between treatments. Urine potassium and sodium excretion are plotted in figures 34.2 and 34.3. There is no difference between treatments in sodium and potassium excretion.

Figure 34.2. Urine Potassium (mmol/L)
(mmol/L)

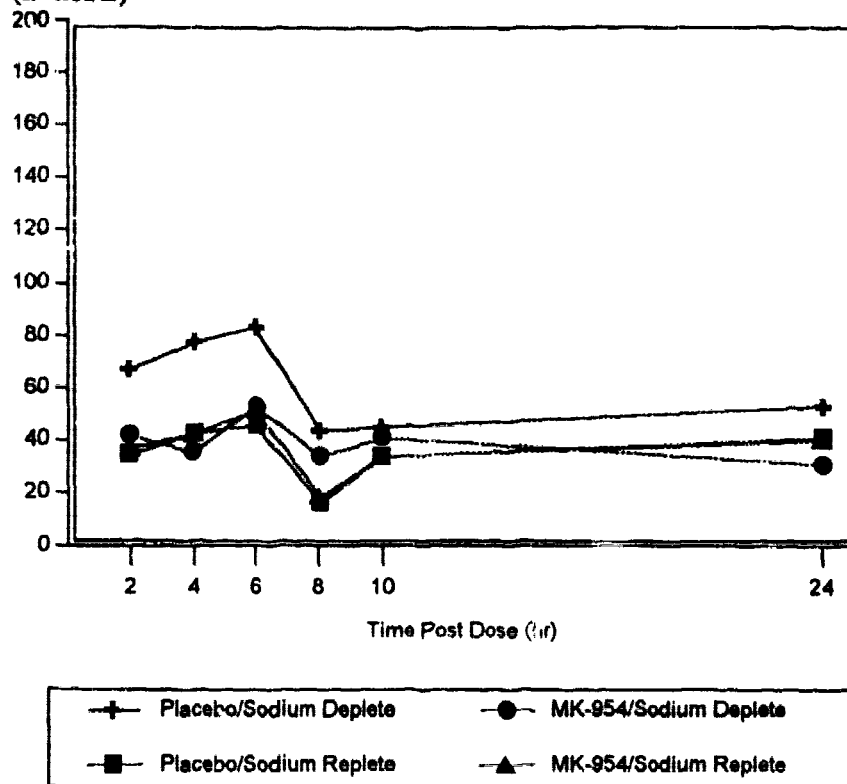
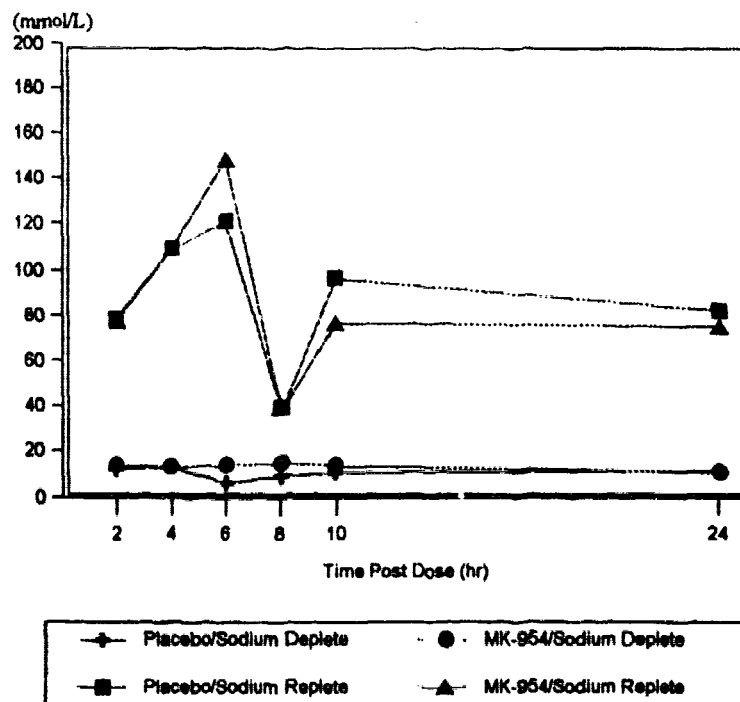


Figure 34.3. Mean Urinary Sodium (mmol/L)



Twenty-four hour urinary aldosterone collections were provided for 3 to 6 subjects depending on the diet/treatment regimen.

Of the 12 subjects who entered and completed the study, 7 (58%) subjects had at least one adverse experience after treatment with study drug. Overall, these 7 subjects had 13 adverse experiences that were considered by the investigator to be drug related. All but 2 of these events occurred on the sodium-depleted diet. The most frequent adverse events on the sodium-depleted regimen involved postural hypotension (7 subjects, 58%; including orthostatic effects and hypotension). Other

adverse events included nausea (3 subjects, 25%), vomiting (2 subjects, 17%), headache (1 subject, 8%) and paresthesia (1 subject, 8%). In the sodium-depleted regimen, the percentage of subjects experiencing at least one AE was significantly greater after losartan administration (58%) compared to placebo (8%). This difference was due primarily to the occurrence of orthostatic-related events (defined as adverse experiences involving lightheadedness and postural hypertension in the sodium-depleted/losartan-treated group).

Two subjects (AN 1 and AN 2) experienced laboratory adverse events which were probably related to test therapy according to the investigator. In both cases, elevations in serum urea and serum creatinine occurred at 8 hours after the losartan 100 mg dose on the sodium-depleted diet regimen. No increases were noted with losartan treatment on the sodium-replete diet regimen for these subjects.

Serum urea for AN 1 increased from a predose value of 6.2 mmol/L to 9.2 mmol/L at 8 hours postdose (normal range 2.5 to 7.5 mmol/L). At 24 hours postdose, serum urea was still elevated (8.8 mmol/L), but returned to within normal range at 48 hours postdose (5.3 mmol/L). For AN 2, serum urea increased from 6.7 mmol/L (predose) to 8.9 mmol/L at 8 hours postdose. The serum urea was still elevated at 24 hours (8.8 mmol/L), but returned to normal at 48 hours postdose (5.8 mmol/L).

Serum creatinine for AN 1 increased from a predose value of 81 μ mol/L to 214 μ mol/L (normal range 60 to 110 μ mol/L), but returned to normal at 24 hours (99 μ mol/L). For AN 2, serum creatinine increased from 95 μ mol/L predose to 193 μ mol/L at 8 hours postdose. The value was normal at 24 hours (101 μ mol/L).

Study 035.

This study was a double blind, placebo controlled, single dose, 4-period crossover study. Healthy male subjects received single oral doses of placebo, enalapril 10 mg, losartan 20 mg and losartan 100 mg. Each dose was separated by a 7 day washout period. Approximately 5 - 7 hours after each dose, subjects received sequential 6 minute intraarterial infusions of saline, angiotensin I (16, 64, 256, 1024 pmol/min.), angiotensin II (16, 64, 256, 1024 pmol/min.) and bradykinin (10, 30, 100 pmol/min.). For the last 3 minutes of each 6-minute intra-arterial infusion of saline or one infusion rate of one agonist, blood flow was measured. Forearm blood flow was measured using a mercury-in-Silastic strain gauge as previously established by the investigator. Briefly, on each study day, at the appropriate time, inflatable cuffs were placed on each wrist and each arm (above the elbow) and connected to calibrated air pumps for inflation to appropriate, timed, preset pressures (200 mmHg at the wrists, 40 mmHg at arm). Strain gauges were applied to each arm and adjusted until the blood flow signal was similar for each arm. It was anticipated that the infusion rate for angiotensin I and angiotensin II would be increased until forearm blood flow decreased to 50% or until the maximum infusion rate was achieved. For bradykinin, the infusion rate was increased until forearm blood flow had increased approximately 3-fold (150 to 300%), or the maximal rate had been achieved.

During each of the four treatment periods, forearm blood flow rates (ml/min) were measured in both the infused arm and the other, noninfused, arm during both saline and agonist administration. These flow rates were designated as follows:

$F_{Ag,Inf}$ = Flow rate during agonist in the infused arm,

$F_{Sal,Inf}$ = Flow rate during saline in the infused arm,

$F_{Ag,Nif}$ = Flow rate during agonist in the control (noninfused) arm, and

$F_{Sal,Nif}$ = Flow rate during saline in the control (noninfused) arm.

The agonist/saline ratio of flow rates for each arm are:

$R_{Inf} = F_{Ag,Inf}/F_{Sal,Inf}$, and

$R_{Nif} = F_{Ag,Nif}/F_{Sal,Nif}$

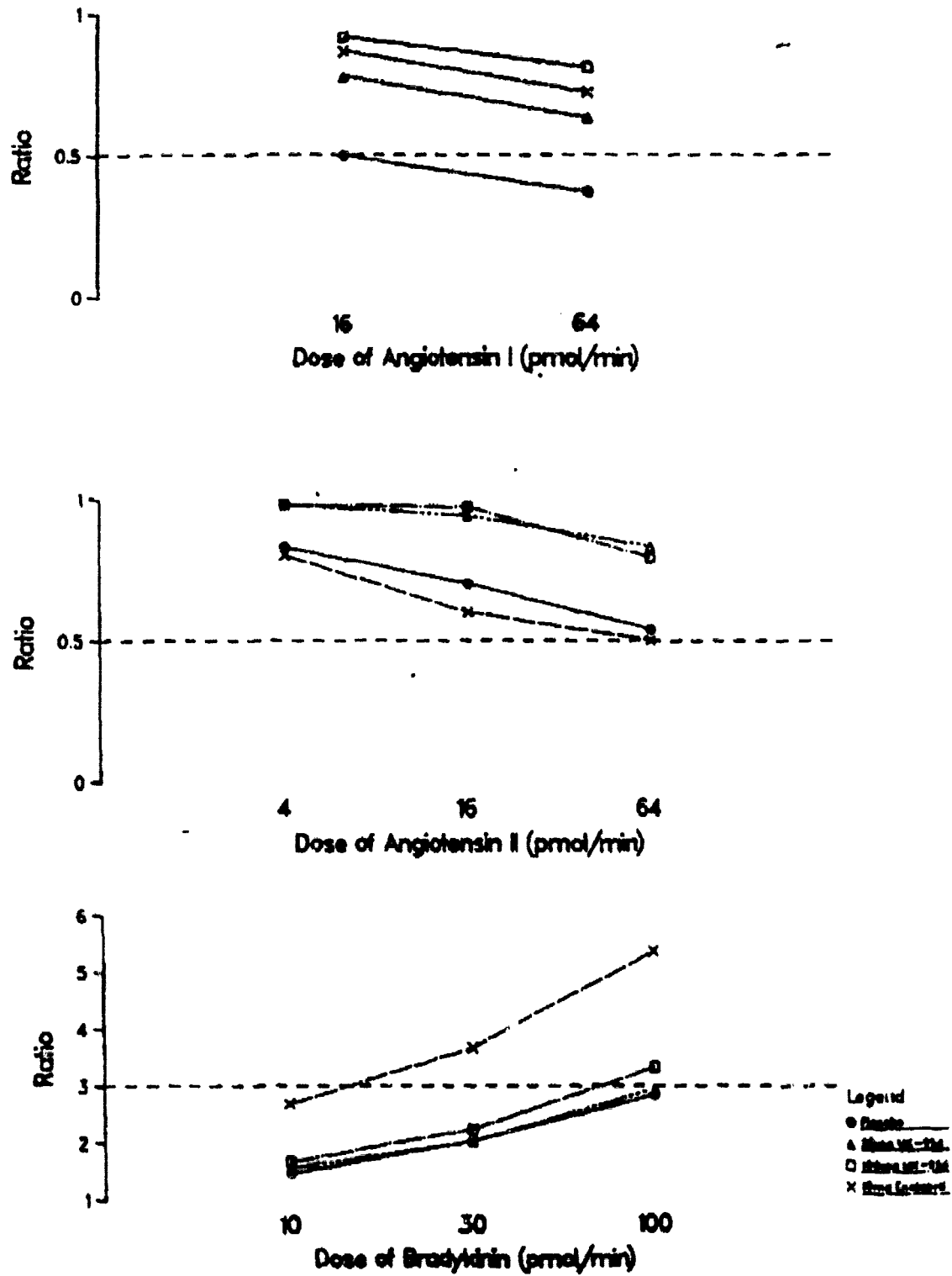
The primary hypothesis of the trial was that during angiotensin II administration, the geometric mean ratio of R_{Inf}/R_{Nif} following MK-954 100 mg to the R_{Inf}/R_{Nif} following placebo will be ≥ 1.8 , i.e., during at least one infusion rate of angiotensin II, the blood flow following MK-954 will be 1.8 times that following placebo (or enalapril).

Secondary hypothesis stated that during angiotensin I administration, the geometric mean ratio of R_{Inf}/R_{Nif} following MK-954 100 mg to the R_{Inf}/R_{Nif} following placebo will be > 1.8 . This will also be the response following 10 mg enalapril. During bradykinin administration, the geometric mean ratio of R_{Inf}/R_{Nif} following enalapril 10 mg to the R_{Inf}/R_{Nif} following placebo will be ≥ 1.5 , i.e., at least 50% enhancement of the response.

Nine healthy male, caucasian volunteers ranging in age from 22 to 47 years of age were enrolled in the study. Complete data from only five patients is included in the analysis. Selective data from four patients is included. As a consequence, it is difficult to determine whether there is some investigator/sponsor bias in the the data presentation. If the results from this trial are to be included in labeling, a complete audit of the data is warranted.

Figure 35.1 plots the geometric mean ratios for some of the doses agonist infused. During angiotensin I infusion, the enalapril and losartan treatments should blunt the pressor effect compared to placebo. This is suggested from the plot. During angiotensin II infusion, losartan but not enalapril should blunt the pressor effect compared to placebo. This is suggested from the plot. During bradykinin infusion, enalapril should enhance the vasodilatory response compared to losartan and placebo. This is suggested from the plot.

Figure 35.1. Within Treatment Geometric Mean Ratios of Forearm Blood Flow



The interpretations of these graphs are further supported by the comparison of the ratios in tables 35.1 - 3.

Table 35.1. Treatment Comparison of Ratios during Angiotensin I Infusion.

Treatment		vs. Placebo		vs. Enalapril		100 mg losartan vs. 20 mg losartan	
		16	64	16	64	16	64
20 mg losartan	Ratio	1.56	1.72	0.90	0.87		
	95% C.I.	(1.42, 1.70)	(1.42, 2.08)	(0.81, 0.99)	0.72, 1.05		
	P-Value	<.0001	<.0001	.023	.13		
100 mg losartan	Ratio	1.84	2.20	1.06	1.12	1.18	1.28
	95% C.I.	(1.67, 2.02)	(1.80, 2.70)	(0.96, 1.17)	(0.91, 1.36)	(1.07, 1.30)	(1.05, 1.56)
	P-Value	<.0001	<.0001	.24	.26	.0022	.019
10 mg Enalapril	Ratio	1.74	1.97				
	95% C.I.	(1.58, 1.91)	(1.63, 2.38)				
	P-Value	<.0001	<.0001				

Table 35.2. Treatment Comparison of Ratios during Angiotensin II Infusion.

Treatment		vs. Placebo			vs. Enalapril			vs. 20 mg losartan		
		4	16	64	4	16	64	4	16	64
20 mg losartan	Ratio	1.18	1.34	1.55	1.23	1.57	1.65			
	95% C.I.	(1.00, 1.38)	(1.08, 1.65)	(1.23, 1.94)	(1.04, 1.43)	(1.28, 1.93)	(1.30, 2.08)			
	P-Value	.042	.010	.0021	.014	.0002	.0023			
100 mg losartan	Ratio	1.19	1.38	1.47	1.23	1.62	1.56	1.00	1.03	0.95
	95% C.I.	(1.00, 1.41)	(1.10, 1.73)	(1.17, 1.85)	(1.04, 1.46)	(1.30, 2.02)	(1.23, 1.98)	(0.85, 1.20)	(0.83, 1.29)	(0.76, 1.20)
	P-Value	.051	.0080	.0039	.019	.0003	.0043	.92	.78	.67
10 mg Enalapril	Ratio	0.96	0.86	0.94						
	95% C.I.	(0.82, 1.13)	(0.69, 1.05)	(0.74, 1.19)						
	P-Value	.61	.13	.65						

Table 35.3. Treatment Comparison of Ratios during Bradykinin Infusion.

Treatment		vs. Placebo			vs. Enalapril			100 mg MK-954 vs. 20 mg MK-954		
		10	30	100	10	30	100	10	30	100
20 mg Losartan	Ratio	1.07	1.00	1.04	0.58	0.55	0.55			
	95% C.I.	(0.86, 1.33)	(0.82, 1.20)	(0.81, 1.32)	(0.49, 0.73)	(0.45, 0.67)	(0.43, 0.70)			
	P-Value	.51	.95	.74	<.0001	<.0001	<.0001			
100 mg Losartan	Ratio	1.14	1.10	1.17	0.62	0.61	0.62	1.07	1.10	1.13
	95% C.I.	(0.91, 1.43)	(0.90, 1.33)	(0.91, 1.51)	(0.49, 0.78)	(0.49, 0.74)	(0.48, 0.80)	(0.85, 1.34)	(0.90, 1.35)	(0.87, 1.46)
	P-Value	.23	.33	.20	.0003	<.0001	.0009	.58	.34	.36
10 mg Enalapril	Ratio	1.84	1.81	1.89						
	95% C.I.	(1.49, 2.26)	(1.50, 2.18)	(1.50, 2.39)						
	P-Value	<.0001	<.001	<.0001						

Ratios of R_{inf}/R_{Nif} between treatments, 95% confidence interval, and test that the ratio between the treatments is different from 1.0.

Study 060.

This was an open, three-period crossover study in 6 healthy male subjects. ^{14}C -losartan (MK-954) was administered in a randomized manner in the first and third periods as a single 100 mg oral dose (100 μ Ci) and as a single 30 mg intravenous dose (100 μ Ci). At least 7 days separated periods 1 and 2 and 2 and 3, providing a total of at least 14 days between the two radioactive treatments. During the second treatment period, E-3174 (without radioisotope) was administered as a single 20 mg intravenous dose. Blood samples were collected up to 48 hours after dosing. Urine samples were collected up to 96 hours after dosing. Feces were collected over the 168-hour period following each radioisotope (Periods 1 and 3) drug administration.

Six healthy male volunteers (5 caucasians, 1 black) between the age range of 22 and 30 years entered and completed the study. Following the completion of this study (#060), subject AN 0012 was identified from Study #075 who, based upon analysis of his plasma following three separate administrations of losartan 50 mg, had barely detectable E-3174 in plasma. To further investigate the metabolism of losartan in this subject, this protocol was amended (Amendments 060-01/02) to enroll this subject as subject number 007 and to specifically investigate his metabolism of losartan, using radiolabelled drug and to incorporate metabolic phenotyping using specified probe drugs. The data from the six subjects (AN 001-006) who completed the study were included in the pharmacokinetic analyses. Data from patient AN 007 was not included in the summary of this study.

Table 60.1 lists the pharmacokinetic parameters measured after each treatment. The mean (harmonic) elimination half life is approximately 3 hours for losartan and 6 - 8 hours for E-3174. The absolute bioavailability of the oral solution is approximately 39%.

Table 60.1. Pharmacokinetics Parameters (mean±S.D.) of Losartan and E-3174

	Intravenous E-3174 20 mg	Intravenous Losartan 30 mg (100 µCi)		Oral Losartan (Solution) 100 mg (100 µCi)	
	E-3174	Losartan	E-3174	Losartan	E-3174
C _{20min} , ng/mL	3720.7 ± 342.2	1452.8 ± 636.4	-	-	-
C _{max} , ng/mL	-	-	148.9 ± 78.9	659.1 ± 244.0	652.6 ± 259.1
T _{max} , hr	-	-	4.0 ± 2.1	0.46 ± 0.29	2.33 ± 0.52
AUC _{0-∞} , ng/mL·hr	5969.27 ± 709.03	851.18 ± 234.54	1331.96 ± 490.24	1091.35 ± 397.46	4072.54 ± 1252.91
λ, hr ⁻¹	0.1105 ± 0.0228	0.2181 ± 0.0531	0.1304 ± 0.0501	0.2418 ± 0.0502	0.0881 ± 0.0092
t _{1/2} , hr ^a	6.27 ± 1.36	3.18 ± 0.78	5.32 ± 2.12	2.87 ± 0.57	7.87 ± 0.82
V _{dss} , L	10.33 ± 1.09	46.59 ± 20.50	-	-	-
CL, mL/min	46.93 ± 5.79	558.71 ± 188.01	-	-	-
CL _r , mL/min	25.88 ± 5.59	64.39 ± 25.96	25.25 ± 7.00	64.63 ± 17.28	27.00 ± 6.10
Recovered in Urine (mg)	9.129 ± 1.414	3.020 ± 0.836	1.911 ± 0.616	4.297 ± 1.878	6.516 ± 2.186
% Dose ^c	55.07 ± 8.95	11.50 ± 3.49	7.59 ± 2.30	4.77 ± 2.08	7.63 ± 2.58
F, % ^b	-	-	-	38.90 ± 14.67	-

^a Harmonic mean and pseudo standard deviation.

^b Oral Bioavailability, geometric mean was 36.47% with 90% confidence interval limits of 26.11% to 50.94%.

^c % dose recovered in the urine as losartan.

Radioactivity in plasma, urine and feces was determined after the administration of 100 mg (100 µCi) of oral losartan (solution) and 30 mg (100 µCi) of intravenous losartan as listed in Table 60.2. Plasma radioactivity following I.V. and oral administration was primarily accounted for by losartan and E-3174. Metabolic profiling of urine was determined after the 100 mg (100 µCi) of oral losartan (solution) and 30 mg (100 µCi) of I.V. losartan. Metabolic profiling in the feces was a qualitative assessment using specimens following I.V. administration from subjects 001 and 002; therefore only these individual data are presented. The three major metabolites identified in the urine were L-158,795, L-158,796, E-3174, and L-158,783 was considered a minor metabolite.

Table 60.2. Total Radioactivity and Metabolic Profiling (% dose)

	I.V. Losartan 30 mg (100 µCi)		Oral Losartan 100 mg (100 µCi)*	
	Urine	Feces	Urine	Feces
Total Radioactivity	43.3 ± 8.4	49.5 ± 13.3	35.2 ± 6.2	57.7 ± 7.9
Metabolic Profile		AN001	AN002	
Losartan	11.4 ± 4.0	12.8	7.7	4.51 ± 2.27
L-158,795	9.35 ± 1.73	8.20	8.38	9.09 ± 1.79
E-3174	6.44 ± 2.45	6.92	13.38	6.41 ± 2.22
L-158,796	8.24 ± 1.76	7.37	9.44	7.64 ± 1.80
L-158,783	0.267 ± 0.109	0.794	1.31	-

* 30 mg radioactive losartan + 70 mg of non-radioactive losartan

Study 067.

This was a randomized, open, three-period crossover pharmacokinetic study in 9 patients with Class A or B hepatic insufficiency. Patients received 3 different treatments in a randomized sequence. Each treatment was separated by a 7-day washout. The 3 treatments were a single oral 50 mg tablet of losartan, a single 10 mg I.V. dose of losartan and a single 10 mg I.V. dose of E-3174.

Subjects had a clinical diagnosis of hepatic insufficiency due to alcoholic liver disease, met the Child-Pugh Classification as having Class A (5-6) or B (7-9) liver disease, had a serum creatinine and EUN within 150% of normal range values and had a creatinine clearance ≥ 65 mL/min/1.73m². Table 67.1 lists the criteria used in the Child-Pugh classification. Each variable is given a point score of 1 to 3 and then totaled giving a class of severity.

Table 67.1. Pugh's Modification of Child's Classification of the Severity of Liver Disease

Points Score for Increasing Abnormality	1	2	3
Encephalopathy (grade)	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Bilirubin (mg/100 mL)	1-2	2-3	>3
Albumin (g/l)	>35	28-35	<28
Prothrombin time (seconds over control)	1-4	4-6	>6
Bilirubin in PBC (mg/100 mL) ¹	1-4	4-10	>10

¹The Bilirubin classification criteria differs for patients with primary biliary cirrhosis. PBC = Primary Biliary Cirrhosis

Nine patients with hepatic insufficiency between the ages of 42 and 63 entered and completed the study. All patients had a Child-Pugh score greater than 5, ranging from 5-9. Table 67.2 gives the demographic characteristics of the patients who entered and completed the study. All subjects had elevations in the prothrombin time at some point in the study. Other lab abnormalities related to liver dysfunction varied between patients. For example, only 3 of 9 had abnormal total bilirubin.

Table 67.2. Patient Characteristics

Patient	Age Years	Sex	Race	Weight (lbs)	Child-Pugh Score	CrCL mL/min
1	59	M	Caucasian	171.5	5	89.3
2	57	F	Caucasian	172.5	5	83.85
3	48	M	Caucasian	191.0	7	195
4	53	M	Caucasian	200.0	7	106
5	63	M	Caucasian	115.5	8	65
6	60	M	Caucasian	151.0	7	92.6
7	55	M	Caucasian	181.0	7	110.8
8	61	M	Caucasian	250.0	5	116.4
9	42	M	Caucasian	201.0	9	113.9
Mean	55.3			181.5	-	108.09
Range	42 to 63			115.5 to 250	5-9	65 to 195

Data from these patients was compared to data from other pharmacokinetic trials (study 74 and 75) that enrolled healthy males. In general, the AUC, C_{max} and absolute bioavailability of losartan was increased compared to healthy male subjects. Total clearance and volume of distribution was decreased. The terminal elimination half-life and time to maximum concentration was unchanged. For E-3174, the volume of distribution and systemic clearance were decreased slightly. The area under the curve was increased by approximately 50%. The C_{max} increased by approximately 20%. The elimination rate constant was essentially unchanged. Tables 67.3 - 67.4 list the pharmacokinetic parameters for losartan and E-3174.

Table 67.4. Pharmacokinetic Parameters for Oral Losartan

	STUDY	N	Mean	Median	95% CI for the mean
AUC (ng·hr/mL) for losartan					
	Study 67	9	2162.84	2267.56	(1320.85, 3004.82)
	Study 74	12	475.56	474.17	(348.78, 602.35)
	Study 75	17	402.80	377.77	(351.13, 454.47)
Volume of Distribution (Liters) of Losartan					
	Study 67	9	19.65	16.31	(12.14, 27.15)
	Study 60	6	46.59	43.12	(25.07, 68.10)
	Study 74	12	28.36	23.02	(19.72, 37.01)
C_{max} (ng/mL) of Losartan					
	Study 67	9	1171.77	1186.10	(658.98, 1684.56)
	Study 74	12	296.38	242.30	(158.48, 434.28)
	Study 75	17	209.24	168.70	(157.89, 260.58)
Systemic Clearance (mL/min) of Losartan					
	Study 67	9	285.04	301.55	(210.13, 359.96)
	Study 60	6	558.71	500.59	(361.40, 756.01)
	Study 74	12	635.95	644.32	(567.71, 704.19)
AUC (ng·hr/mL) for E-3174 Following Oral Losartan					
	Study 67	9	3131.19	3254.55	(2193.73, 4068.62)
	Study 74	12	1915.25	1811.52	(1573.53, 2256.96)
	Study 75	17	1778.33	1808.31	(1555.03, 2001.63)
C_{max} for E-3174 (ng/mL) Following Oral Losartan					
	Study 67	9	296.21	264.80	(212.54, 379.88)
	Study 74	12	249.40	245.00	(202.60, 296.20)
	Study 75	17	225.42	211.40	(165.41, 285.43)
Systemic Clearance (mL/min) of E-3174 Following IV E-3174					
	Study 067	9	33.18	26.32	(23.06, 43.30)
	Study 060	6	46.93	47.64	(40.85, 53.01)

Table 67.5. Bioavailability of Losartan

STUDY	N	Mean	Geometric Mean	Median	95% CI for the mean	95% CI for the Geometric mean
67	9	64.76	61.31	56.31	(48.02, 81.50)	(45.61, 82.41)
74	12	35.80	32.65	35.26	(25.93, 45.66)	(25.27, 42.17)

Diastolic blood pressure on average did not appear to decline precipitously. The maximum mean decrease from baseline in supine DBP was -5.0 mmHg. The greatest individual decline in supine DBP was -13 mmHg. Although the blood pressure data in this study did not suggest that on average there is dramatic decline secondary to the increased C_{max}, consideration should be given to starting with a lower initial dose in patients with hepatic insufficiency and titrating carefully based on effect.

Study 72.

This was a single blind, single dose, 2 period study in 15 healthy males subjects. The trial consisted of 2 treatment periods. In period one, all subjects received a single dose of losartan on Day 1. After a 48 hour washout, period two commenced, consisting of a 16-day course of either phenobarbital or placebo and a single dose of losartan between doses 14 and 15 of phenobarbital/placebo. Ten subjects received 14 days of phenobarbital followed by a single dose of losartan and five subjects received 14 days of placebo and a single dose of losartan. Table 72.1 lists the pharmacokinetic parameters measured in the study. Phenobarbital administration caused the AUC of losartan and E-3174 (L-158,641) to decrease by approximately 20%.

Table 72.1. Pharmacokinetic Parameters

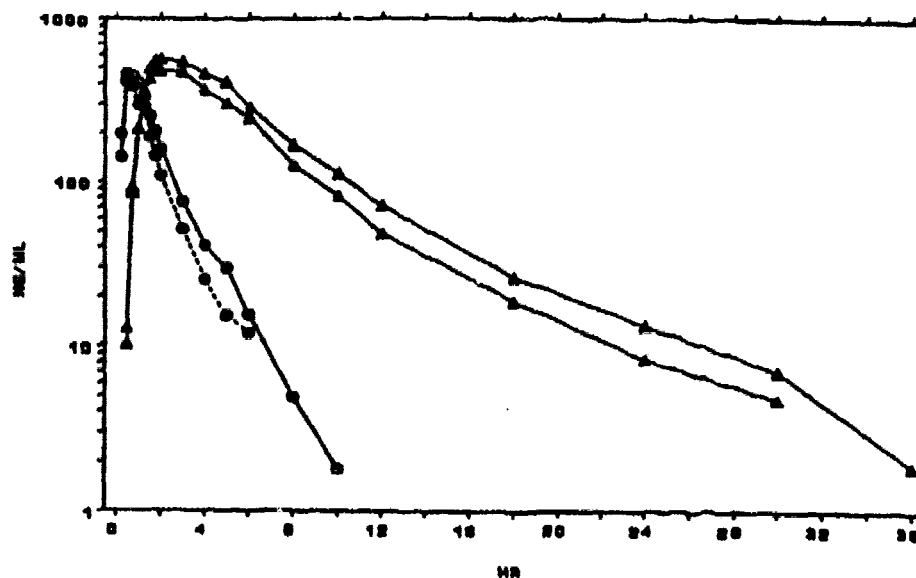
	Period I - 100 mg of MK-954 Given Prior to Phenobarbital or Placebo Administration		Period II - 100 mg of MK-954 Taken on Day 15 of Phenobarbital or Placebo Administration		
	MK-954	L-158,641	MK-954	L-158,641	
	Phenobarbital Treatment Group (n=10), 100 mg Once a Day for 16 Days				
C_{max} , ng/mL	588.4 ± 300.1	646.3 ± 136.8	586.9 ± 268.8	583.8 ± 132.9	
T_{max} , hr	0.88 ± 0.29	2.23 ± 0.70	0.88 ± 0.46	2.38 ± 1.14	
AUC, ng·hr/mL	854.31 ± 193.97	3784.92 ± 468.61	673.84 ± 124.98	3022.17 ± 361.38	
λ , hr ⁻¹	0.4041 ± 0.1298	0.1012 ± 0.0391	0.4049 ± 0.1100	0.1102 ± 0.0482	
$t_{1/2}$, hr ^a	1.72 ± 0.55	6.85 ± 2.76	1.71 ± 0.45	6.29 ± 2.88	
CL_T , mL/min	69.55 ± 4.96	22.70 ± 2.08	68.50 ± 6.29	22.19 ± 3.11	
Urinary Recovery	mg	3.725 ± 0.931	5.105 ± 0.504	2.825 ± 0.634	3.964 ± 0.429
	% Dose	3.75 ± 0.94	5.42 ± 0.54	2.84 ± 0.64	4.21 ± 0.45
Placebo Treatment Group (n=5), Placebo Once a Day for 16 Days ^b					
C_{max} , ng/mL	381.5 ± 140.7	470.9 ± 119.3	355.8 ± 83.8	444.4 ± 172.2	
T_{max} , hr	1.31 ± 0.13	3.50 ± 0.58	1.25 ± 0.41	3.50 ± 1.29	
AUC, ng·hr/mL	684.10 ± 206.49	3048.38 ± 909.43	697.93 ± 189.38	3179.42 ± 1098.9	
λ , hr ⁻¹	0.4098 ± 0.0622	0.0958 ± 0.0438	0.3172 ± 0.083	0.0656 ± 0.0248	
$t_{1/2}$, hr ^a	1.69 ± 0.25	7.23 ± 3.13	2.18 ± 0.59	10.56 ± 4.02	
CL_T , mL/min	78.87 ± 8.26	26.37 ± 2.19	77.13 ± 5.64	24.77 ± 1.09	
Urinary Recovery	mg	3.440 ± 1.125	4.816 ± 1.654	3.291 ± 0.929	4.655 ± 1.798
	% Dose	3.46 ± 1.13	5.11 ± 1.76	3.31 ± 0.93	4.94 ± 1.91
^a Harmonic mean and pseudo standard deviation.					
^b C_{max} , T_{max} , AUC, λ , $t_{1/2}$, CL_T and urinary recovery: n=4, data for subject #5 excluded.					

Patient #5 had had low levels of the metabolite and therefore this subject was considered to be an outlier. To further investigate the metabolism of losartan in this subject, the protocol was amended (Amendments 072-01/02). The results of the amendments did not make the in-house cutoff date (1/14/93) for the clinical study report and are not included in the sponsor's summary. This patient's data was not included in the calculations of the pharmacokinetic parameters.

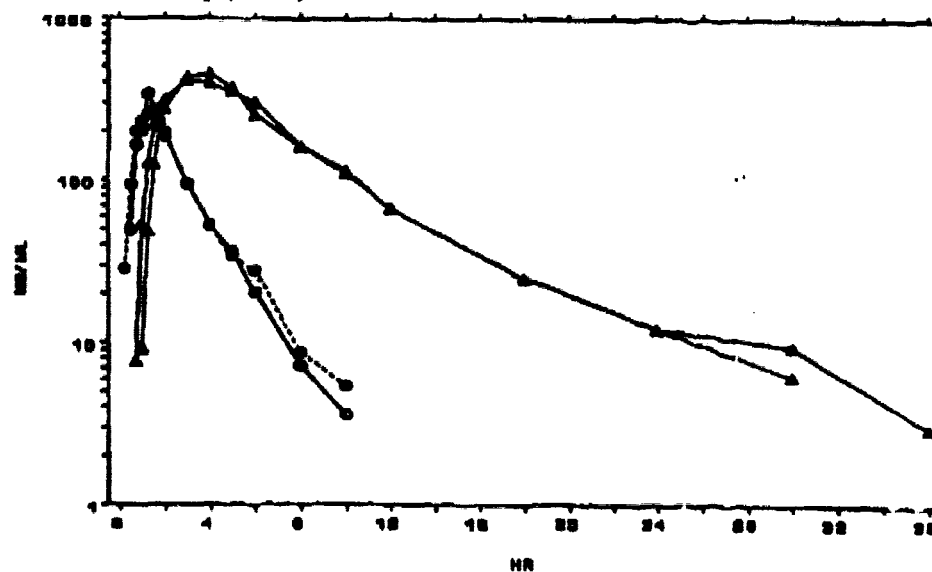
Figure 72.1 plots the mean concentrations for losartan and E-3174.

Figure 72.1. Mean Plasma Concentration vs. Time Profiles For Losartan and L-158,641 in the Groups which Received Phenobarbital (TOP) and Placebo (BOTTOM)

Phenobarbital Group(N=10)



Placebo Group(N=4)



○ = MK-954 Pre-Rx; ● = MK-954 During Rx; △ = L-158,641 Pre-Rx;
▲ = L-158,641 During Rx

The data do indicate that the metabolism of losartan, and probably L-158,641, can be influenced by induction of cytochrome P450. While levels of induction achieved with phenobarbital are minor and are unlikely to result in a clinically important affect on the activity of losartan, the data do not eliminate the possibility of interaction of P450 induction with other patient factors which influence drug metabolism.

Study 70.

This as a double-blind, randomized, placebo-controlled, two-period crossover study in ten normal volunteers. In each period, each subject received, according to a random allocation schedule, either losartan 100 mg orally or matched placebo for 12 days, with a single 30 mg oral dose of sodium warfarin on Day 7. This treatment scheme is illustrated in Table 70.1.

Table 70.1. Treatment Scheme

Day:	1	2	3	4	5	6	7	8	9	10	11	12	13
Warfarin, 30 mg (1 dose)							X						
Losartan or placebo, 100 mg q.d.	X	X	X	X	X	X	X	X	X	X	X	X	

After the completion of the first treatment period (randomized to losartan or placebo) followed by a 2-week washout period, each subject was crossed over to the complementary treatment period identical except for the substitution of losartan for placebo and vice versa. The two warfarin doses, one in each treatment period, were separated by 4 weeks.

Just prior to and at intervals following warfarin administration, blood was drawn for determination of levels of (R) and (S) warfarin and prothrombin time.

The primary pharmacodynamic measurement was prothrombin time (reported in two units -- seconds and INR). Two summary measures were calculated for each subject: area under the curve (0 to 144 hours) with respect to changes from baseline in prothrombin time and the maximum change in prothrombin time by subject. An ANOVA model containing terms for subject, period, and treatment was used to analyze the differences between treatments with respect to these summary measures.

Separate analyses were carried out for the pharmacokinetics of each enantiomer (R and S) of warfarin, based on results of a stereospecific assay. Ln-transformed area under the plasma concentration curve (lnAUC), ln-transformed maximum plasma concentration (lnC_{max}), maximum plasma concentration (C_{max}) and time until maximum plasma concentration (T_{max}) were the primary pharmacokinetic measurements analyzed.

Ten healthy male volunteers ranging in age from 18 to 29 years were enrolled. Patient #3 withdrew prematurely for personal reasons after day 10 of losartan therapy (2nd sequence). Data for patient #3 is not included in the summary by the sponsor. Table 70.2 and 70.2a list the mean pharmacokinetic parameters of the R and S enantiomers of warfarin. There does not appear to be a significant difference between parameters with losartan therapy.

Table 70.2. Pharmacokinetics (arithmetic mean ±S.D.)

Parameter	R-Warfarin		S-Warfarin	
	Losartan	Placebo	Losartan	Placebo
AUC(ng•hr/mL)	87861.0	87195.4	70266.0	70194.9
(± S.D.)	(14941.7)	(22525.9)	(13956.1)	(17945.9)
C _{max} (ng/mL)	1656.3	1496.3	1647.0	1615.6
(± S.D.)	(382.9)	(256.1)	(308.8)	(258.1)
λ(hr ⁻¹)	0.015	0.016	0.020	0.020
(± S.D.)	(0.002)	(0.003)	(0.003)	(0.003)
t _{1/2} (hr) ¹	44.97	44.34	34.97	36.00
(± S.D.)	(2.49)	(3.11)	(2.06)	(2.20)

Table 70.2a. Pharmacokinetics (geometric mean ratios and treatment differences)

Parameter	Least Square Means		Trt Diff ²	90% CI
	Losartan	Placebo		
R-Warfarin				
AUC(ng•hr/mL) ³	87040.29	84199.81	1.034	(.967, 1.105)
C _{max} (ng/mL) ³	1608.71	1489.29	1.080	(.953, 1.224)
T _{max} (hr)	2.90	2.77	.125	(-1.59, 1.836)
S-Warfarin				
AUC(ng•hr/mL) ³	69461.29	67787.18	1.024	(.945, 1.111)
C _{max} (ng/mL) ³	1616.49	1603.22	1.008	(.928, 1.096)
T _{max} (hr)	1.70	2.08	-.375	(-.999, 0.249)

1 Harmonic mean and pseudo standard deviation.

2 Treatment effect estimates are geometric mean ratios for log-transformed values, otherwise treatment estimates reflect arithmetic mean differences (losartan - placebo)

3 Log transformed for analysis by ratio.

Tables 70.3 and 70.3a list the AUC and maximum change in prothrombin time. There is a slight increase with losartan treatment but this difference is not significant. The AUC and C_{max} difference is illustrated in figure 70.1.

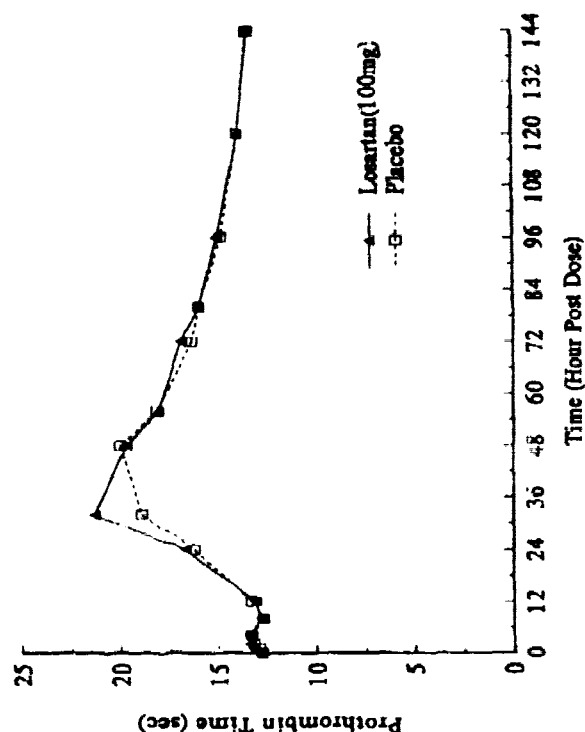
Table 70.3. AUC (0-144 hr) for Prothrombin Time

Subject	Seconds*hr		INR*hr	
	Losartan	Placebo	Losartan	Placebo
0001	661.20	867.70	138.24	197.42
0002	352.20	426.90	63.93	73.47
0004	279.95	225.55	51.59	38.44
0005	577.30	485.55	107.21	86.36
0006	214.00	358.55	38.20	64.65
0007	478.05	499.70	88.25	105.42
0008	785.00	381.60	96.98	69.83
0009	375.80	247.80	73.82	48.34
0010	226.70	194.05	41.46	36.02
Overall				
Mean	438.91	409.71	77.74	80.00
Std	200.71	204.31	33.13	49.40
LS Mean	433.20	415.42	76.64	81.10
Median	375.80	381.60	73.82	69.83
Min	214.00	194.05	38.20	36.02
Max	785.00	867.70	138.24	197.42

Table 70.3a. Maximum Change in Prothrombin Time

Subject	Seconds		INR	
	Losartan	Placebo	Losartan	Placebo
0001	10.30	17.90	2.39	4.94
0002	6.30	5.60	1.22	1.02
0004	4.20	3.00	0.81	0.53
0005	8.70	7.30	1.77	1.41
0006	4.10	6.90	0.76	1.35
0007	7.00	10.90	1.37	2.59
0008	32.00	7.00	2.17	1.37
0009	6.50	5.80	1.36	1.19
0010	4.60	4.20	0.87	0.80
Overall				
Mean	9.30	7.62	1.41	1.69
Std	8.76	4.44	0.59	1.35
LS Mean	9.04	7.88	1.37	1.73
Median	6.50	6.90	1.36	1.35
Min	4.10	3.00	0.76	0.53
Max	32.00	17.90	2.39	4.94

Figure 70.1. Prothrombin Time (Seconds) Means Across Time



This study appears to show a lack of a pharmacokinetic interaction between losartan and warfarin. It is not clear that this has any clinical relevance. The pharmacodynamic conclusions are weak. It is not clear that the design of this study is adequate to make any statement regarding the effect on prothrombin time. The sponsor cites a reference supporting the use of this design (Rocci ML, et al. Norfloxacin does not alter warfarin disposition or anticoagulant effect. *J Clin Pharmacol* 1990;30:728-732.). In the norfloxacin study, warfarin concentration (R and S) measured by AUC and Cmax was not changed by norfloxacin. Prothrombin time measured by AUC and prothrombin time maximum were not different. However, it is recognized, as stated in the labeling, that norfloxacin "may enhance the effects of the anticoagulant warfarin or its derivatives". This interaction may result from increased levels of free warfarin. That is where this study fails. Since < 1% of warfarin is free drug, measuring total drug is inadequate to assess an interaction. The design of this trial failed to predict a pharmacodynamic enhancement of warfarin by another drug. Consequently, the labeling for losartan should not include the results of this study. [Reviewer's Note: Patient #1031 in study 47 had gingival bleeding and an increased prothrombin time when treated with losartan and warfarin.]

Study 063.

This was a single center, open, 2-period, cross-over, single dose pharmacokinetic study in 10 (5 male and 5 female) elderly (>65 years of age) hypertensive patients. Patients were withdrawn from their usual antihypertensive regimen for at least 1 week. On each study day, patients received either the 50 mg losartan tablet or the 10 mg losartan I.V. solution in accordance with a randomized allocation schedule. The intravenous doses were administered over a 20-minute interval and each dose was separated by a 14-day washout period.

The average age of patients was 69.9 years of age (range: 65 - 75). All of the patients were caucasian. Tables and figures 63.1 - 63.4 list the AUC, Cmax, absolute bioavailability and systemic clearance for losartan in study 063 compared to studies that included predominantly healthy males. In study 063, females generally had higher AUC, Cmax and absolute bioavailability compared to males in study 063. Systemic clearance generally was lower in females. Males throughout several studies had similar results where as females differed.

Table 63. 1. $AUC_{0-\infty}$ (ng·hr/ml) for Plasma Losartan Concentration Versus Time

Study	Sex	N	Age Range	Mean	LSmeans	95% Confidence Interval
Hypertensive Subjects						
004	Both	18	32-65	641.29	722	(514.19, 768.39)
004	Female	5	43-58	822.54		(428.81, 1216.27)
004	Male	13	32-65	571.58		(450.61, 692.54)
Young Healthy Males						
007	Male	10	18-31	413.00	678	(283.64, 542.35)
015	Male	8	19-29	416.32	681	(339.90, 492.74)
022	Male	8	21-35	361.22	626	(204.11, 518.32)
Elderly Hypertensives						
063	Both	10	65-75	743.25	743	(494.56, 991.97)
063	Female	5	66-75	1008.38		(671.29, 1345.46)
063	Male	5	65-73	478.15		(291.69, 664.62)

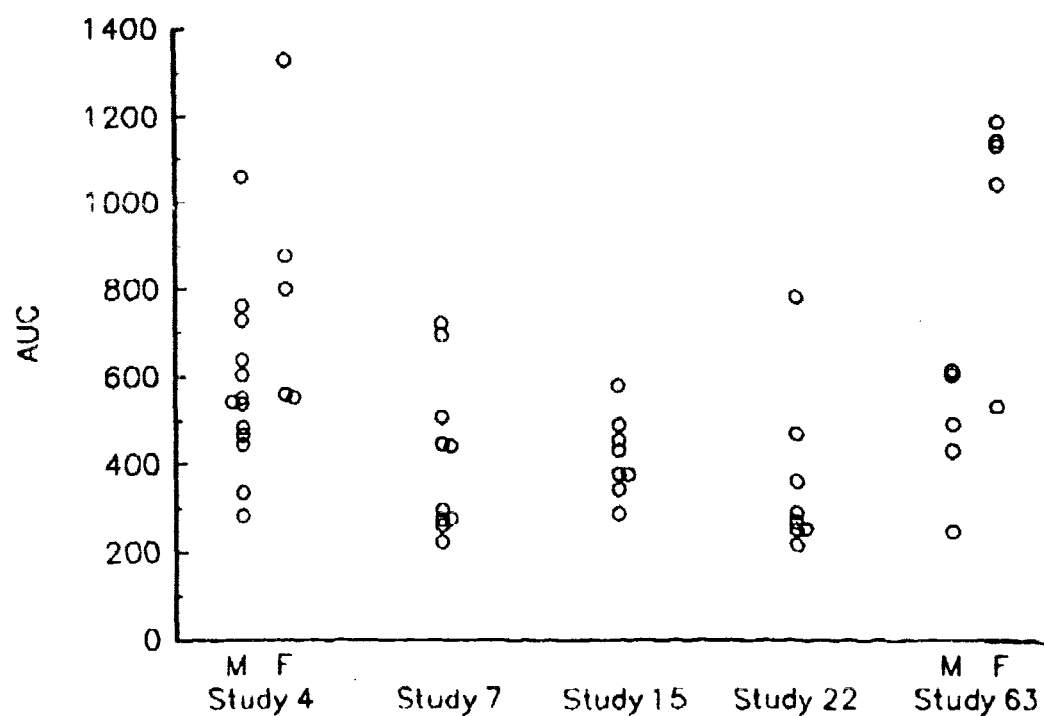
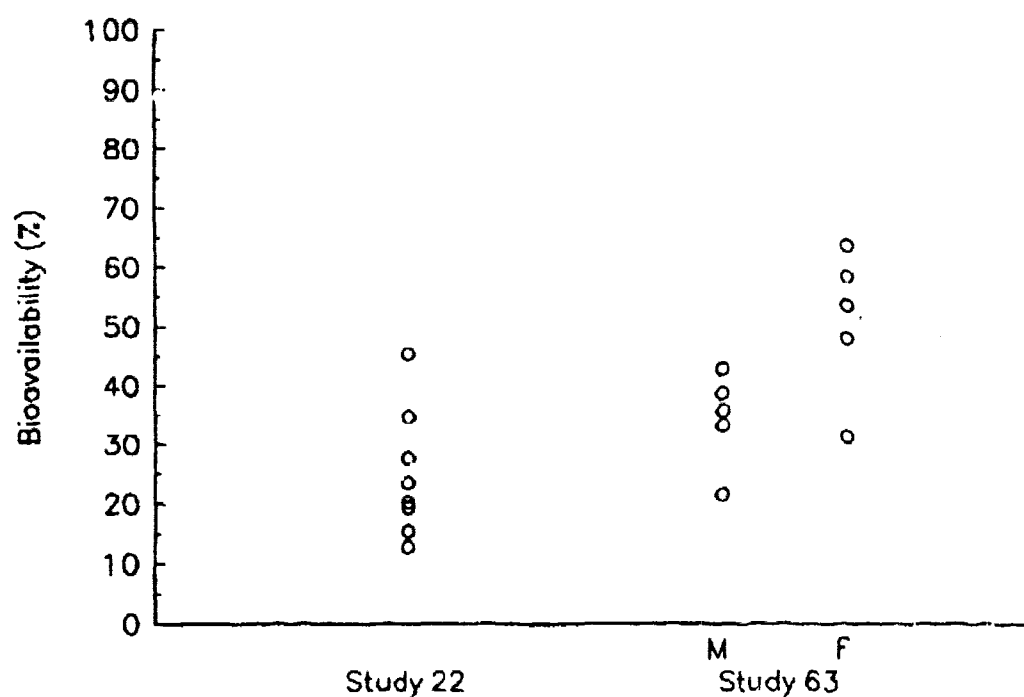
Figure 63.1. $AUC_{0-\infty}$ (ng·hr/ml) for Losartan

Table 63.2. Losartan Absolute Bioavailability

Study	Sex	N	Mean	LSmeans	95% Confidence Interval	Geometric Mean	90% Geometric Mean C.I.
<u>Young Healthy Males</u>							
022	Male	8	25	33	(16, 34)	22.9	(17.3, 30.3)
<u>Elderly Hypertensives</u>							
063	Both	10	43	43	(33, 52)	40.6	(33.5, 49.2)
063	Male	5	34		(24, 44)	33.4	(25.9, 43.0)
063	Female	5	51		(35, 66)	49.4	(37.9, 64.5)

Figure 63.2. Absolute Bioavailability (%) of Losartan**Table 63.3. Maximum Losartan Plasma Concentration (C_{max} ng/ml)**

Study	Sex	N	Mean	LSmeans	95% Confidence Interval
<u>Young Healthy Males</u>					
015	Male	8	259.07	401	(175.29, 342.86)
022	Male	8	243.08	385	(146.22, 339.95)
<u>Elderly Hypertensives</u>					
063	Both	10	391.07	391	(230.97, 551.17)
063	Female	5	533.08		(263.42, 802.74)
063	Male	5	249.06		(96.38, 401.74)

Figure 63.3. C_{max} (ng/ml) for Losartan

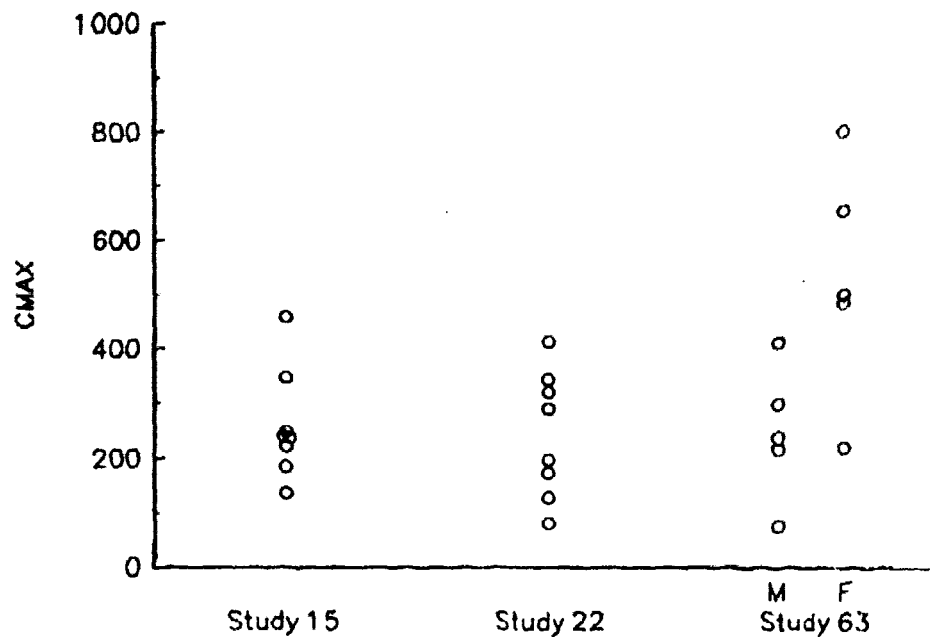
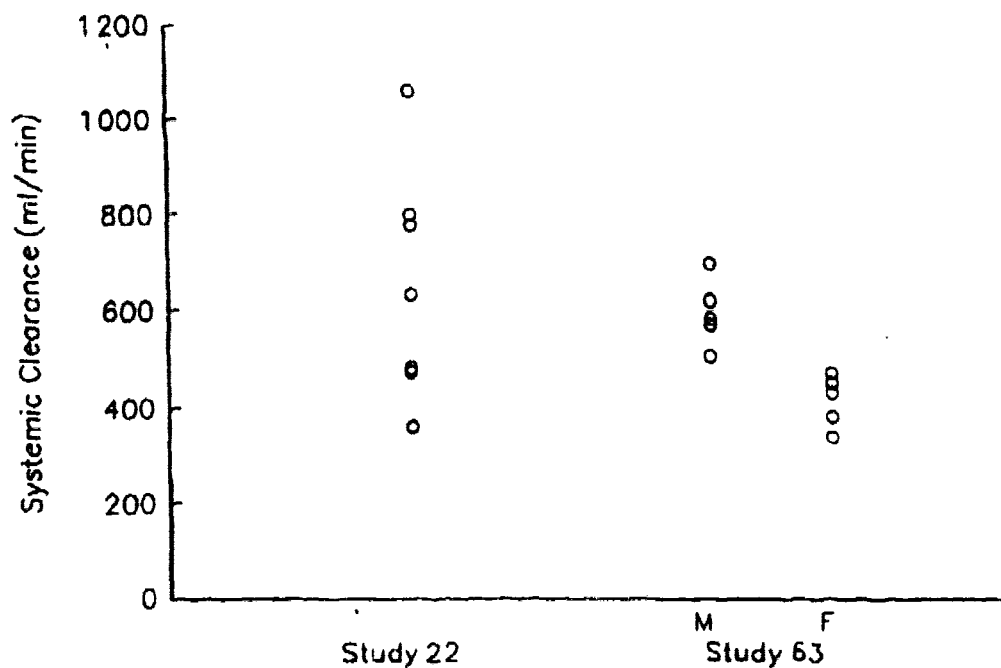


Table 63.4. Systemic Clearance (ml/min)

Study	Sex	N	Mean	LSmeans	95% Confidence Interval
<u>Young Healthy Males</u>					
022	Male	8	618.04	527.45	(411.61, 824.46)
<u>Elderly Hypertensives</u>					
063	Both	10	506.57	506.57	(426.18, 586.96)
063	Female	5	416.0		(347.89, 484.09)
063	Male	5	597.16		(510.31, 684.00)

Figure 63.4. Systemic Clearance (ml/min) for Losartan



In general, elderly hypertensive patients had greater AUC but not Cmax for E-3174 compared to healthy younger males in other studies.

Table 63.5. AUC_{0-∞} (ng·hr/ml) for Plasma L-158,641

Study	Sex	N	Age Range	Mean	LSmeans	95% Confidence Interval
Hypertensive Subjects						
004	Both	18	32-65	2707.48	2789	(2346.77, 3068.18)
004	Female	5	43-58	2952.59		(2065.79, 3839.39)
004	Male	13	32-65	2613.21		(2168.87, 3057.54)
Young Healthy Males						
007	Male	10	18-31	1843.34	2048	(1443.16, 2243.52)
015	Male	8	19-29	1561.13	1766	(1294.46, 1827.81)
022	Male	8	21-35	1780.36	1985	(1493.63, 2067.09)
Elderly Hypertensives						
063	Both	10	65-75	2681.70	2682	(2128.65, 3234.75)
063	Female	5	66-75	2886.59		(1691.35, 4081.82)
063	Male	5	65-73	2476.81		(1781.87, 3171.76)

Figure 63.5. AUC (ng·hr/ml) for L-158,641

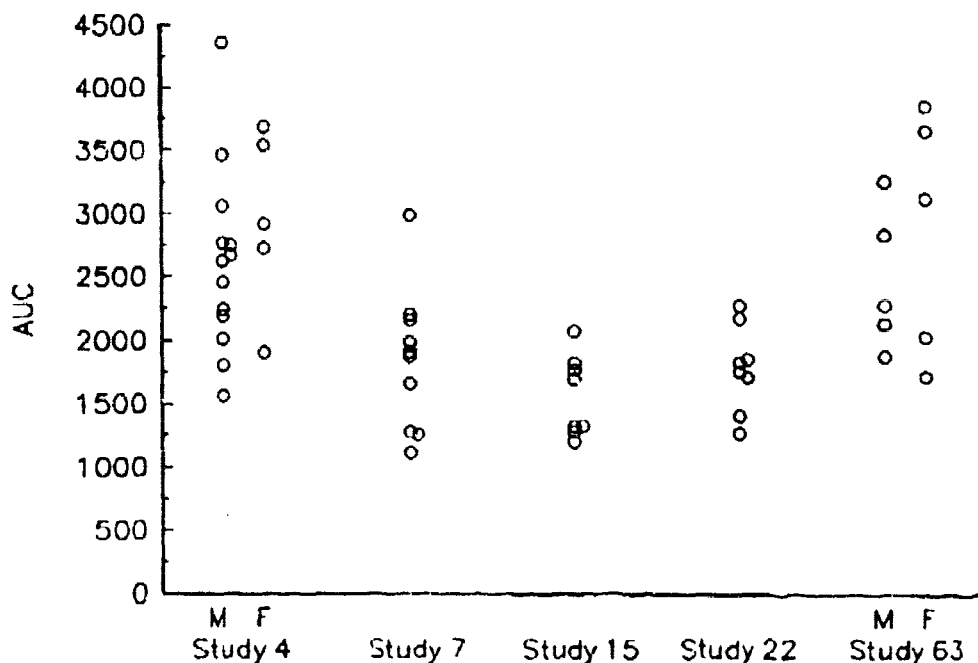
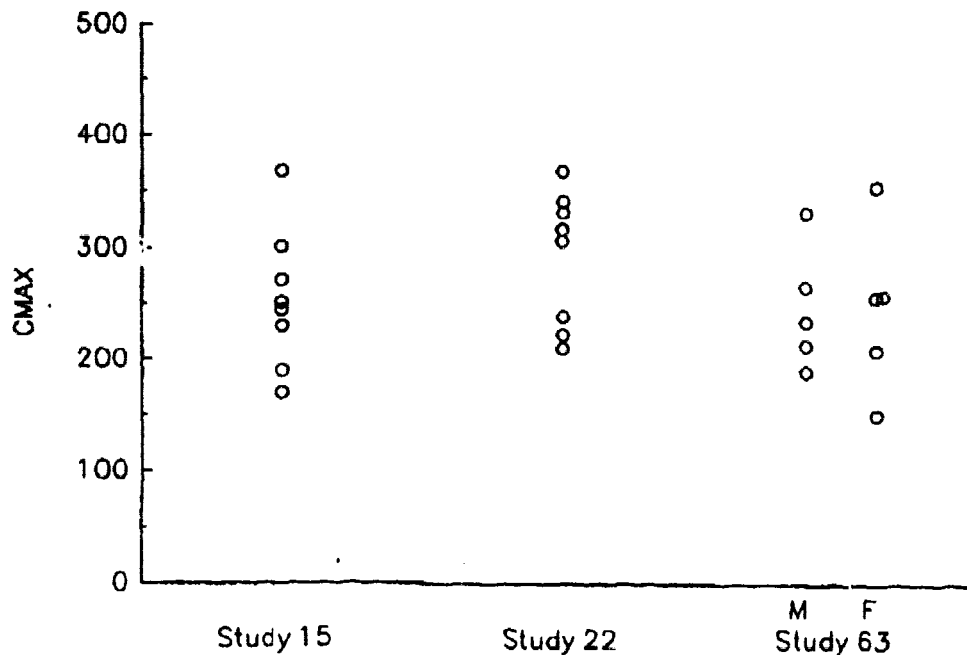
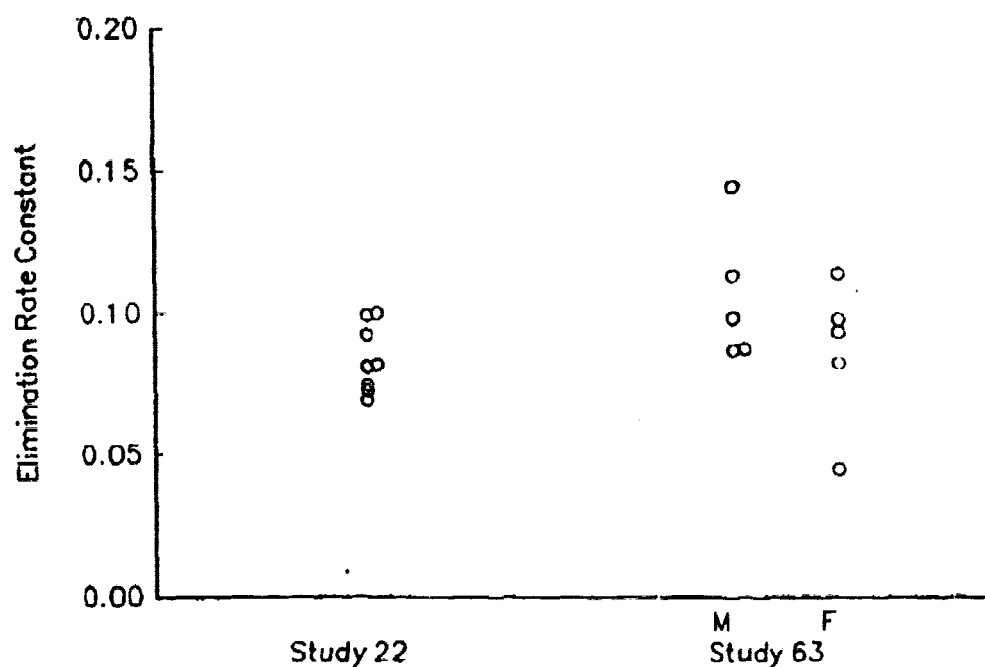


Table 63.6. Maximum L-158,641 Plasma Concentration (C_{max} ng/ml)

Study	Sex	N	Mean	LSmeans	95% Confidence Interval
Young Healthy Males					
015	Male	8	253.16	252	(200.75, 305.58)
022	Male	8	291.98	291	(242.01, 341.95)
Elderly Hypertensives					
063	Both	10	246.62	247	(202.04, 291.20)
063	Female	5	246.02		(152.37, 339.67)
063	Male	5	247.22		(178.68, 315.76)

Figure 63.6. C_{max} (ng/ml) for L-158,641

The elimination rate constant for E-3174 was not different between sexes and studies (figure 63.7).

Figure 63.7. Elimination Rate Constant (hr^{-1}) for L-158,641

Study 79.

This was a double-blind, randomized, two-period crossover study in 13 healthy volunteers. Subjects received 50 mg losartan (MK-954) or placebo daily for 15 days in each period. On Days 4 and 11 of each period, subjects also received single 0.5 mg intravenous (Day 4) and oral (Day 11) doses of digoxin. Thirteen healthy male subjects (10 Caucasians, 2 Haitians, 1 Iranian) between the ages of 19 and 32 years old were deemed acceptable for participation in the study. Eleven subjects completed the study according to protocol. Two subjects were discontinued during the study (AN 0005, adverse laboratory experience; AN 0007, withdrew from study). 1.

Two subjects did not complete the study. Patient # 0005 was discontinued during period 1 (losartan) due to increased liver function tests (ALT, AST). Patient #0007 was discontinued during period 1 (Day 5) since he inadvertently received the

medication for a different subject (patient # 0008) 24 hours post the Day 4 digoxin infusion. The data from these 2 subjects (patient #0005 and patient # 0007) were not included in the pharmacodynamic/pharmacokinetic analysis. Data for all 13 subjects who entered the study were included in the safety analysis.

Some pharmacokinetic data could not be included in the treatment comparisons. In 2 subjects, due to assay sensitivity, AUC_{0-48} could not be calculated for I.V. (patients 0001, 0203) and oral (patients 0009, 0203) digoxin. In four I.V. subjects (patients 0002, 0010, 0011, 0012) and 3 oral subjects (patients 0006, 0011, 0203), incomplete or apparently erroneous urine collections precluded use of their data in the urinary excretion analysis.

Table 79.1 lists the pharmacokinetic parameters for digoxin. There is a slight increase in digoxin C_{max} (13%) and AUC (5%) with losartan therapy.

Table 79.1. Digoxin Pharmacokinetic Parameters (arithmetic mean $\pm$ S.D.)

Parameter	With Losartan				Without Losartan			
	Day 4 (I.V.)	N	Day 11 (Oral)	N	Day 4 (I.V.)	N	Day 11 (Oral)	N
C_{max} (ng/mL)	--	--	3.46 (0.70)	11	--	--	3.07 (0.53)	11
AUC_{0-48} (ng•hr/mL)	28.76 (2.93)	10	23.63 (3.67)	11	28.45 (3.92)	9	22.43 (2.57)	9
AU (% dose)	54.01 (7.20)	7	51.16 (6.30)	8	51.89 (6.48)	7	46.26 (2.44)	8
T_{max} (hr)	--	--	0.64 (0.23)	11	--	--	0.86 (0.74)	11

AU = urinary excretion

Patient 005 had an increase in AST on day 1 (73 IU/L), day 4 (120 IU/L) and day 5 (99 IU/L). ALT was also increased with maximum ALT occurring on day 4 (184 IU/L). It is unlikely that elevations in transaminases are due to losartan since the increases started on day 1.

Study 043. Double-blind, Randomized, Placebo-controlled Study to Investigate the RAAS Effects of MK-954 and Enalapril in Patients With Mild to Moderate Hypertension

This is a randomized, double-blind, placebo controlled, multi-center trial whose primary hypothesis is that at treatment Week 2 and Week 6, the geometric mean fold-increase from placebo baseline in plasma renin activity and angiotensin II concentrations at 4 and/or 8 hours postdosing with losartan will be ≥ 5 and will be ≥ 2.9 times larger in the losartan dose groups than in the placebo treatment group. The trial consisted of a 2- to 4-week medication tapering/placebo Run-In period followed by a 6-week double-blind treatment period. The trial enrolled nonblack patients, 21 - 70 years of age, with a history of uncomplicated hypertension, no other medical problems and receiving no medication that could affect the RAAS. At the end of the placebo run-in period, patients were required to have a supine DBP between 95 and 110 mmHg on 2 consecutive visits (DBP did not differ by more than 7 mmHg between visits) to be randomized to treatment. Patients could be randomized to either placebo, losartan 25 mg, losartan 100 mg or enalapril 20 mg once daily. Table 43.1 - 43.3a list the outline of the study and the procedures performed during the trial.

Table 43.1 Entire Study Flowsheet

Procedure	Week:	1		2		3		Bsl.		6		10		12				
	Visit:	1	1a**	1b**	1c**	2	3	4	4a	5	6	6a	7	7a	7b	7c	8	9
Medical History		X																X
Physical Examination		X																X
Discontinuation of Medications*		X	X*	X*	X*													
q.d. Placebo		X	X	X	X	X	X	X	X	X								
Supine/Standing BP/HR		X	X	X	X	X	X	X	X			X		X	X	X		X
Laboratory Safety						X	X		X			X					X	X
Body Weight		X				X			X	X		X					X	X
ECG						X			X			X					X	X
Admission (night before)									X	X		X					X	
24-hr Urine Collection									X	X		X					X	
Serial Supine/Standing BP/HR									X	X		X					X	
Serial PRA, All, Aldo., Catecholamine									X	X		X					X	
PRA, All Sampling to 72 hours																	X	
Supine BP/HR to 72 hours																	X	
Drug Level MK 954												X					X	
Overnight Stay (second night)									X	X		X					X	
Randomization												X						
Double-blind Therapy (q.d.)												X	X	X	X	X	X	
Restart Prior Medication																		X

* Or tapering, if appropriate. ** = occur 1 - 7 days apart. Bsl. = baseline run-in

Table 43.3. Hemodynamic and Other Measurements

Measurement	Time Relative to Dose Administration
Supine BP/HR	-30 min, 0, 30 min, 1 hour, 1.5, 2, 3, 4, 6, 8, 12, 24 hours (28, 32, 36, 48, 72 hours Visit 8 only)
Standing BP/HR	0 hour, 1 hour, 2, 4, 4.5*, 6, 8, 12, 24 hours
RAAS*** Profile	0 hour, 4 hours, 4.5*, 8, 12**, 24 hours (1 hour supine except for 4.5 hours) (28, 32, 36, 48, 72 hours Visit 8 only for PRA and All)
Catecholamines	0 hour, 4 hours, 4.5*, 8, 12, 24 hours (1 hour supine except for 4.5 hours)
Plasma Drug Level	0, 2, 4, 6, 8, 12, 24 hours (Visits 6 and 8)
24-Hour Urine for Na ⁺ , K ⁺ , Creatinine, Aldosterone, Protein, Catecholamines	0-24 hours
* Patient ambulated from 4 to 4.5 hours.	
** PRA and catecholamines only at 12 hours.	
*** RAAS profile is PRA, angiotensin II (by RIA and/or HPLC-RIA) and aldosterone concentrations in plasma.	

Study 43.3a. Flowchart for Visits 5, 6, 7, 8 - Sample Collection Days

Procedure	Time (Hours)																					
	-12	-0.5	0	0.5	1	1.5	2	3	4	4.5 ⁺	5	6	8	12	24	28 ^a	32 ^a	36 ^a	48 ^a	72 ^a		
Admission	x																					
Lab Safety (Visits 5, 7, 8)		x													x ^a	x ^a						
ECG		x																				
Dosing			x																			
Supine BP/HR		x ^{**}	x	x	x	x	x	x	x			x	x	x	x	x	x	x	x	x	x	x
Standing BP/HR			x		x		x	x	x	x		x	x	x	x							
Supine PRA, All ^{**} , Aldo., Catecholamines			x ⁺⁺						x ⁺⁺				x	x ⁺⁺⁺	x	x	x	x	x	x	x	x
Standing PRA, All, Aldo., Catecholamines									x													
Drug Level ⁺⁺⁺⁺			x				x		x			x	x	x	x							
24-Hr Urine NA ⁺ , K ⁺ , Creatinine, Aldo., Protein, Catecholamine									x													
Light Meal						x					x		x	x								
Overnight Stay	x	x											x	x	x							

a = visit 8 only; * = Visit 8 only - PRA and All, only

** = For -30 minute supine BP/HR and all supine PRA, All, etc., the subjects must be supine for 1 hour prior to sample collection.

+ = Ambulating from 4 to 4.5 hours.

++ = Two samples for All only - one for RIA, one for HPLC-RIA

+++ = PRA only

++++ = Visits 6 and 8 only

Results

Fifty-one patients were randomized (placebo = 14; losartan 25 mg = 11; losartan 100 mg = 14; enalapril 20 mg = 12). All except one patient was caucasian. Thirty-five patients were male. Four centers participated and enrollment ranged from 6 - 17 per center. The mean age was 52.2 years. Forty-eight patients completed the study. Three patients dropped out due to clinical adverse events, two in the placebo group and one in the losartan 100 mg group.

Figures 43.1 - 43.3 show the changes in suDBP blood pressure after the first dose, 2 weeks of dosing and 6 weeks of dosing. Losartan lowers suDBP.

Figure 43.1 - 43.2. Changes from Run-In in Supine Diastolic Blood Pressure

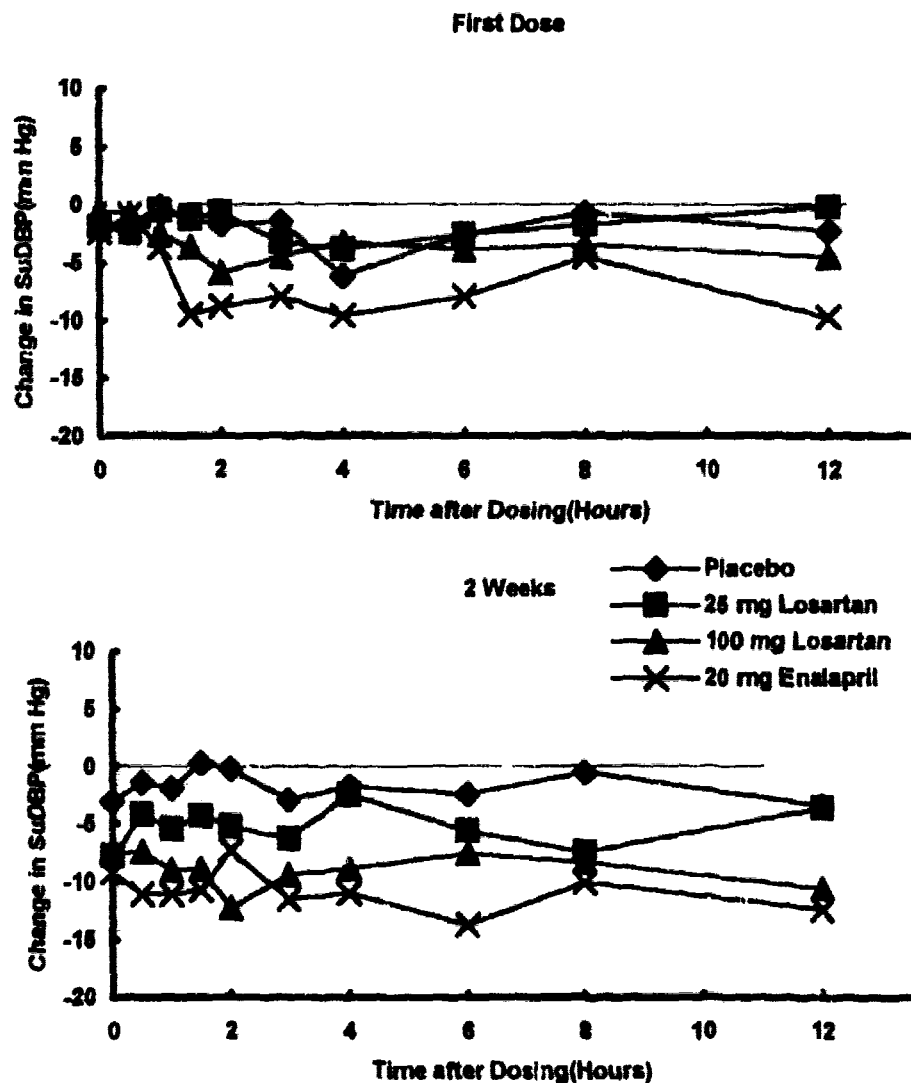


Figure 43.3. Changes from Run-In in Supine Diastolic Blood Pressure

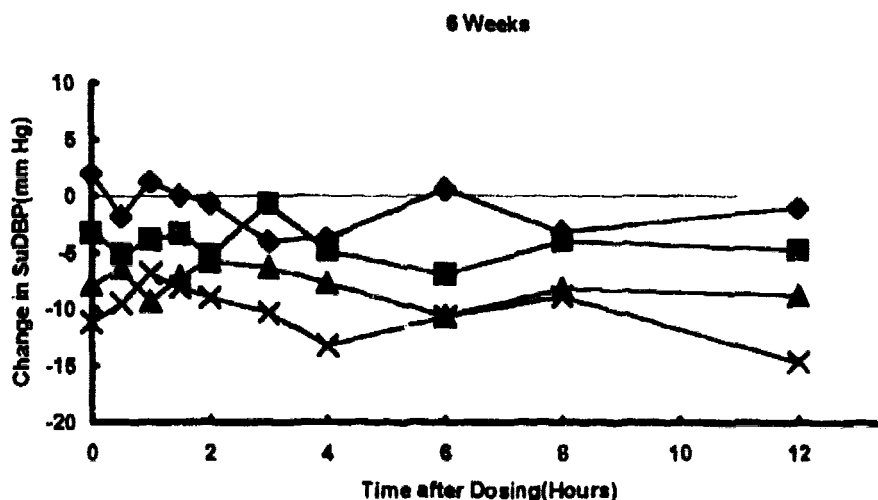


Table 43.4 lists the AUC for neurohormone concentrations. Renin and angiotensin II levels increase. Aldosterone levels decrease and norepinephrine levels are variable. Urinary excretion of aldosterone decreased with both losartan 100 mg and enalapril 20 mg.

Table 43.4. AUC for Neurohormone Concentrations

N=	Difference or Ratio vs. Run-In			
	First Dose	Week 2	Week 6	
Supine Plasma Renin Activity; R; 0-8 h; ng AI/mL/hr				
Placebo	12	-0.923	0.663	0.722
25 mg Losartan	11	0.658 ^a	5.820 ^a	4.178
100 mg Losartan	13	4.721 ^{a,b,d}	11.022 ^{a,b}	7.700 ^{a,b,d}
20 mg Enalapril	12	5.085 ^{a,b,d}	11.787 ^{a,b}	9.981 ^{a,b}
Supine Angiotensin II (Direct RIA); R; 0-8 h; pg/mL/hr				
Placebo	12	-0.486	1.092	0.856
25 mg Losartan	11	0.986 ^c	3.319 ^{a,c}	2.661 ^{a,c}
100 mg Losartan	13	2.927 ^{a,b,c,d}	5.516 ^{a,b,c}	4.682 ^{a,b,c}
20 mg Enalapril	12	-2.815 ^{a,b}	-1.641	-1.885 ^{a,b}
Plasma Aldosterone; D; 0-8 h; ng/dL/hr				
Placebo	12	6.5	15.0	19.9
25 mg Losartan	11	-5.6 ^d	-12.4 ^b	-15.8 ^b
100 mg Losartan	13	-23.1 ^{a,b}	-17.8 ^{a,b}	-40.3 ^{a,b,d}
20 mg Enalapril	12	-18.1 ^d	-26.2 ^{a,b}	-25.9 ^{a,b}
Plasma Norepinephrine; D; 0-12 h; ng/mL/hr				
Placebo	11	33.4	-349.7	-240.6
25 mg Losartan	11	360.5	757.6 ^{a,b,c}	81.5
100 mg Losartan	11	198.7	617.3 ^{a,b}	-238.7 ^d
20 mg Enalapril	10	-165.7	-65.4	-479.7

* For each variable: Name; R (=ratio) or D (=difference); AUC interval (hours); AUC units. N is the number of patients with 6-week data for analysis. a = p<.05 vs. Run-In; b = p<.05 vs. Placebo; c = p<.05 vs. Enalapril; d = p<.05 vs. Week 2

Table 43.5 shows that the AUC and C_{max} for losartan increases approximately 20% with multiple dosing compared to the first dose. The AUC for E-3174 increased by 5% but there is little change in the C_{max}.

Table 43.3. Mean AUC and C_{max} for Losartan and L-158,641 (E-3174) after the First Dose and 6 Weeks of Once-Daily Administration at Doses of 25 and 100 mg/day

	25 mg Losartan				100 mg Losartan			
	Losartan		L-158,641		Losartan		L-158,641	
	AUC*	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC	C_{max}
First Dose	244	57	945	26	647	222	3656	471
6 Weeks	248	56	1088	45	779	269	3821	474
Ratio (Wk6/First Dose)	1.04	1.04	1.13	1.11	1.17	1.17	1.04	0.97
90% C.I.	(0.90, 1.18)	(0.80, 1.13)	(1.04, 1.23)	(0.99, 1.23)	(0.87, 1.56)	(0.82, 1.64)	(0.98, 1.11)	(0.84, 1.12)

*AUC_{0-24 hr} = ng·hr/mL, C_{max} = ng/mL

In the sponsor's clinical summary of study 043, multiple analysis comparing neurohormone levels or drug concentrations with the change in blood pressure were performed. Refer to study 043 clinical summary report for a discussion of these analysis.

Safety

Table 43.6 shows that similar numbers of patients in each treatment group experienced adverse events. Headache was the most common adverse experience.

Table 43.6. Clinical Adverse Experience

Clinical Adverse Experience Summary	Losartan 25 mg	Losartan 100 mg	Enalapril 20 mg	Placebo
Number (%) of Patients	N=11	N=14	N=12	N=14
With One or More Adverse Experiences	9 (82%)	9 (64%)	8 (67%)	7 (50%)
With Serious Adverse Experiences	0	0	0	1 (7%)
Withdrawn Due to Adverse Experiences	0	1 (7%)	0	2 (14%)

Table 43.7 lists three patients who were discontinued for adverse events. In all cases, the patients recovered after therapy was stopped.

Table 43.7. Patients Discontinued for Clinical Adverse Experiences

AN	Age (Years)	Sex	Dose	Adverse Reaction	Onset (Day)	Duration	Relative Day of Discontinuation	Serious
0052	65	F	Placebo	Chest Pain	21	1 Hour	21	Yes
0055	62	M	Placebo	Arm Pain	4	3 Days	4	No
				Blood Pressure Increased	4	3 Days	4	No
0056	62	M	Losartan 100 mg	Hypotension	1	30 mins.	1	No

Patient 52 experienced severe chest pain of 1-hour duration, with nausea, which required subsequent hospitalization.

Patient 56 discontinued on relative Study Day 1 of the randomized treatment phase (100 mg losartan) following a severe hypotensive episode which was probably related to drug therapy. Predose, his respective supine and standing blood pressures (heart rate) were 149/92 mmHg (62 bpm) and 134/96 mmHg (66 bpm). Four hours after dosing, when standing for blood pressure measurements, symptoms included diaphoresis, lightheadedness and blurring of vision. At that time, his respective supine and standing blood pressures (heart rate) were 140/80 mmHg (64 bpm) and 122/96 mmHg (120 bpm). He appeared extremely pale when symptomatic and standing. Symptoms were promptly relieved by resumption of the supine position. However, for the next 3-4 hours, he was unable to stand for upright blood pressure measurements. Twenty-four hours after dosing, he felt well and was discharged. A detailed evaluation of this patient (captopril challenge/imaging study) did not reveal any underlying basis for his apparently greater sensitivity to losartan. Of note, his supine PRA predose and on the Run-In day was low (0.12 to 0.28 ng AI/mL/hr), as were his supine plasma aldosterone levels (3-5 ng/dL).

Patient 19 (losartan 25 mg) had an unexplained decrease in hemoglobin from a baseline of 13.1 Gm/dl to 10.3 Gm/dl on day 43. A repeat hemoglobin on day 58 off drug was 13.3 Gm/dl.

Study 018. A 12-week, Single-blind, Longitudinal, Pilot Study of the Effect of Losartan on Prostaglandin Synthesis in Patients With Mild to Moderate Hypertension

Protocol

This study attempted to determine the effect of losartan on prostaglandin synthesis by measuring renal and extrarenal prostaglandin synthesis. Since prostaglandin synthesis is stimulated by increased levels of angiotensin II, blockage of the angiotensin II receptor could potentially cause changes in prostaglandin synthesis. This was a single-blind, single center study

[Michael J. Dunn, M.D., University Hospitals of Cleveland] in female hypertensive patients consisting of a 4 week placebo baseline period, a 4 week losartan 50 mg treatment period and a 4 week placebo washout period. Table 18.1 lists the renal and systemic prostaglandins measured during the trial. PGE₂ is synthesized mainly in the kidney and its measurement is based on urinary excretion of unmetabolized compound. Prostacyclin is synthesized in the kidney and in the systemic vasculature. The prostacyclin metabolites, 6-keto-PGF_{1α} and urinary 2,3-dinor-6-keto-PGF_{1α}, are indicative of renal prostacyclin synthesis (6-keto-PGF_{1α}) and systemic prostacyclin synthesis (urinary 2,3-dinor-6-keto-PGF_{1α}). Thromboxane A₂ is primarily synthesized by platelets but also in the kidney and is detected in urine as the metabolites 2,3-dinor-TXB₂ and TXB₂, respectively.

Table 18.1. Prostaglandins Measured.

Prostaglandin	Metabolite	Source
PGE ₂	*	Renal
Prostacyclin	6-keto-PGF _{1α}	Renal
	2,3-dinor-6-keto-PGF _{1α}	Systemic
Thromboxane A ₂	TXB ₂	Renal
	2,3-dinor-TXB ₂	Systemic

* Detected in urine as unmetabolized compound.

The study enrolled non-black, female hypertensive patients within 30% of ideal body weight and with supine DBP 95 - 115 mmHg at week -1 and day -1 of the baseline placebo period. Table 18.2 lists the procedures performed during the study. In brief, prostaglandin measurements were obtained during baseline at week -1 and day -1 visits, during losartan treatment at week 2 and 4 and during placebo washout at weeks 6 and 8.

Table 18.2. Study Procedures.

	Placebo Baseline					Losartan				Placebo Washout			
	Week				Day	Week				Week			
	-4	-3	-2	-1	-1	1	2	3	4	5	6	7	8
History	X												
PE	X												X
12-Lead ECG	X												X
Study Medication Dispensing	X				X				X				
Study Med. Accounting		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant med. Recording		X	X	X	X	X	X	X	X	X	X	X	X
BP/HR/Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Experience Recording		X	X	X	X	X	X	X	X	X	X	X	X
24-Hour Urine for Creatinine Clear.		X		X									X
24-Hour Urine*				X	X		X		X		X		X
PRA and Aldosterone				X	X				X				X
Chem/Hem/UA	X**			X**					X				X

* 24-hour urine for sodium, creatinine, PGE-2, 6-Keto-PGF_{1α}, urinary 2,3-dinor 6 keto-PG_{1α}, TXB₂, and 2,3-dinor TXB₂.

** Clinically significant abnormalities from these tests were repeated.

Renal PGE-2 was measured by RIA. Systemic metabolites were measured by gas chromatograph mass spectroscopy.

No analysis of the data was specified in the protocol. Changes from baseline in prostaglandin levels, blood pressure, heart rate, weight, ECG, and laboratory parameters were analyzed using the signed rank test to test the null hypothesis that the median change was zero.

Sixteen female hypertensive patients (suDBP 95 - 115 mmHg) were enrolled. They ranged in age from 51 to 66 years with a mean age of 59 years. They had been diagnosed as being hypertensive from 0 to 42 years ago, with a mean duration of disease of 13 years. All but one of the 16 patients who entered the study completed it. One patient (# 7) was discontinued during the first week of losartan therapy when it was discovered that nitrate therapy (protocol deviation) was to be initiated by the patient's private physician because of an increase in shoulder pain for which an exercise stress test was performed. The protocol stated that any patient who discontinued must be replaced; however, #7 was not replaced due to difficulty in recruiting patients for the study.

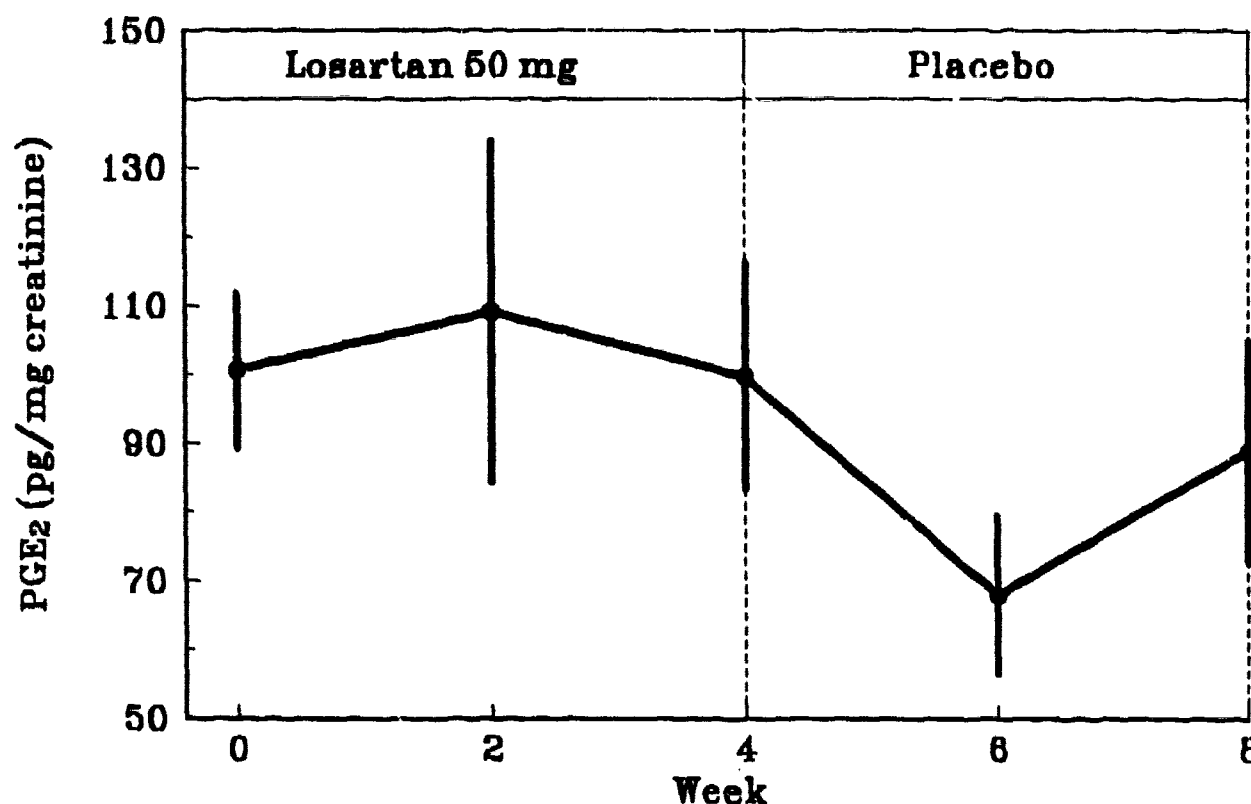
PGE₂ is synthesized mainly in the kidney and is excreted in the urine as unmetabolized compound. There was no significant change from baseline in the 24-hour urinary excretion of PGE₂ after 2 or 4 weeks of treatment with losartan (Table 18.3 and Figure 18.1). At Week 6, 2 weeks into the placebo washout period, the amount of PGE₂ excreted in 24 hours

was significantly lower than during baseline ($p=0.015$). At Week 8, after 4 weeks on placebo, there was no significant difference from baseline in urinary PGE₂ excretion.

Table 18.3 24-Hour Urine PGE₂ (pg/mg creatinine). Change From Average Baseline Measurement

Week	N	Average Baseline Value			Weekly Response			Change from Baseline			Within Grp Comparison (p-Value)
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	
2	15	100.6	110.5	44.1	109.1	97.0	95.7	8.5	-13.0	67.7	0.901
4	15	100.6	110.5	44.1	99.7	77.0	63.4	-0.9	-6.0	45.9	0.890
6	15	100.6	110.5	44.1	67.9	56.0	44.0	-32.8	-35.5	45.6	0.015
8	15	100.6	110.5	44.1	88.8	64.0	62.3	-11.8	-17.5	50.9	0.303

Figure 18.1. Mean $\pm$ Standard Error of 24-Hour Urinary PGE₂ Excretion



Note: Baseline measurement (Week 0) is the average of the last two measurements of the placebo baseline period. N=15 at all time points.

Examining the average value for each patient in each treatment period (averaging the week 2 + 4 and 6 + 8 visits), there was no significant change from baseline during treatment with losartan in PGE₂ excretion (Table 18.4). However, the average excretion during the placebo washout period was significantly lower than during placebo baseline ($p=0.035$). [Note: It would also be significantly different from the treatment period.]

Table 18.4 24-Hour Urine PGE₂ (pg/mg creatinine) - Average Measurement. Change From Average Baseline Measurement

Treatment Period	N	Average Baseline Value			Average Response			Change from Baseline			Within Grp Comparison (p-Value)
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	
Losartan	15	100.6	110.5	44.1	104.4	77.5	74.9	3.8	-10.0	48.6	0.922
Placebo Washout	15	100.6	110.5	44.1	78.3	68.0	44.6	-22.3	-26.5	37.6	0.035

Prostacyclin is synthesized in the kidney and in the systemic vasculature. The prostacyclin metabolites, 6-keto-PGF₁ α and 2,3-dinor 6-keto-PGF₁ α , are indicative of renal and systemic prostacyclin synthesis, respectively.

There was no significant change from baseline in the 24-hour excretion of 6-keto-PGF_{1α} during treatment with losartan or with placebo (Tables 18.5).

Table 18.5 24-Hour Urine 6-keto-PGF_{1α} (pg/mg creatinine). Change From Average Baseline Measurement

Week	N	Average Baseline Value			Weekly Response			Change from Baseline			Within Grp Comparison (p-Value)
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	
2	15	45.1	42.0	16.7	52.8	52.0	15.5	7.7	5.0	18.9	0.127
4	15	45.1	42.0	16.7	41.0	37.0	17.0	-4.1	-1.5	14.7	0.446
6	15	45.1	42.0	16.7	48.7	48.0	21.2	3.6	4.5	18.3	0.277
8	15	45.1	42.0	16.7	45.9	48.0	13.4	0.7	3.0	13.9	0.934

There was a notable ($p=0.066$) increase from baseline in 24-hour urinary excretion of 2,3-dinor 6-keto-PGF_{1α} at Week 2, but at Week 4 there was no significant change from baseline (Table 18.6). The amount of metabolite excreted at Week 6 and Week 8 was also similar to baseline. Average excretion during treatment (averaging the week 2 + 4 and 6 + 8 visits) with losartan and placebo was similar to baseline.

Table 18.6 24-Hour Urine 2,3-dinor 6-keto-PGF_{1α} (pg/mg creatinine). Change From Average Baseline Measurement.

Week	N	Average Baseline Value			Weekly Response			Change from Baseline			Within Grp Comparison p-Value)
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	
2	15	124.2	121.0	36.4	139.3	135.0	41.3	15.0	8.5	41.9	0.066
4	15	124.2	121.0	36.4	130.7	137.0	41.9	6.5	3.5	50.5	0.429
6	15	124.2	121.0	36.4	143.0	146.0	56.5	18.8	-5.5	53.5	0.389
8	15	124.2	121.0	36.4	124.0	111.0	54.5	-0.2	-11.5	62.9	0.561

Thromboxane A₂ is primarily synthesized by platelets, but it is also synthesized in the kidney. It is detected in the urine as the metabolites 2,3-dinor TXB₂ and TXB₂, respectively.

There was no significant difference from baseline in the amount of TXB₂ excreted after 2 or 4 weeks of treatment with losartan (Table 18.7). After 2 weeks of treatment with placebo, there was no significant difference from baseline in the excretion of TXB₂. However, after four weeks of treatment with placebo, there was a notable decrease ($p=0.085$). The mean and median decreases were similar to those at other weeks, but there was less variability in the changes. The average excretion during the losartan and placebo periods (averaging the week 2 + 4 and 6 + 8 visits) was similar to that during baseline.

Table 18.7 24-Hour Urine TXB₂ (pg/mg creatinine) Change From Average Baseline Measurement

Week	N	Average Baseline Value			Weekly Response			Change from Baseline			Within Grp Comparison (p-Value)
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	
2	15	37.1	26.5	22.2	32.8	26.0	19.9	-4.3	-2.0	12.7	0.246
4	15	37.1	26.5	22.2	29.3	29.0	12.8	-7.8	-3.5	18.9	0.247
6	15	37.1	26.5	22.2	31.5	22.0	30.9	-5.6	-8.5	26.4	0.147
8	15	37.1	26.5	22.2	29.8	27.0	20.4	-7.3	-3.5	16.0	0.085

After 2 weeks of treatment with losartan, the excretion of 2,3-dinor TXB₂ was significantly greater than during baseline ($p=0.003$) (Table 18.8). However, at Week 4 there was no significant difference from baseline. Urinary excretion of 2,3-dinor TXB₂ at Weeks 6 and 8 during treatment with placebo was also similar to baseline.

Table 18.8 24-Hour Urine 2,3-dinor TXB₂ (pg/mg creatinine) Change From Average Baseline Measurement

Week	N	Average Baseline Value			Weekly Response			Change from Baseline			Within Grp Comparison (p-Value)
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	
2	15	180.0	187.0	69.1	218.7	206.0	89.2	38.7	40.5	38.2	0.003
4	15	180.0	187.0	69.1	191.1	186.0	87.9	11.1	23.0	96.3	0.669
6	15	180.0	187.0	69.1	163.9	143.0	79.3	-16.0	-12.5	79.9	0.762
8	15	180.0	187.0	69.1	170.6	127.0	107.1	-9.4	-7.5	84.1	0.730

There was a significant decrease in mean SBP and DBP. Plasma renin activity increased significantly ($p = .001$) at week 4. There was a significant ($p=0.002$) decrease from baseline in aldosterone at Week 4 (Table 18.9). At Week 8 there was no significant change from baseline for aldosterone levels.

Table 18.9. Aldosterone (ng/dl) Change From Baseline

Week	N	Baseline Value			Weekly Response			Change from Baseline			Within Grp Comparison (p-Value)
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	
4	15	9.7	6.0	6.5	5.1	3.0	3.9	-4.6	-3.0	4.6	0.002
8	15	9.7	6.0	6.5	7.4	6.0	3.8	-2.3	-1.0	5.4	0.198

Study 069. A Double-Blind, Placebo-Controlled, Parallel Study to Evaluate the Pharmacodynamic Activity of Intravenous E-3174, An Angiotensin II Receptor Antagonist, in Hypertensive Patients.

Protocol

Study 69 was performed at a single center to assess the relationship between blood pressure changes and plasma drug levels of E-3174 when E-3174 20 mg is given as a 4-hour infusion to hypertensive patients. The study consisted of a 2 week outpatient placebo baseline period, a one day in-patient period during which a 4 hour placebo infusion was administered and a 1 day in-patient double-blind period during which a 4 hour infusion of either placebo or E-3174 (an active metabolite of losartan in humans) 20 mg was administered. Patients were between 21 and 65 years of age, non-black and fulfilled blood pressure criteria as outlined in table 69.1 prior to randomization.

Table 69.1. Blood Pressure Criteria for Randomization.

Study Day	Mean suDBP*
Day 1 (after 1 week washout of antihypertensive meds)	90-120 mmHg
Day 8 (after 1 week on oral placebo)	100-120 mmHg
Day 15 (after 2 weeks on oral placebo)	100-120 mmHg
Day 16: 20 minutes & immediately prior to initiation of I.V. placebo	95-120 mmHg and mean; values must not differ by more than 7 mmHg
1, 2, 3, 4, 5, 7, 8 & 9 hours after the initiation of placebo infusion	All values ≥ 90 mmHg and 5 of the 8 values 95-120 mmHg
Day 17: 20 minutes & immediately prior to initiation of I.V. double-blind drug	≥ 90 mmHg and mean values must not differ by more than 7 mmHg

* Mean supine diastolic blood pressure (suDBP): the calculated average of three consecutive readings at 1-minute intervals. All individual readings were to be read to the nearest 2 mmHg.

None of the 3 readings may have differed from the average by >5 mmHg.

Results

Twenty patients were randomized to treatment on day 17. Twelve (5 male, 7 female; 3 caucasian, 9 hispanic) received E-3174 and eight (5 male, 3 female; 1 caucasian, 7 hispanic) received placebo. The ages of patients ranged from 37 to 63 years. There were no dropouts. The number of patients screened for enrollment is not provided. In addition to blood pressure and E-3174 concentration measurements, plasma renin activity, aldosterone levels, 24-hour electrolyte excretion (i.e., sodium, potassium and chloride), fractional excretion of uric acid, plasma uric acid levels, creatinine clearance and urine volume output were evaluated. Within-group changes from baseline were analyzed using a Wilcoxon Signed-Rank test. Between-group analyses were done using Wilcoxon Rank sum test using mean rank for ties. The comparison of Day 16 to Day 17 was done using a Paired T-test.

Figure 62.1 shows the change in suDBP on day 17. Twelve of 17 post-baseline E-3174 supine DBP measurements were significantly different from placebo measurements (comparing change from day 17 baseline between treatments).

Figure 69.1. Supine Diastolic Blood Pressure

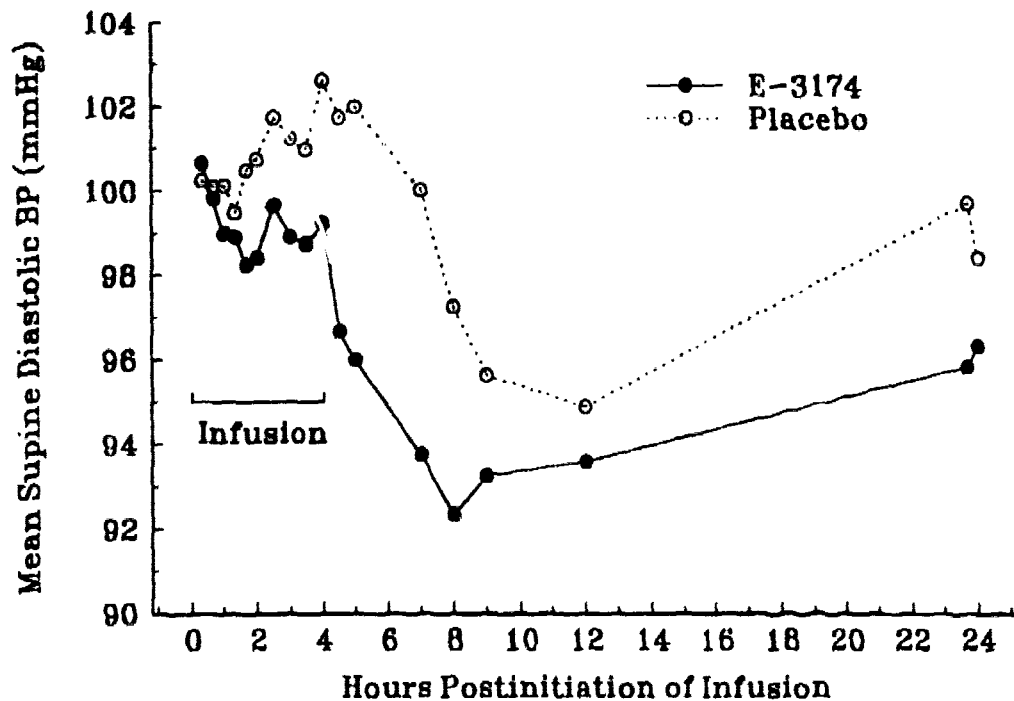
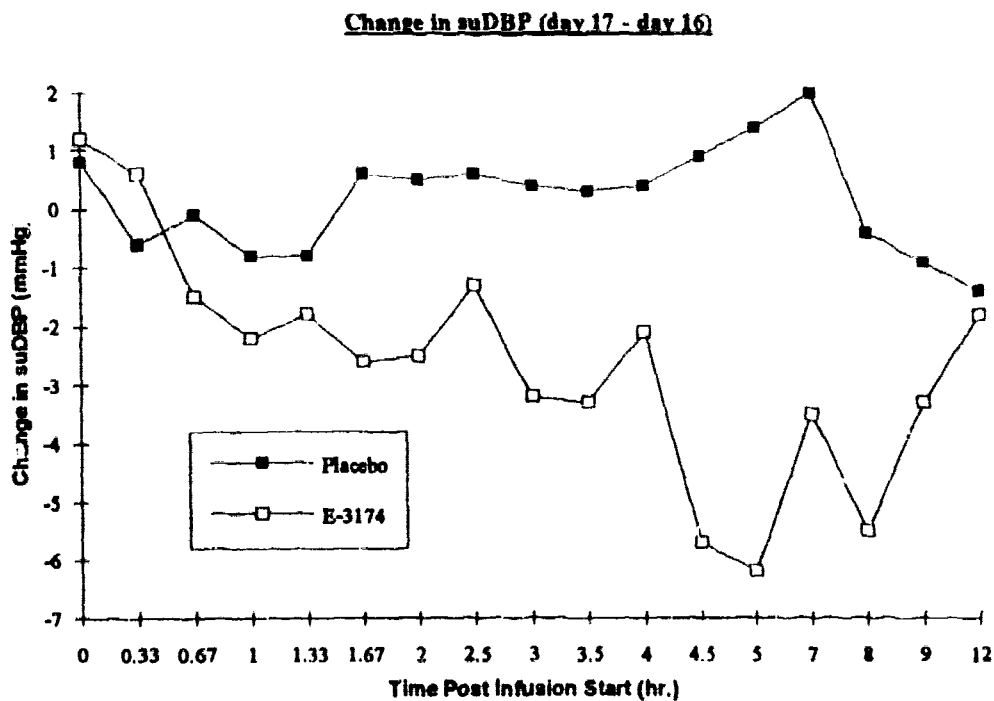


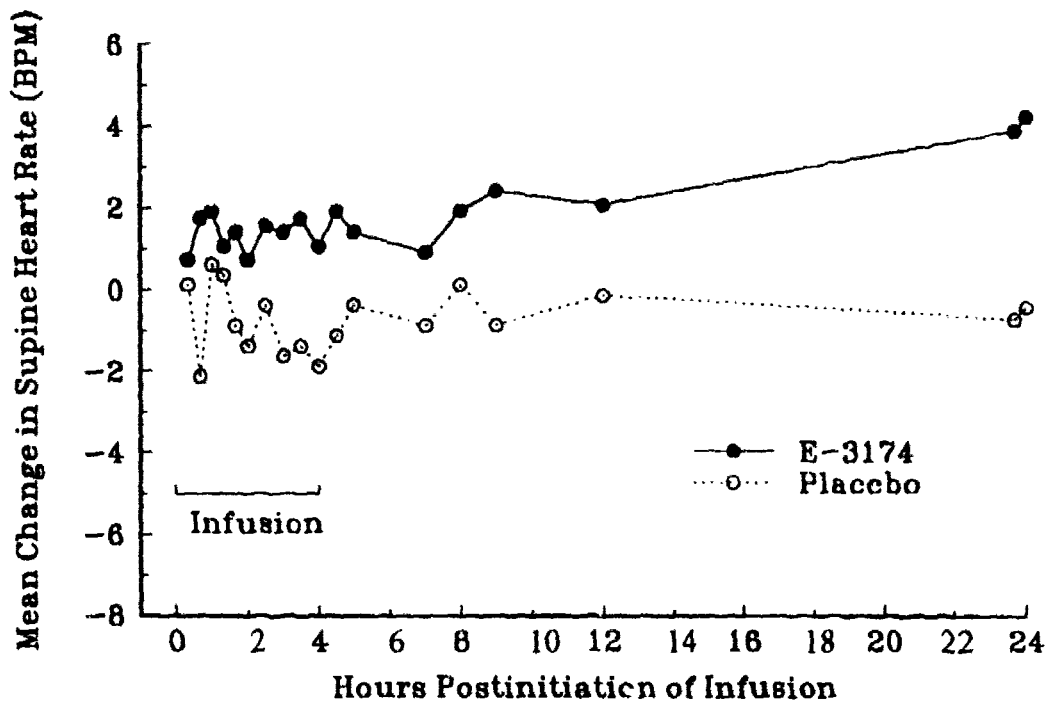
Figure 69.1a shows the change in suDBP between comparable timepoints on day 17 and day 16 for each treatment. The change in suDBP equals the change on day 17 minus the change on day 16 for each measurement post start of infusion (data from appendix 6, volume 1.137). Note that the time axis does not reflect equal time intervals. The maximum effect on blood pressure occurs after the infusion was completed.

Figure 69.1a.



There is a 1 - 2 bpm increase in supine heart rate in the E-3174 treatment group compared to placebo. Figure 69.1b illustrates the change in heart over time. This effect on heart rate is not seen with standing heart rate.

Figure 69.1b. Supine Heart Rate: Mean Change From Baseline



Figures 69.1c and 69.1d plot the between treatment change in suDBP on day 17 and the concentrations of E-3174 versus time respectively

Figure 69.1c. Plasma Drug Levels of E-3174 in Relation to Supine Diastolic Blood Pressure (Δ Between Treatments) Over 24 Hours

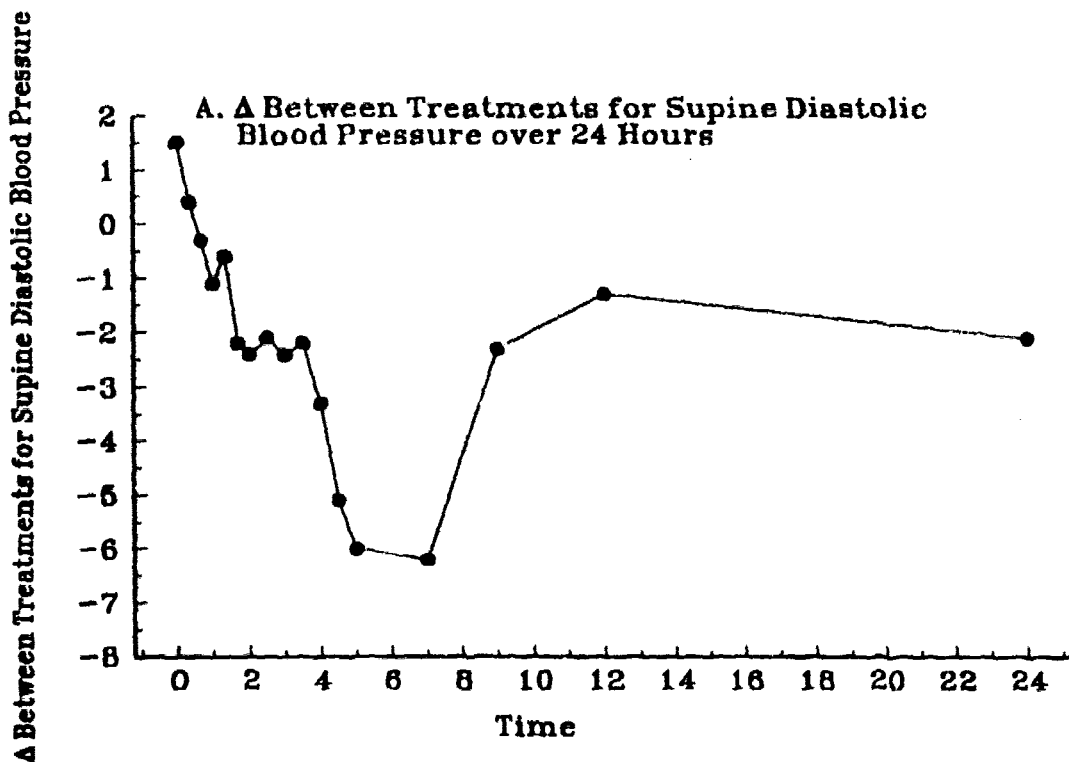
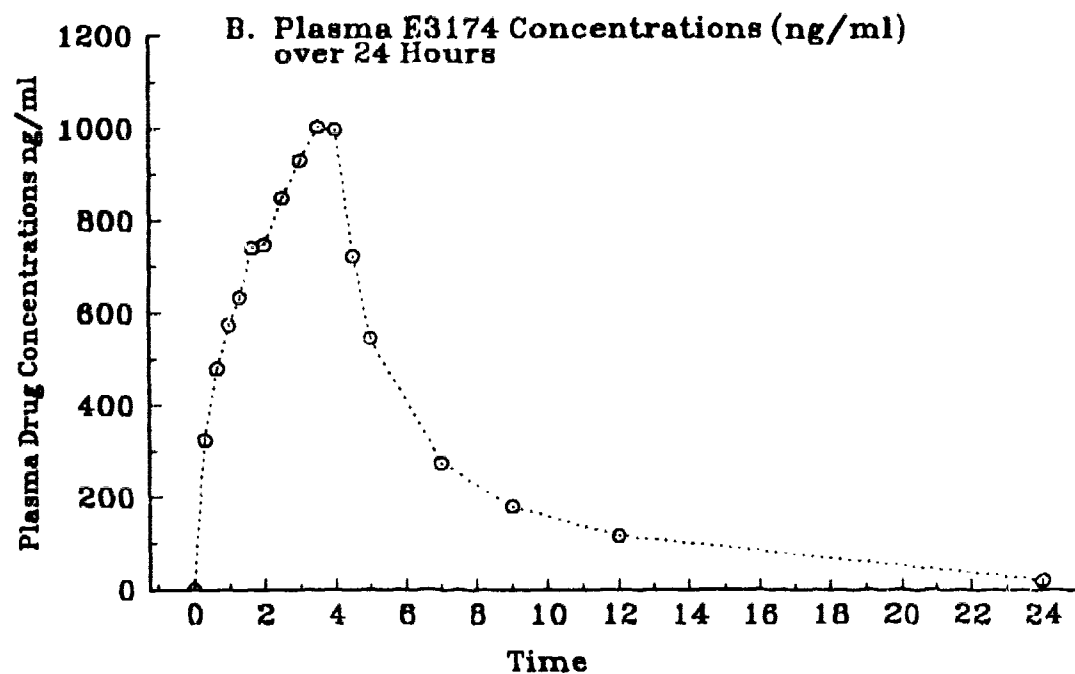


Figure 69.1d.



There was no difference between treatments in urinary electrolyte excretion, urinary aldosterone, plasma uric acid, fractional excretion of uric acid, creatinine clearance and urinary volume. As shown in figure 69.2, mean renin levels increased slightly with E-3174 infusion but this increase was not significantly different from the placebo group measurements and was comparable magnitude to changes noted during the infusion of placebo on day 16 in the same patients (table 69.3).

Figure 69.2. Plasma Renin Activity Following Double-Blind Test Drug

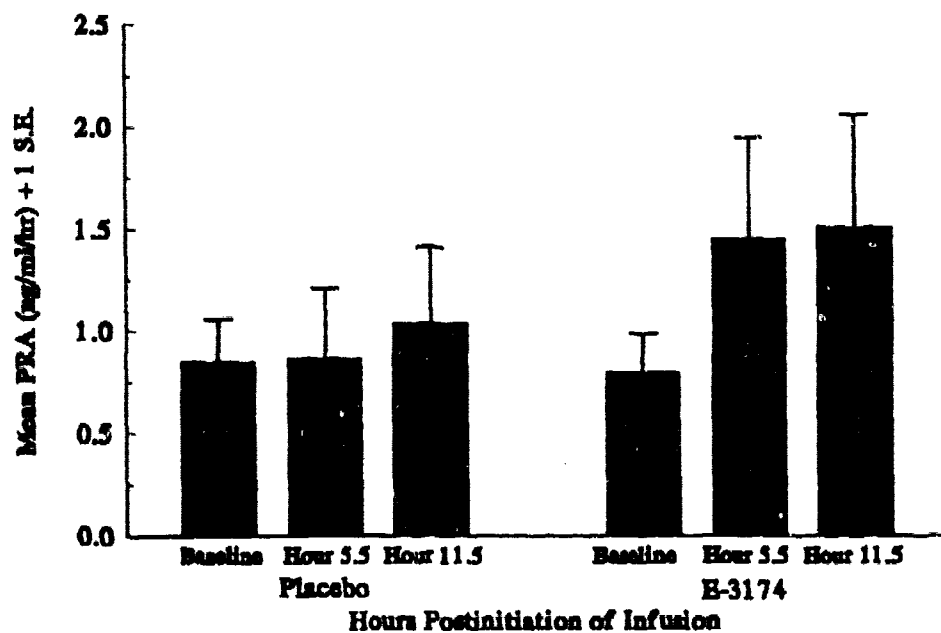


Table 69.3. Summary Statistics For Plasma Renin Activity (ng/mL/hr) Comparison Of Day 17 To Day 16

HOUR	TREATMENT	N	Day 16			Day 17			Change			Comparison	
			Mean	S.D.	Median	Mean	S.D.	Median	Mean	S.D.	Median	vs. B	COMPARISON
-1	PLACEBO	8	0.95	0.63	0.96	0.85	0.59	0.8	-0.11	0.72	-0.26	0.259	0.692
	E-3174	11	0.9	0.75	0.7	0.8	0.63	0.7	-0.1	0.5	0	--	0.506
5.5	PLACEBO	8	1.68	2.19	0.65	0.87	0.97	0.56	-0.81	1.79	-0.12	0.049	0.241
	E-3174	11	1.05	0.85	0.92	1.45	1.65	0.92	0.4	1.3	0.05	--	0.329
11.5	PLACEBO	8	0.79	0.75	0.5	1.04	1.06	0.52	0.24	0.51	0	0.812	0.222
	E-3174	11	1.07	0.92	1.1	1.51	1.83	1	0.44	1.14	0	--	0.229

Of the 20 patients who entered the trial, only 1 had an adverse experience. Patient #7 reported mild chills 3.5 hours after the start of the E-3174 infusion.

Active Control Trials						
Study #	Design/ Patient Population	Treatment Groups	N	Primary Endpoint	Other Measures	Page
044	- r, db, ac, 12 wk Rx period - hypertensives - International Trial - 30% of patients will have moderate HTN	- losartan 50 mg od - captopril 50 mg od (titrate to 100 mg at wk 6 if siDBP $\geq$ 90 mmHg)	109 54	Change in trough sitting DBP from baseline at week 12.	- plasma renin	142
045	- r, db, ac, 12 week Rx period - hypertensives - International Trial (non-U.S.)	- losartan 50 mg od - atenolol 50 mg od (titrate to 100 mg at wk 6 if siDBP $\geq$ 90 mmHg)	134 68	Change in trough sitting DBP from baseline at week 12.	- check for rebound increased bp	146
055	- r, db, ac, > 64 years of age, 12 wk Rx period - hypertensives - International Trial - no more than 30% black, 33% to have moderate (106 - 115 mmHg) HTN	- losartan 50 - 100 mg od - Felodipine ER 5 - 10 mg od	89** 43**	Change in siDBP at weeks 6 and 12 of db treatment		151
056	Three phase study: 1) positive control, 2) placebo control, 3) db treatment period Phase 3 is db, r, ac, 8 wk Rx period Hypertensives with hx of ACEI induced cough	- losartan 50 mg od - lisinopril 20 mg od - HCTZ 25 mg od	48 46 41	incidence of dry cough on 2 consecutive visits		156
064	- r, db, ac, p, 12 wk Rx period - severe hypertensives (siDBP > 115 mmHg)	- losartan 50 mg - enalapril 20 mg Titration: Dose doubled then +/- HCTZ 25 mg, C ₁ channel blocker	50 25	Change in siDBP		161

wk = week, db = double-blind, ol = open label, od = once a day, bid = twice a day, r = randomized, ac = active control, pc = placebo control, nc = no control, p = parallel, co = crossover, hx = history, HTN = hypertension, ACEI = angiotensin converting enzyme inhibitor, NE = norepinephrine, Epi = epinephrine, PRA = plasma renin activity

** = does not include data from 1 of 17 centers due to cut-off date restrictions.

Study 044. A Randomized, Double-blind, Parallel Study of the Safety and Antihypertensive Efficacy of Losartan Compared to Captopril in Patients with Mild to Moderate Hypertension.

Protocol

This is a randomized, double-blind, multicenter, parallel dose trial comparing the clinical efficacy of losartan and captopril administered once a day. Hypertensive patients had to have a baseline siDBP between 95 and 115 mmHg on 2 consecutive baseline visits in order to be randomized (2:1 for losartan:captopril) to either losartan 50 mg or captopril 50 mg once a day for 12 weeks of therapy. Patients were stratified based on the severity of hypertension. After 6 weeks of therapy, the doses of losartan and captopril could be increased to 100 mg once a day if the siDBP remained $\geq$ 90 mmHg. Procedures performed in the trial are outlined in table 44.1. The primary efficacy parameter to be analyzed in this study was change from baseline in sitting diastolic blood pressure after 12 Weeks on double-blind therapy.

Table 44.1. Study Procedures Performed at Each Study Week

Procedure	Pre-Placebo	Baseline		Double-blind Treatment				Off-Drug Period	
		2	4	7	10	13	16	17 ³	17 ⁴
Medical History	X								
Obtain Informed Consent	X								
Complete Physical Exam	X						X		X
Body Weight	X	X	X	X	X	X	X	X	X
Fasting Trough BP and HR ¹	X	X	X	X	X	X	X	X	X
Fasting Laboratory Tests	X ²	X			X		X		X
12-Lead ECG		X					X		
Plasma Renin Activity			X		X		X	X	X
Assess Adverse Experiences		X	X	X	X	X	X	X	X

1 = Measurements made in both the sitting and standing positions and taken 24 hours (range 22-26 hours) after the last study dose, if applicable.

2 = Evaluation performed if patient did not have known history or if prior tests were not available.

3 = Visit occurred 2 to 3 days after last study dose.

4 = Visit occurred 7 days after last study dose.

Result

Demographics

Sixteen centers received drug shipments. Fourteen of the centers were in Europe and 2 in Central America. Fourteen (14) investigators recruited patients and submitted case report forms as of the cut-off date for the NDA. One center did not recruit patients. One center recruited patients but did not submit the case report forms by the due date (3/31/93) and as a result, information on these patients are not included. One hundred and nine were randomized to losartan 50 mg and 54 patients were randomized to Captopril 50 mg. The median number of patients recruited at each site was 12 and the range was 2-21. There was no significant difference in demographic parameters between treatment groups. Sixty-one percent of the patients were male. The mean age was 54.1 years of age. Table 44.1 lists the distribution of patients based on race, severity of hypertension and the mean baseline siDBP. There were no statistically significant differences between treatment groups.

Table 44.1a. Baseline Patient Demographic Characteristics.

	Losartan (N=109)	Captopril (N=54)	Total (N=163)
Racial Origin			
Caucasian	97 (89%)	48 (89%)	145 (89%)
Oriental	2 (2%)	0	2 (1%)
Latin American	6 (6%)	3 (6%)	9 (6%)
Black	3 (3%)	1 (2%)	4 (2%)
Asian	1 (1%)	2 (4%)	3 (2%)
Severity of Hypertension (siDBP, mmHg)			
Mild (95-105)	73 (67%)	36 (67%)	109 (67%)
Moderate (106-115)	36 (33%)	18 (33%)	54 (33%)
siDBP (mmHg)			
Mean	103.1	103.3	103.2
Median	101	103	102
Range	95-115	95-115	95-115

Disposition

Table 44.2 provides information on patients disposition during the trial. Twenty-one patients, including thirteen losartan patients, discontinued the trial prematurely. Ten losartan patients withdrew due to adverse events.

Table 44.2. Patient Accounting

	LOSARTAN (N=109)	CAPTOPRIL (N=54)
	n (%)	n (%)
Completed Double-blind Phase/Not Continuing Into Extension Protocol	38 (34.9)	15 (27.8)
Completed Double-blind Phase/Continuing into Extension Protocol	58 (53.2)	31 (57.4)
Discontinued Double-blind Phase	13 (11.9)	8 (14.8)
Clinical Adverse Experience	10 (9.2)	5 (9.3)
Laboratory Adverse Experience	0 (0.0)	0 (0.0)
Clinical & Laboratory Adverse Experience	0 (0.0)	0 (0.0)
Therapy Ineffective	0 (0.0)	1 (1.9)
Patient Uncooperative	0 (0.0)	0 (0.0)
Patient Withdrew	1 (0.9)	0 (0.0)
Protocol Deviation	1 (0.9)	0 (0.0)
Lost to Follow-up	1 (0.9)	2 (3.7)

Table 44.2a lists the patients withdrawn and the reason for discontinuation.

Table 44.2a. Premature Withdrawals.

Patient Number	Treatment Regimen	Reason Discontinued	Days on Treatment
3025	Losartan	Clinical AE	21
3035	Captopril	Clinical AE	80
3036	Losartan	Clinical AE	19
3043	Losartan	Clinical AE	24
3044	Losartan	Clinical AE	62
3048	Losartan	Clinical AE	55
3049	Losartan	Clinical AE	18
3050	Captopril	Clinical AE	55
3078	Losartan	Clinical AE	70
3120	Captopril	Clinical AE	20
3125	Losartan	Clinical AE	68
3142	Losartan	Clinical AE	74
3172	Captopril	Clinical AE	5
3190	Captopril	Clinical AE	4
3191	Losartan	Clinical AE	53
3045	Captopril	Lost to Follow-up	87
3135	Losartan	Lost to Follow-up	89
3153	Captopril	Lost to Follow-up	1
3089	Losartan	Protocol Deviation	7
3001	Captopril	Therapy Ineffective	20
3092	Losartan	Patient Withdrew	44

Efficacy

There is an inherent problem with the design of this trial. The purpose of the study was to test the hypotheses that losartan and captopril have equivalent antihypertensive efficacy in patients with mild to moderate essential hypertension, as measured by a decrease in sitting diastolic blood pressure. Captopril is at best a twice a day therapy in the treatment of hypertension. Consequently, any study that doses captopril once a day is going to underestimate the blood pressure effect. Since captopril is given only once a day in this trial, there is little that can be said about the comparison of captopril with losartan. Additionally, data from one center is not included from the analysis provided in the NDA. Only the safety portion of this trial will be reported in this review.

Safety

Thirty nine percent (39%) of the losartan patients in the study reported at least one adverse experience vs. 37% of the captopril patients. There was no significant difference between treatments for adverse experiences based on body system. Headache was the most common reported adverse event. For the most part, there is no difference in the incidence of specific adverse events between treatment groups. "Orthostatic effects" were reported in three losartan and none of the captopril

patients. However, these adverse experiences were not associated with standing blood pressure changes that are normally associated with symptoms. Thus, the symptoms are not related to changes in blood pressure.

Table 44.3 lists the patients withdrawn for clinical adverse events. Dizziness was a factor in discontinuing three losartan and two captopril patients. In two of the losartan patients with dizziness (#3043, #3078), elevated blood pressures may have been the contributing factor.

Table 44.3. Patients Withdrawn for Adverse Events.

Patient Number	Treatment	Adverse Event	Day Discontinued	AE Start Day	AE Stop Day
3182	Captopril	PALPITATION	5	1	7
		DIZZINESS	5	3	7
3025	Losartan	COUGH	21	2	24
		RHINITIS, ALLERGIC	21	2	24
3049	Losartan	PSORIASIS	18	3	19
3120	Captopril	DEPRESSION	20	3	20
		DYSPNEA	20	3	20
		HEADACHE	20	3	20
		DIZZINESS	4	4	4
3048	Losartan	DIZZINESS	55	4	56
		SWEATING	55	4	56
3050	Captopril	PAIN, CHEST	55	13	13
		PAIN, SHOULDER	55	13	13
		PAIN, CHEST	55	15	15
		PAIN, ANKLE	84	18	18
		PAIN, CHEST	55	22	51
		PAIN, CHEST	55	52	56
3036	Losartan	ORTHOSTATIC EFFECTS	19	19	24
3043	Losartan	DIZZINESS	24	23	23
		RETINOPATHY, HYPERTENSIVE	24	24	24
3044	Losartan	HEADACHE	62	28	41
3191	Losartan	INFLUENZA	53	38	43
3035	Captopril	HEADACHE	80	53	63
3078	Losartan	NAUSEA	70	59	59
		DIZZINESS	70	59	61
		PAIN, CHEST	70	62	62
		HYPERTENSION INCREASED	70	62	70
3035	Captopril	HEADACHE	80	64	83
3125	Losartan	SALPINGO-OOPHORITIS	69	66	75
3142	Losartan	ARTHRITIS	84	34	43
		NAUSEA	53	42	53
		ANGINA PECTORIS	84	84	91
		PERITONITIS	84	84	91

Two losartan patients and two captopril patients had serious adverse experiences. Summaries for the losartan patients are provided in table 44.3a.

Table 44.3a. Losartan Patients with Serious Adverse Event

Patient #	Summary of Adverse Event
3125	60-year-old female with a history of cholecystectomy in 1989 began treatment with losartan 50 mg on June 3, 1992. The dosage was increased to 100 mg on July 15. On July 19 the patient developed a high fever, pain and swelling in the lower abdomen. Subsequently the patient's condition worsened and she was hospitalized on July 22 with a probable diagnosis of ovarian abscess. Study drug was discontinued on July 22.
3142	38-year-old male with hyperuricemia and a history of knee and ankle gout, hepatomegaly, and arrhythmia began treatment with losartan 50 mg on October, 14, 1992. During the placebo baseline phase of the study the patient complained of leg pain. On October 31 the patient developed ankle pain which recurred throughout remainder of the trial. The investigator commented on the case report form that the event may have been gout but decided that the experience should be termed "arthritis" since gout could not be confirmed. On November 25 the losartan dosage was increased to 100 mg once-daily. In early January, 1993, the patient developed pharyngitis, tonsillitis, and angina and was treated with ciprofloxacin, metallic bismuth and codeine. Due to ankle pain, study drug was discontinued on January 5, 1993. On January 18 the patient was hospitalized. A rheumatological examination revealed a probable diagnosis of gout. The patient's uric acid levels are listed in table 44.3b.

Table 44.3b. Patient # 3142 Uric Acid Levels

Uric Acid Levels (Normal Range: 140-460 umol/l)	
14Sep92	596 umol/l (prestudy)
30Sep92	529 umol/l (prestudy)
25Nov92	463 umol/l (after 6 weeks on losartan 50 mg)
11Jan93	365 umol/l (6 days after drug discontinued)
18Jan93	360 umol/l (13 days after drug discontinued)

Ten patients (7 losartan, 3 captopril) had laboratory adverse events during the double blind treatment period. Most were of no clinical significance. However, three losartan (#3020, #3181, #3238) and one captopril patient (#3023) had increased creatinine. Patient 3020 had a minimal increase from a baseline of 1.1 mg/dl to a maximum value of 1.25 mg/dl. The other patients had clinically relevant increases which are depicted in table 44.4. Two losartan patient had an increase of the serum potassium. These cases are listed in table 44.4.

Table 44.4. Patients With Increased Creatinine or Potassium

Patient	Treatment	Baseline Creatinine (mg/dl)	Maximum Creatinine (mg/dl)	Comment
3181	losartan	1.4	2.3	Creatinine decreased, but not to baseline, after losartan discontinued. Baseline BUN = 61 mg/dl, Maximum BUN = 72 mg/dl.
3238	losartan	1.1	1.5	Creatinine decreased, but not to baseline, after losartan discontinued. Baseline BUN = 26 mg/dl, Maximum BUN = 53 mg/dl.
3023	captopril	1.25	2.4	Creatinine decreased, but not to baseline, after losartan discontinued. Baseline BUN = 17 mg/dl, Maximum BUN = 32 mg/dl.
Patient	Treatment	Baseline Potassium (Meq/dl)	Maximum Potassium (Meq/dl)	Comment
3072	losartan	4.6	5.9	No changes in other electrolytes.
3240	losartan	4.9	5.32	After drug discontinued, potassium 5.75. Creatinine unchanged. BUN increased from 23 mg/dl to 32 mg/dl.

There were no significant mean changes in laboratory parameters. Uric acid did decrease by .41 mg/dl in the losartan group. Table 44.5 shows the mean change in plasma renin compared to baseline. It is not clear why only approximately half of the patients randomized have renin values included in the mean values. The mean values for both groups decreased after drug therapy was discontinued.

Table 44.5 Mean Changes in Plasma Renin Activity

Week	Treatment	N	BASELINE			TREATMENT			CHANGE			COMPARISON	
			Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	vs. B	COMPARISON
6	Losartan (A)	60	1.94	1.24	2.37	3.59	1.717	4.787	1.649	0.408	4.009	0.216	0
	Captopril (B)	29	1.863	1.4	1.539	2.351	1.8	1.957	0.489	0.4	1.453	--	0.041
12	Losartan (A)	49	1.426	1.1	1.345	2.685	1.8	2.625	1.259	0.7	2.034	0.205	0
	Captopril (B)	30	1.711	1.365	1.407	2.294	1.55	1.925	0.583	0.261	1.874	--	0.077

The sponsor analyzed the number of patients with lab changes during treatment outside of predefined limits. Table 44.6 lists some lab parameters that require additional discussion. Serum uric acid decreased by > 2.0 mg/dl in 6.6% of losartan and in 2.0% of captopril patients. Serum sodium decreased by > 5 Meq/L in 5.7% of losartan and in 2.0% of captopril. Serum sodium did not decrease below 132 Meq/L in any patient. None of the captopril patients who had increases of serum sodium > 5.0 Meq/L exceeded a sodium of 148 Meq/L. Patients with increases in serum potassium greater than 5.5 Meq/L in the losartan group have been reviewed in table 44.4.

Table 44.6 Number of Patients (%) With Laboratory Test Result Changes From Baseline Outside Predefined Limits

Lab Test	Predefined Limit	Treatment	Decrease > Limit	Within Limits	Increase > Limit	Total
Serum Uric Acid ^c	Change > 2.0 mg/dl	Losartan	7 (6.6%)	98 (92.5%)	1 (0.9%)	106 (100%)
		Captopril	1 (2.0%)	47 (95.9%)	1 (2.0%)	49 (100%)
Serum Sodium ^c	Change > 5.0 mEq/L	Losartan	6 (5.7%)	99 (94.3%)	0 (0.0%)*	105 (100%)
		Captopril	1 (2.0%)	45 (91.8%)	3 (6.1%)	49 (100%)
Serum Potassium ^c	Change > 0.5 mEq/L	Losartan	7 (6.7%)	84 (80.0%)	14 (13.3%)	105 (100%)
		Captopril	4 (8.2%)	42 (85.7%)	3 (6.1%)	49 (100%)

^c The distribution of patients was compared between treatment groups using Kruskal-Wallis test (based on Ridit Scores).

* Statistically significant difference between groups (p < 0.05).

Study 045. A Randomized, Double-Blind Parallel Study of the Safety and Antihypertensive Efficacy of Losartan (MK-954, DuP 753) as Compared to Atenolol in Patients with Mild to Moderate Hypertension

Protocol

This is a randomized, double-blind, parallel, international (non-U.S.) multi-center trial attempting to show that losartan has similar anti-hypertensive efficacy and safety as atenolol after 12 weeks of therapy. The trial consisted of a placebo baseline period of 4 weeks duration. Sitting trough DBP during this period between 95 - 115 mmHg at week 2 and 4 visits was required for randomization into a 12 week double blind treatment period. Patients were randomized (2:1) to either losartan 50 mg once a day or atenolol 50 mg once a day. After 6 weeks of treatment in the double blind period, any patients with siDBP $\geq$ 90 mmHg had the dose of therapy increased to 100 mg. Patients with siDBP < 90 mmHg continued on 50 mg. After 12 weeks of therapy, patients had BP measured 3 and 7 days after discontinuing therapy. Participation in an open label follow-up study was optional. The open label study data was not included in this NDA. Table 45.1 outline the procedures performed during the trial.

Table 45.1. Clinical and Laboratory Measurements Study Week⁵

Procedure	Pre-Placebo	Baseline		Double-blind Treatment			Off-Drug Period	
		Week 2	Week 4	Week 7	Week 10	Week 13	Week 16	Week 17 ^{3,4}
Medical History	X							
Obtain Informed Consent	X							
Complete Physical Exam	X						X	X ⁴
Body Weight	X	X	X	X	X	X	X	X ^{3,4}
Fasting Trough BP and HR ¹	X	X	X	X	X	X	X	X ^{3,4}
Fasting Laboratory Tests	X ²	X	X ⁶		X		X	X ⁴
12-Lead ECG		X					X	
Assess Adverse Experiences		X	X	X	X	X	X	X ^{3,4}

1 Measurements made in both the sitting and standing positions and taken 24 hours (range 22-26 hours) after the last study dose, if applicable.

2 Evaluation performed if patient does not have known history or if prior tests are not available.

3 Visit occurred 2 to 3 days after last study dose.

4 Visit occurred 7 days after last study dose.

5 Note that throughout the Protocol and the study design section of CSR, baseline is referred to as Weeks 1-4, double-blind as Weeks 5-16 and off-drug as Week 17; however, throughout the results and analyses sections baseline is referred to as Weeks -4 to -1, double-blind as Weeks 1-12 and off-drug as Week 13.

6 Repeat labs, if necessary.

The study was powered so that if 117 patients completed the study, there would be 80% probability of detecting a 5 mmHg difference between treatment groups in sitting diastolic blood pressure (SiDBP), assuming a standard deviation of 9 mmHg or less, and a 5% level of significance for a 2-sided test. Based upon the resulting sample sizes from this study (132 patients in the losartan group and 66 patients in the atenolol group at Week 12) and the mean squared error from the analysis of covariance model [64 (mmHg)² for Week 12 change from baseline in trough SiDBP], the observed power to detect a 5 mmHg difference between treatment groups was 99%. There was at least 80% power to detect a 3.4 mmHg difference. Comparisons between treatment groups with respect to change from baseline sitting blood pressures were performed using adjusted means based upon an analysis of covariance for a randomized block (investigators as blocks) design with baseline blood pressure as the covariate.

Results

Two hundred and nine patients were randomized to 15 centers. Only data from 14 centers was validated by the cut-off date of the NDA. Consequently, data for 202 patients (134 losartan and 68 atenolol) is included in the NDA. The number of patients per center ranged from 1 to 24 with a median of 15. Table 45.2 lists the demographic characteristics of the treatment groups.

Table 45.2. Baseline Patient Demographic Characteristics

	Losartan (N=134)	Atenolol (N=68)	Total (N=202)
Sex			
Female	59 (44%)	22 (32%)	81 (40%)
Male	75 (56%)	46 (68%)	121 (60%)
Age (years)			
Mean	52.4	53.9	52.9
S.D.	10.1	9.3	9.8
Range	28-73	34-74	28-74
Racial Origin			
Caucasian	112 (84%)	59 (87%)	171 (85%)
Oriental	1 (1%)	0	1 (0%)
Black	3 (2%)	0	3 (1%)
Hispanic	16 (12%)	9 (13%)	25 (12%)
Mulatto	2 (1%)	0	2 (1%)
Duration of Primary Diagnosis (years)			
Mean	8.5	8.2	8.4
S.D.	8.9	6.9	8.3
Median	6	6	6
Range	0.5-51	0.5-47	0.5-51
Severity of Hypertension (SiDBP, mmHg)			
Mild (95-105)	90 (67%)	44 (65%)	134 (66%)
Moderate (106-115)	44 (33%)	24 (35%)	68 (34%)
SiDBP (mmHg)			
Mean	103.1	103.6	103.3
Median	102.5	102	102
Range	94-115	95-115	94-115

There were no significant differences in demographics between treatment groups.

Table 45.3 presents the patient disposition during the trial. Sixteen patients discontinued from the study during the double-blind phase, 9 patients discontinued on or before week 6 and therefore did not have the option to titrate at week 6: 4 patients in the losartan group (#4058, #4220, #4217, #4129) and 5 patients in the atenolol group (#4032, #4053, #4045, #4111, #4126). Thus, for the all-patients-treated analyses, there were a total of 193 patients available to evaluate the effect of titration on blood pressure response between weeks 6 and 12: 130 patients in the losartan group and 63 patients in the atenolol group.

Table 45.3. Patient Disposition

	Losartan (n=134)	Atenolol (n=68)
	n (%)	n (%)
Completed Double-blind Phase/Not Continuing Into Extension	36 (26.9)	21 (30.9)
Completed Double-blind Phase/Continuing into Extension	87 (64.9)	42 (61.8)
Discontinued Double-blind Phase	11 (8.2)	5 (7.3)
Clinical Adverse Experience	2* (1.5)	5 ⁺ (8.8)
Laboratory Adverse Experience	0 (0.0)	0 (0.0)
Clinical & Laboratory AE	0 (0.0)	0 (0.0)
Therapy Ineffective	4 (3.0)	0 (0.0)
Patient Uncooperative	0 (0.0)	0 (0.0)
Patient Withdrew	2 (1.5)	0 (0.0)
Protocol Deviation	1 (0.7)	0 (0.0)
Lost to Follow-up	2 (1.5)	0 (0.0)

* Statistically significant difference between groups ($p < 0.05$).

⁺ 1 atenolol patient discontinued during off-drug follow-up week is not included as a dropout

Table 45.3a lists the patients withdrawn from the study.

Table 45.3a. Patients Withdrawn

Patient Number	Treatment Regimen	Reason Discontinued	Day Discontinued
4032	Atenolol	Clinical AE	4
4053	Atenolol	Clinical AE	4
4111	Atenolol	Clinical AE	21
4126	Atenolol	Clinical AE	26
4045	Atenolol	Clinical AE	35
4129	Losartan	Clinical AE	40
4061	Losartan	Clinical AE	78
4058	Losartan	Lost To Follow-up	2
4217	Losartan	Lost To Follow-up	49
4102	Losartan	Protocol Deviation	62
4254	Losartan	Therapy Ineffective	55
4224	Losartan	Therapy Ineffective	58
4187	Losartan	Therapy Ineffective	62
4225	Losartan	Therapy Ineffective	62
4220	Losartan	Patient Withdrew	22
4167	Losartan	Patient Withdrew	52

Tables 45.4 and 45.5 list the mean change in trough siDBP and siSBP at weeks 6 and 12. There was no significant difference between treatments at 6 and 12 weeks.

Table 45.4. Mean Change in Trough Sitting Diastolic Blood Pressure (mmHg) at Week 6 and 12 All-Patients-Treated Approach

Week	Treatment Group	N	Baseline		Treatment		Change		Change	Comparison
			Mean	S.D.	Mean	S.D.	Mean	S.D.	Adj Mean	vs. B
6	Losartan (A)	132	103.1	5.8	94.1	8.8	-9.0	7.7	-9.2	NS
	Atenolol (B)	66	103.6	6.1	92.7	9.8	-11.0	8.5	-10.8	--
12	Losartan (A)	132	103.1	5.8	94.5	9.7	-8.6	8.8	-8.3	NS
	Atenolol (B)	66	103.6	6.1	93.1	10.0	-10.6	8.2	-10.1	--

NS = not statistically significant [analysis of covariance for a randomized block (investigators as blocks) design with baseline blood pressure as the covariate]

Table 45.5. Mean Change in Trough Sitting Systolic Blood Pressure (mmHg) at Week 6 and 12 All-Patients-Treated Approach

Week	Treatment Group	N	Baseline		Treatment		Change		Change	Comparison
			Mean	S.D.	Mean	S.D.	Mean	S.D.	Adj Mean	vs. B
6	Losartan (A)	132	156.9	19.8	145.1	18.4	-11.8	12.2	-13.8	NS
	Atenolol (B)	66	160.2	16.7	147.8	21.9	-12.4	18.3	-13.1	--
12	Losartan (A)	132	156.9	19.8	145.4	19.5	-11.4	16.4	-12.2	NS
	Atenolol (B)	66	160.2	16.7	148.3	22.4	-11.9	19.9	-11.3	--

NS = not statistically significant [analysis of covariance for a randomized block (investigators as blocks) design with baseline blood pressure as the covariate]

Blood pressure measurements post-treatment withdrawal were not obtained for the majority of patients.

Figure 45.1 and figure 45.2 displays the response rate for each treatment. At both 6 and 12 weeks, the response rate was greater with atenolol but the difference was not statistically significant.

Figure 45.1. and 45.2. Trough Sitting DBP-Categories of Antihypertensive Response at Weeks 6 (fig. 45.1) and 12 (fig. 45.2).

Figure 45.1. Week 6 Response Rates

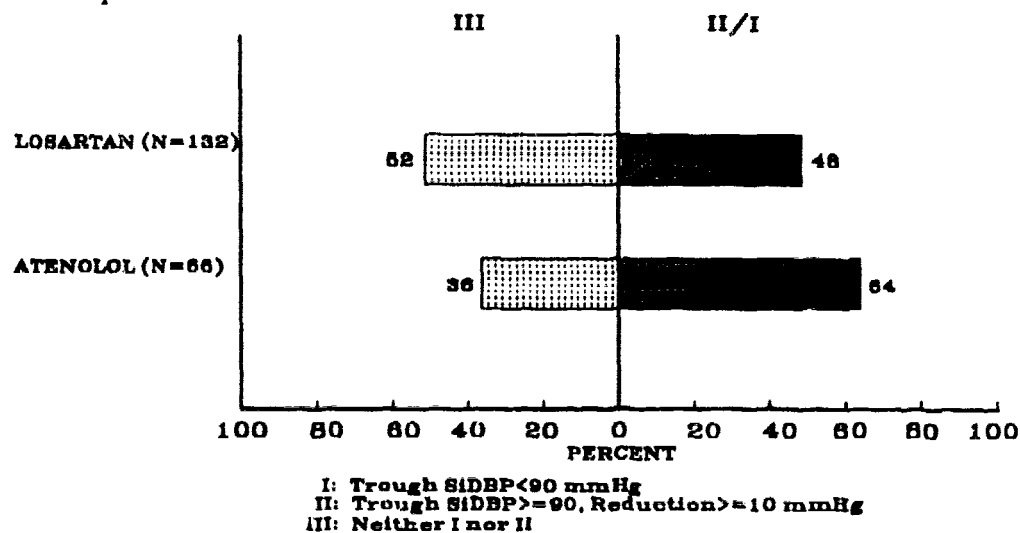
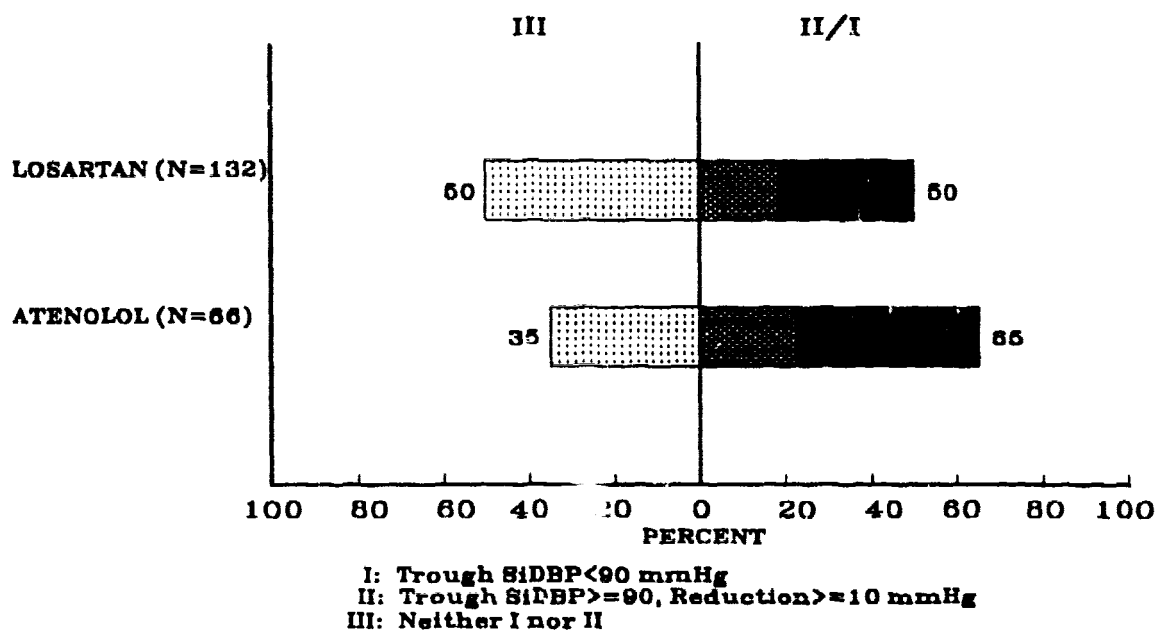


Figure 45.2. Week 12 Response Rates



Sixty-seven losartan (50%) patients and 38 (56%) atenolol patients experienced at least one adverse event in the double blind treatment period. Bradycardia occurred in 3 atenolol patients and none of the losartan patients. URI occurred in 8 (6%) losartan and 1 (1.5%) atenolol patients. Other adverse event incidence rates did not appear to be different between treatments. An inquiry into the database comparing the incidence of adverse events between treatments based on gender showed no difference in male patients. However, in female patients, table 45.5a. lists several adverse events that appear to be more prevalent in losartan treated females than in atenolol treated females. However, when the incidence rates of adverse events in female losartan treated patients are compared to male losartan treated patients, there does not appear to be a higher frequency in females relative to males.

Table 45.5a. Adverse Events in Female Patients

Adverse Event	Losartan (N = 59)	Atenolol (N = 22)
asthenia/fatigue	5 (8.5%)	1 (4.5%)
dizziness	6 (10.3%)	1 (4.5%)
headache	12 (20.3%)	3 (13.6%)
URI	5 (8.5%)	0 (0%)
Abdominal Pain	5 (8.5%)	1 (4.5%)

Within the losartan treatment group, 58% of the female patients and 44% of the male patients experienced at least one adverse event.

A total of 7 patients (4.0%) were discontinued from the study due to a clinical adverse experience. Two (1.5%) of the patients in the losartan group and 5 (7.4%) in the atenolol group were discontinued due to a clinical adverse experience. Table 45.6 lists the patients discontinued due to adverse experiences.

Table 45.6. Patients Withdrawn due to Clinical Adverse Events

Patient Number	Treatment	Adverse Event	AE Start Day	AE Stop Day	Day Withdrawn
4129	Losartan	PAIN, ABDOMINAL	-22	1	40
		PAIN, ABDOMINAL	2	41	
4053	Atenolol	ALKALINE PHOSPHATASE INCREASED	-14		4
		ALT INCREASED	-14		
		PAIN, ABDOMINAL	-14	-11	
		PAIN, ABDOMINAL	4	8	
		NAUSEA	8	8	
4032	Atenolol	ALKALINE PHOSPHATASE INCREASED	25		4
		HEADACHE	1	5	
		SOMNOLENCE	1	6	
		COLD EXTREMITIES	4	5	
		SWELLING, JOINT	4	5	
4111	Atenolol	RASH	4	7	21
		BRADYCARDIA	5	22	
4126	Atenolol	ASTHENIA/FATIGUE	10	28	26
		DIZZINESS	10	28	
		RASH	24	44	
		EOSINOPHILS INCREASED	44		
4045	Atenolol	ASTHENIA/FATIGUE	19	36	35
		CRAMP, MUSCLE	19	36	
		PAIN, NECK	19	36	
		PHARYNGITIS	19	36	
		SWEATING	19	36	
4061	Losartan	DIZZINESS	43	43	78
		DIZZINESS	64	82	

Four patients (two from each treatment group) experienced serious adverse experiences. Summaries for the losartan patients with serious adverse events are presented in table 45.6a.

Table 45.6a. Losartan Patients with Serious Adverse Events

Patient #	Summary
4189	57-year-old male hypertensive patient with a history of myocardial infarction (1975), diverticulitis (1984) and psoriasis (1989) was hospitalized for a pulmonary embolism/infarct while on losartan 100 mg. He had begun treatment with losartan 50 mg and was subsequently titrated to losartan 100 mg after 45 days. There was no concomitant therapy. After 23 days on losartan 100 mg, the patient complained of pain in the left calf which resolved in 4 days. Ten days after the onset of the calf pain, the patient developed sudden pleuritic chest pain on the left side. He was hospitalized and a severe pulmonary embolism/infarct was confirmed. Study drug therapy was interrupted for one day. The patient was treated with heparin 10,000 IU and warfarin 5 mg; he subsequently recovered.
4129	70-year-old female hypertensive patient with a history of arthrosis (1982) and acute pancreatitis (1991) had been on losartan 50 mg for 2 days when she developed severe abdominal pain. During the placebo baseline phase of the study she had complained of moderate abdominal pain which increased in severity to severe during the blinded phase. The patient was discontinued from the study.

No patient in the study was discontinued due to a laboratory adverse experience. Eleven losartan and 4 atenolol patients had laboratory adverse experiences. None of the laboratory adverse events were of clinical relevance. There was no significant change in mean weight, pulse or ECG intervals in the losartan group. Mean pulse and ECG rate decreased in the atenolol group as expected. An analysis examining the number of patients who exceeded pre-defined changes in laboratory parameters was performed. This was generally unremarkable. Of note, was the observation that 21.5% of losartan patients had changes in alkaline phosphatase greater than 20 U/L as opposed to 7.8% of the atenolol patients. Alkaline phosphatase decreased greater than 20 U/L in 15.6% of atenolol and 4.6% of the losartan patients.

Study 055. A Randomized, Double-blind, Parallel Study of the Safety and Antihypertensive Efficacy of Losartan (MK-954, DuP-753) Compared to Felodipine Extended Release (ER) in Elderly Patients with Mild to Moderate Hypertension

Protocol

This is a randomized, double-blind, parallel, international (Europe, S. America, Mexico, Australia, Hong Kong) multi-center trial in hypertensive patients greater than 64 years of age. Trial consisted of a 4 week placebo period and a 12 week treatment period. To be randomized, patients were required to have a siDBP between 95 and 115 mmHg on 2 consecutive visits in the placebo period. The difference in siDBP between the two visits could not be greater than 7 mmHg. Eligible patients were randomized to either felodipine ER 5 mg or losartan 50 mg. During the double blind treatment period, patients had trough sitting and standing blood pressures measured every 3 weeks. After 6 weeks of treatment, if the trough siDBP was ≥ 90 mmHg, the patient could have the dose felodipine or losartan doubled. Table 55.1 lists the procedures performed throughout the trial.

Table 55.1. Procedures Performed During the Trial.

Study Weeks	Pre-Placebo	Baseline		Treatment			
		2	4	7	10	13	16
Medical History	X						
Complete Physical Exam	X						X
Sign Informed Consent	X						
Body Weight	X	X	X	X	X	X	X
Clinic Visits ^a	X	X	X	X	X	X	X
Sitting and standing BP and HR ^c	X ^{e,i}	X ^f	X ^g	X	X	X	X
Chest X-ray		X ^j					
Laboratory Safety Tests ^h	X ^b	X	X ^d		X		X
12-lead ECG		X			X		X
AE Evaluation		X	X	X	X	X	X
Dispense Baseline Medication	X ⁱ						
Dispense Double-blind Medications			X	X	X	X	
Discontinue double-blind Medications							X

^a Clinic Visits (Weeks 2-16) occurred as indicated between 0630 and 1000 hours. Patients were to be in the fasted state at all clinic visits (i.e., no food or liquids were to be taken during the 8 hours prior to each clinic visit)

NOTE: Amendment I allowed for patients not to be fasted prior to clinic visits

^b Perform tests if patient does not have known history or if prior tests are not available

^c Measurements were to be taken 24 hours (range 22 to 26 hours) after the last morning study dose.

^d Repeat labs, if necessary.

^e Mean siDBP was 90-115 mmHg or patient could not continue in the study.

^f Mean siDBP was 95-115 mmHg or patient could not continue in study

^g Mean siDBP was 95-115 and Week 2 and Week 4 values must be ≤ 7 mmHg or patient could not continue in study.

^h Fasting hematology, blood chemistry and urinalysis

NOTE: Amendment I allowed for patients not to be fasted for laboratory tests

ⁱ Patient was off antihypertensive medication at least 7 full days or patient returned for another evaluation when an adequate washout period was achieved.

^j A chest X-ray was taken if one was not available from the previous 12-month period.

NOTE: If a patient did not complete the study, all procedures scheduled for treatment Week 16 were done on the day the patient discontinued treatment.

The primary efficacy parameter to be analyzed in this study was the change from baseline in sitting diastolic blood pressure after 12 weeks on double-blind therapy, although other blood pressure measurements (e.g., sitting systolic blood pressure) and timepoints were also analyzed.

The study was powered such that if at least 117 patients (78 in the losartan group and 39 in the felodipine group) completed the study there would be 80% (61%) probability of detecting a 5 (4) mmHg difference between treatment groups with respect to change in blood pressure (assuming a standard deviation of 9 mmHg or less, and a 5% level of significance for a 2-sided test).

Results

Demographics and Disposition

One hundred and forty patients were randomized at seventeen centers. One center enrolled no patients. The median number of patients recruited at each site was 9 and the range was 2-29. The summary report of the sponsor contains information on 132 patients. Data on eight patients is not included because their data was not received by the CANDA data cut-off date of 3/31/93. This includes all seven patients from site #13 and one patient from site #12 (patient 5308). Of the 132 patients with information in the CANDA, 89 were randomized to losartan and 43 to felodipine ER.

Table 55.2 lists the demographic characteristics of the 132 patients included in the summary. Fifty-five percent (55%) of the patients were female. The mean age was 70 years and the range was 65 to 87 years; 81% of the patients were between 65 and 74 years of age. More than half of the patients (58%) were Caucasian, 22% were Asian, 11% were Hispanic, and 9% were Mestizo. Although the protocol allowed for up to one-third of the patients to be black, no black patients were enrolled.

Table 55.2. Baseline Patient Demographic Characteristics

	Losartan (N=89)	Felodipine (N=43)	Total (N=132)
Sex			
Female	48 (54%)	25 (58%)	73 (55%)
Male	41 (46%)	18 (42%)	59 (45%)
Age (years)			
Mean	70.4	69.9	70.2
S.D.	4.5	5.3	4.8
Range	65-82	65-87	65-87
Racial Origin			
Caucasian	52 (58%)	24 (56%)	76 (58%)
Asian	19 (21%)	10 (23%)	29 (22%)
Hispanic	10 (11%)	5 (12%)	15 (11%)
Mestizo	8 (9%)	4 (9%)	12 (9%)
Duration of Primary Diagnosis (years)			
Mean	9.6	7.9	9.0
S.D.	8.1	7.1	7.8
Severity of Hypertension (SiDBP, mmHg)			
Mild (95-105)	65 (73%)	32 (74%)	97 (73%)
Moderate (106-115)	24 (27%)	11 (26%)	35 (27%)
Mean	102.0	102.5	102.1
S.D.	5.6	5.6	5.6
Range	95-115	95-115	95-115

There were no statistically significant differences between treatment groups.

Table 55.3 outlines the disposition of patients in the trial. One hundred twenty-one (121, 91.7%) out of 132 patients completed the study according to protocol. Seventy-eight (78) of those patients continued into an open-label extension. Eleven (11, 8.3%) patients discontinued the study: 5 patients in the losartan group (5.6%) and 6 patients in the felodipine group (14.0%).

Table 55.3. Patient Disposition

	LOSARTAN (N= 89)	FELODIPINE (N=43)
	n (%)	n (%)
Completed Double-blind Phase/Not Continuing Into Extension	32 (36.0)	11 (25.6)
Completed double-blind Phase/Continuing into Extension	52 (58.4)	26 (60.5)
Discontinued double-blind Phase	5 (5.6)	6 (14.0)
Clinical Adverse Experience	3 (3.4)	5 (11.6) +
Laboratory Adverse Experience	0 (0.0)	0 (0.0)
Clinical & Laboratory		
Therapy Ineffective	1 (1.1)	0 (0.0)
Patient Uncooperative	0 (0.0)	0 (0.0)
Patient Withdrew	0 (0.0)	0 (0.0)
Protocol Deviation	0 (0.0)	0 (0.0)
Lost to Follow-up	1 (1.1)	1 (2.3)

+ One patient (AN 5085) had a clinical adverse experience during placebo baseline that continued without change into double-blind

Table 55.3a. lists the patients withdrawn prematurely and reasons for withdrawal. The primary reason for discontinuing the study was due to a clinical adverse experience both in the losartan (3.4%) and felodipine (11.6%) treatment groups. One patient in the losartan group discontinued the study because of ineffective therapy and one patient in each treatment group was lost to follow-up. Two patients who discontinued the study were lost to follow-up. Patient #5275 who entered the study with a baseline sitting blood pressure of 150/107 mmHg was randomized to treatment with felodipine ER 5 mg. No adverse experiences were reported at the final (Week 3) clinic visit and the mean trough sitting blood pressure at this visit was 125/86 mmHg. After approximately 6 weeks of treatment, the patient's wife phoned the investigator to cancel his appointment. At this time she indicated that he was without symptoms. The patient never returned for his Week 6 visit. The actual duration of treatment is therefore unknown. Patient #5160 who entered the study with a baseline sitting blood pressure of 146/101 mmHg was randomized to treatment with losartan 50 mg. After 6 weeks of treatment, his mean trough sitting blood pressure was 129/87 mmHg and no adverse events were reported. He did not return for his Week 9 visit and no additional information was provided regarding his status.

Table 55.3a. Withdrawals

Patient Number	Treatment Regimen	Reason Discontinued	Day Discontinued
5158	Felodipine	Clinical AE	2
5271	Losartan	Clinical AE	3
5085	Felodipine	Clinical AE	4
5053	Losartan	Clinical AE	10
5036	Felodipine	Clinical AE	24
5273	Losartan	Clinical AE	42
5221	Felodipine	Clinical AE	47
5045	Felodipine	Clinical AE	68
5275	Felodipine	Lost To Follow-up	38
5160	Losartan	Lost To Follow-up	41
5230	Losartan	Therapy Ineffective	78

Efficacy

One hundred and twenty-nine of 132 patients had efficacy data available. One hundred and twenty-four patient had week 6 efficacy data and were eligible for dose titration. Tables 55.4 and 55.5 list the mean change in siDBP and siSBP at weeks 6 and 12. There was a significant difference between treatments at week 6 but this difference was not apparent at week 12.

Table 55.4 Mean Change In Trough Sitting Diastolic Blood Pressure At Week 6 And 12 All-Patients-Treated Approach (mmHg)

WEEK	TREATMENT GROUP	N	BASELINE		Treatment		Change		Change	COMPARISON vs. B
			Mean	S.D.	Mean	S.D.	Mean	S.D.	Adj Mean	
6	Losartan (A)	88	101.9	5.5	93.0	10.3	-8.8	8.4	-9.5	**
	Felodipine (B)	41	102.2	5.6	89.1	9.2	-13.1	7.7	-13.7	--
12	Losartan (A)	88	101.9	5.5	88.7	9.6	-13.2	7.8	-12.9	NS
	Felodipine (B)	41	102.2	5.6	88.2	9.1	-14.0	7.6	-13.4	--

NS -- NOT STATISTICALLY SIGNIFICANT

** -- TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, $P < 0.01$

Table 55.5 Mean Change In Trough Sitting Systolic Blood Pressure At Week 6 And 12 All-Patients-Treated Approach (mmHg)

WEEK	TREATMENT GROUP	N	BASELINE		Treatment		CHANGE		CHANGE	COMPARISON vs. B
			Mean	S.D.	Mean	S.D.	Mean	S.D.	Adj Mean	
6	Losartan (A)	88	171.5	19.1	158.9	21.1	-12.6	16.4	-13.5	NS
	Felodipine (B)	41	171.8	18.8	155.6	20.4	-16.2	13.1	-16.7	--
12	Losartan (A)	88	171.5	19.1	154.3	20.7	-17.2	16.5	-17.0	NS
	Felodipine (B)	41	171.8	18.8	152.9	21.5	-19.0	15.0	-18.3	--

NS -- NOT STATISTICALLY SIGNIFICANT

Sixty percent of the losartan and 44 percent of the felodipine patients underwent dose titration at week 6 (for siDBP > 90 mmHg). Table 55.6 shows the change in siDBP at weeks 6 and 12 based on titration status.

Table 55. Mean Change In Blood Pressure At Weeks 6 And 12 By Titration Status All-Patients-Treated Approach

TROUGH SITTING DIASTOLIC BLOOD PRESSURE (mmHg)

	TREATMENT	N	Baseline		Week 6		Week 12		Change					
			Mean	S.D.	Mean	S.D.	Mean	S.D.	Week 6 to 12	Baseline to Week 12	Mean	S.D.	Mean	S.D.
NO	Losartan	34	98.6	4.2	84.2	5.8	82.5	8.1	-1.7	6.4	-16.1	7.9		
	Felodipine	22	99.9	5.1	83.4	7.8	84	8.9	0.7	8.9	-15.8	8.9		
YES	Losartan	51	104.2	5.2	99.7	6.8	93.4	7.5	-6.3	7.6	-10.8	6.7		
	Felodipine	17	104.8	5.2	96.6	5.1	93.5	7	-3.1	6.2	-11.3	4.7		

Note: Patient titrated at Week 6 if siDBP $\geq$ 90 mmHg.

Safety

Approximately half (57.6%) of the patients reported at least one adverse experience. The treatment groups were very similar with respect to all adverse experiences reported. Table 55.7 describes the adverse experience incidence in the trial.

Table 55.7. Clinical Adverse Experience

	LOSARTAN (N=89)	FELODIPINE (N=43)
Number (%) of Patients	N (%)	N (%)
With One Or More Adverse Experiences	53 (59.6)	23 (53.5)
Without Any Adverse Experiences	36 (40.4)	20 (46.5)
With Serious Adverse	1 (1.1)	3 (7.0)
Withdrawn Due To Adverse Experiences	3 (3.4)	5 (11.6) +
Who Died	0	0
With Drug-Related Adverse Experiences	24 (27.0)	10 (23.3)

There were no statistically significant differences between treatment groups.

Eight patients, 3 losartan and 5 felodipine, withdrew due to adverse events. Table 55.8 lists the adverse events in patients who withdrew due to adverse experiences. Patient #5273 withdrew due to hypotension and angina pectoris. Patient #5271 withdrew due to vomiting. Patient #5053 developed ataxia on day 9 and withdrew on day 10.

Table 55.8. Adverse Events in Patients Withdrawn for Adverse Experiences

Patient Number	Treatment	Adverse Event	AE Start Day	AE Stop Day	Discontinued Day
5036	FELODIPINE	RHINITIS	-4	15	24
		VERTIGO	-4	15	
		COUGH	1	24	
		EDEMA/SWELLING	3	16	
		EDEMA/SWELLING	17	24	
		HEADACHE	20	20	
		RHINITIS	21	22	
5045	FELODIPINE	SWEATING	3	23	68
		EDEMA/SWELLING	3	68	
		PAIN, FINGER	6	68	
		DRY MOUTH	28	68	
		THIRST	28	68	
		ALK. PHOS INCREASED	45	.	
		HYPERCHLOREMIA	45	.	
5053	LOSARTAN	ATAXIA	9	12	10
5085	FELODIPINE	HEADACHE	-1	3	4
		FLUSHING	-1	5	
		EDEMA/SWELLING	-1	9	
5158	FELODIPINE	HEADACHE	-16	1	2
		T-WAVE ABNORMALITY	-5	.	
		HEADACHE	1	1	
		NAUSEA	1	1	
		HEADACHE	2	2	
5221	FELODIPINE	PREMATURE BEAT	-18	-18	47
		EPISTAXIS	-11	-4	
		SLEEP DISORDER	7	63	
		EDEMA/SWELLING	27	47	
		EDEMA/SWELLING	48	63	
5271	LOSARTAN	PAIN, FOOT	48	63	3
		HEADACHE	-6	2	
		NERVOUSNESS	-6	2	
		WARM SENSATION	-6	2	
		MALAISE	1	2	
5273	LOSARTAN	VOMITING	1	2	42
		ANGINA PECTORIS	40	43	
		HYPOTENSION	43	43	

Table 55.9 lists the most common adverse experiences (> 4% in any treatment group) in either treatment group. There was no significant difference between treatment groups.

**Table 55.9. Most Common Clinical Adverse Experiences
(Patient Incidence $\geq 4\%$ in Any One Treatment Group)**

	LOSARTAN (N=89) N (%)	FELODIPINE (N=43) N (%)
Body As A Whole/Site Unspec.	15 (16.9)	8 (18.6)
Edema/Swelling	6 (6.7)	6 (14.0)
Asthenia/Fatigue	7 (7.9)	0 (0.0)
Digestive System	10 (11.2)	8 (18.6)
Diarrhea	1 (1.1)	2 (4.7)
Nausea	2 (2.2)	2 (4.7)
Musculoskeletal System	5 (5.6)	7 (16.3)
Pain, Back	4 (4.5)	2 (4.7)
Pain, Foot	1 (1.1)	2 (4.7)
Pain, Knee	0 (0.0)	2 (4.7)
Nervous System & Psychiatric	20 (22.5)	9 (20.9)
Headache	8 (9.0)	6 (14.0)
Respiratory System	18 (20.2)	6 (14.0)
Infection, Respiratory, Upper	10 (11.2)	3 (7.0)
Cough	4 (4.5)	1 (2.3)
Pharyngitis	4 (4.5)	1 (2.3)
Skin & Skin Appendage	4 (4.5)	2 (4.7)
Urogenital System	4 (4.5)	1 (2.3)

Note. This table contains counts of patients. If a patient experienced more than one clinical adverse experience, the patient was counted once with each adverse experience in a body system category, and the patient was counted only once in the body system total. For this reason, the separate adverse experience totals may not add up to the body system total.

There were no statistically significant differences between treatment groups.

There was no significant change in mean laboratory values. Three losartan patients had laboratory changes worthy of comment. Patient #5035 had an increase in serum sodium from a baseline of 144 Meq/L to a week 12 value of 162 Meq/L. Patient #5274 had a baseline creatinine of 1.1 mg/dl and a week 12 value of 1.6 mg/dl. Patient #5188 had a baseline serum potassium of 3.5 Meq/L and a 12 week value of 3.0 Meq/L.

Study 56. A Multicenter, Double-Blind, Randomized, Parallel-Group Study to Investigate the Incidence of Cough in Patients Receiving Losartan (MK-954, DuP 753) (50 mg q.d.) Lisinopril (20 mg q.d.) or Hydrochlorothiazide (25 mg q.d.) who Have Reported Cough with an Angiotensin Converting Enzyme Inhibitor

Protocol

This is a randomized, double-blind study designed to test the hypothesis that the percentage of patients who report a "dry cough" while being treated with losartan 50 mg q.d. will be lower than the percentage of patients who report a "dry cough" while being treated with an ACEI (lisinopril 20 mg q.d.). Hypertensive patients who have previously reported a "dry cough" with an angiotensin converting enzyme inhibitor were enrolled. Patients older than 21 years of age with a history of ACE inhibitor induced "dry cough", a history of a sitting diastolic blood pressure (SiDBP) of 90-110 mmHg and with no history of reversible airway disease or chronic lung disease were eligible for enrollment. Drugs that could affect the incidence of cough (NEAID, codeine, cough suppressants) were not permitted. Cough was assessed by a questionnaire and by a 10 cm visual analog scale (questionnaire can be found in the appendix). The study was divided into 3 phases. Phase 1 was a six week (? - the investigator is unblinded in this phase, it is not clear if the patient is unblinded) positive challenge filter period with lisinopril 20 mg q.d. On two (2) consecutive visits, patients must respond positively for cough (i.e., "moderately", "quite a bit" or "extremely" on the questionnaire - "a little" is not considered a positive response). After the initial visit at which the patient complained of cough, the presence of cough had to be documented on a subsequent visit ≥ 1 day later. Once cough was documented in phase 1, the patient entered phase 2, a single-blind (?) placebo washout period of at least 4 weeks duration. Within 4 weeks, but after a minimum of 2 weeks after starting Phase II, patients must respond negatively for cough (i.e., "not at all" on the questionnaire), documented on 2 consecutive visits which are ≥ 1 day apart. Once the lack of cough was documented in phase 2, patients entered phase 3, a double-blind treatment phase in which they were randomized to either losartan 50 mg daily, lisinopril 20 daily or HCTZ 25 mg daily for up to 8 weeks. Clinic visits are scheduled bi-weekly but may

occur earlier, or more frequently, if clinically indicated. That is, the patient may return to the clinic following the development of a cough that persists for ≥ 1 day. The presence of cough had to be documented on a subsequent visit > 1 day later. At each visit, the patient will independently complete the questionnaire and visual analog scale prior to seeing the physician or study nurse. Additionally, at each visit, safety evaluations of blood pressure, heart rate and adverse experiences will be obtained. If clinically appropriate, patients who respond positively for cough on two (2) consecutive visits will be considered to have completed Phase III of the study.

Procedures performed during the study are outlined in table 56.1.

Table 56.1 Flowchart of Study Visits and Procedures

	Visit: Day: Week:	Prestudy	* Challenge *			Placebo		Double-Blind Treatment			
		Visit	Lisinopril			Washout					
			Filter								
		1	2	3	4	5	6	7	8	9	10
			14	28	42	56	70	84	98	112	126
			2	4	6	8	10	12	14	16	18
Medical History		X									X
Physical Examination		X									X
12-lead ECG		X									X*
Laboratory Tests		X					X				X*
Chest X-ray		X									
Signed informed consent		X									
Body weight		X	X	X	X	X	X	X	X	X	X
Review inclusion/exclusion criteria		X			X		X				
Dispense medications		X			X		X				
Provide patient instructions		X	X			X		X			
Questionnaire		X	X	X	X	X	X	X	X	X	X
Visual analog scale		X	X	X	X	X	X	X	X	X	X
Sitting and standing blood pressure		X	X	X	X	X	X	X	X	X	X
Adverse experiences evaluation			X	X	X	X	X	X	X	X	X
Tablet counts			X	X	X	X	X	X	X	X	X

* Follow-up if abnormal at Visit 10.

NOTE: PATIENTS DISCONTINUED EARLY WERE TO BE COMPLETELY EVALUATED, I.E., VISIT 10 PROCEDURES (SEE SECTION XI 8)

An interim analysis of the data from the two control groups was scheduled to occur after 30 patients completed the study. The sole purpose of this analysis was to assess the accuracy of the "positive" cough definition to be used in the final analysis. Only the two control groups were to be utilized for this assessment. No statistical tests were to be performed, therefore, the size and power of the statistical tests described above will remain unaffected. These data was not shared with the investigators. An interim analysis was performed after 70 patients completed the study. Contrary to what was proposed by the protocol, the results of losartan 50 mg treatment were also included in the summary statistics.

Results

One hundred and thirty-five (135) patients from twenty (20) centers were randomized into the study. Approximately one half (53.3%) of all patients were recruited by four investigators. The number of patients randomized per center ranged from 1 to 25. Table 56.2 lists the demographic characteristics of each treatment group.

Table 56.2. Baseline Patient Demographic Characteristics

	LOSARTAN (N=48)	LISINAPRIL (N=46)	HCTZ (N=41)	TOTAL (N=135)
Sex				
Female	31 (65%)	30 (65%)	26 (63%)	87 (64%)
Male	17 (35%)	16 (35%)	15 (37%)	48 (36%)
Age (years)				
Mean	54.3	57.6	56.9	56.2
S.D.	10.6	12	9	10.7
Range	26-77	37-81	40-77	26-81
Racial Origin				
Caucasian	39 (81%)	45 (98%) ^a	36 (88%)	120 (89%)
Black	5 (10%)	0	3 (7%)	8 (6%)
Oriental	0	0	1 (2%)	1 (1%)
Hispanic	0	1 (2%)	0	1 (1%)
Indian	1 (2%)	0	1 (2%)	2 (1%)
Mestizo	1 (2%)	0	0	1 (1%)
Mulatto	1 (2%)	0	0	1 (1%)
Maori	1 (2%)	0	0	1 (1%)

^a - Statistically significantly different from LOSARTAN treatment group, p<0.05

Table 56.3 lists the severity of the dry cough at the end of the lisinopril positive control period categorized by description from the questionnaire.

Table 56.3. Severity of Dry Cough at the End of Lisinopril Filter Period, By Treatment

Treatment	Number and Percentage of Patients with Dry Cough					Total No.
	Not at All No. (%)	A Little No. (%)	Moderately No. (%)	Quite a Bit No. (%)	Extremely No. (%)	
Losartan 50	0 (0.0)	0 (0.0)	22 (45.8)	18 (37.5)	8 (16.7)	48
Lisinopril 20	0 (0.0)	0 (0.0)	28 (60.9)	12 (26.1)	6 (13.0)	46
HCTZ 25	0 (0.0)	0 (0.0)	28 (68.3)	10 (24.4)	3 (7.3)	41
All	0 (0.0)	0 (0.0)	78 (57.7)	40 (29.6)	17 (12.6)	135

Table 56.4 lists the patient disposition in the study. One hundred and twenty-nine patients completed the study. Six withdrew prematurely from double-blind treatment. One losartan patient withdrew due to an adverse event. Patient #3694 took double-blind therapy for 9 days, at which time the patient was withdrawn for severe asthenia/fatigue. The patient's sitting blood pressure at randomization was 125/76 and on the day of discontinuation was 91/61. One lisinopril patient (#3699) was discontinued for asthenia/fatigue which started in the placebo washout phase. One HCTZ patient (#3683) was discontinued for weight gain and increased blood pressure.

Table 56.4. Patient Accounting

	Losartan (N=48) No. (%)	Lisinopril (N=46) No. (%)	HCTZ (N=41) No. (%)
Completed Double-blind Phase/ Not Continuing into Extension	20 (41.7)	20 (43.5)	13 (31.7)
Completed Double-blind Phase/ Continuing into Extension	27 (56.3)	25 (54.3)	24 (58.5)
Discontinued Double-blind Phase:			
Clinical Adverse Experience	1 (2.1)	1 (2.2)	4 (9.8)
Patient Withdrew	1 (2.1)	1 (2.2) [†]	1 (2.4)
Protocol Deviation	0 (0.0)	0 (0.0)	2 (4.9)
	0 (0.0)	0 (0.0)	1 (2.4)

[†] This patient (AN 3699) was discontinued for a clinical adverse experience which started in baseline and continued into double-blind without change in intensity or frequency.

In order to recognize the differences between the various phases with regard to the definition of a positive or negative response for cough, it is worthwhile to review the questionnaire used in the trial. The definitions for a positive response by treatment phase are outlined in table 56.5. The questionnaire consisted of nine symptoms. In order, they are: dry mouth, cramps in legs, dry cough, racing heart, heartburn, headache, sore throat, getting up at night to pass urine and flushing in the face. For each symptom, based on the previous weeks experience, the patient described it as occurring "not at all", "a little", "moderately", "quite a bit" or "extremely". In phase one (lisinopril positive challenge phase), all patients had to exhibit a positive challenge for dry cough which was defined as a dry cough of moderate severity or greater on 2 consecutive visits. Visits had to be ≥ 1 day apart. In phase two (placebo washout), all patients had to exhibit a negative response which was a response of "not at all" for dry cough on 2 consecutive visits. In phase 3, a positive response for dry cough was defined as a dry

cough of "a little" or greater severity for 2 consecutive visits > 1 day apart. In conclusion, there is a distinction between the definition of a positive response for a dry cough in the positive challenge phase and the double blind treatment phase. The definition in the double blind treatment phase is less rigorous.

Table 56.5. Definition of Positive and Negative Response to Dry Cough

	Positive Response	Negative Response
Phase 1 (lisinopril positive challenge)	moderately, quite a bit, extremely *	Not at all, a little
Phase 2 (placebo washout)	a little, moderately, quite a bit, extremely	Not at all *
Phase 3 (double-blind treatment)	a little, moderately, quite a bit, extremely	Not at all

* Required on two consecutive visits to get to the next phase.

The sponsor has provided 2 different analysis for the data, all patients treated analysis and a per protocol analysis. Neither was specified as the primary analysis in the protocol. The sponsor suggests that the primary analysis of this study included all-patients-treated in the eight-week double-blind phase of the study. However, for some reason the sponsor has chosen to change the definition of the primary endpoint in this analysis. These revised definitions are outlined in table 56.5a. The primary endpoint in the protocol is cough on 2 consecutive visits greater than 1 day apart.

Table 56.5a.

Possible Scenarios	Dry Cough Responses	Disposition for Dry Cough All-Patients-Treated	Disposition for Dry Cough Per-Protocol
Patient completed 8 weeks	1,1,1,1	Negative	Negative
Patient completed 8 weeks	1,1,1,4	Positive	Negative
Patient completed 8 weeks	2,2,1,1 or 1,2,2,1	Positive	Positive
Patient completed 8 weeks	1,2,1,2	Positive	Negative
Patient completed < 8 weeks	2,2	Positive	Positive
Patient completed < 8 weeks	1,2,1	Negative	Not Included
Patient completed < 8 weeks Withdrawn due to extreme cough	5	Positive	Not Included

1 = Not at All (negative), 2 = A Little (positive), 3 = Moderately (positive), 4 = Quite a Bit (positive), 5 = Extremely (positive)

Table 56.6 displays the percentage of patients responding positively to dry cough during the double-blind treatment period, by treatment. This is an all patients treated analysis. It includes patients who were protocol violators and patients who did not fulfill the protocol specified criteria for a positive cough in phase 3 but were counted as positive under a revised criteria for analysis. The criteria for the all patients treated approach were not included in the protocol. One must be concerned that their derivation was data driven. In the sponsors all patients treated analysis and per protocol analysis, the percentage of patients responding positively to dry cough was significantly higher in the lisinopril treatment group compared to both the losartan and HCTZ treatments groups, ($p \leq 0.01$).

Table 56.6 All-Patients-Treated Analysis for Dry Cough

	Dry Cough		Total No.
	No. (%)	Yes No. (%)	
Treatment	No. (%)	No. (%)	No.
Losartan 50	34 (70.8)	14 (29.2)	48
Lisinopril 20	13 (23.3)	33 (71.7) **,†	46
HCTZ 25	27 (65.9)	14 (34.1)	41

** Lisinopril vs. losartan, $p \leq 0.01$. Fisher's Exact Test.
† Lisinopril vs. HCTZ, $p \leq 0.01$ Fisher's Exact Test.
Losartan vs. HCTZ: not statistically significant

Table 56.6a is a per protocol analysis of the primary endpoint. Twenty-one patients were excluded mainly for not having 2 "positive" visits in phase one, 2 "negative" visits in phase two, used concomitant antihypertensive therapy at any phase or did not ingest the correct amount of medication. Patient #3688 (losartan) was not included in the Merck list but should have been because of a failure to have 2 negative visits in phase 2. Of the 49 patients who had dry cough (designated yes) during phase three, 14 of these patients (9 lisinopril, 2 HCTZ, 3 losartan) did not actually fulfill the protocol criteria for cough because the consecutive visits were not greater than one day apart. Six patients (4 losartan, 1 lisinopril, 1 HCTZ) had only one visit positive for cough (the last visit). Table 56.6b is the correct per protocol analysis. Losartan versus lisinopril is significantly different ($p < .001$; Chi-square).

Table 56.6a. Number and Percentage of Patients with Dry Cough By Treatment Per-Protocol Analysis. Sponsors Analysis

Treatment	Dry Cough		Total No.
	No. (%)	Yes. (%)	
Losartan 50	32 (78.1)	9 (22.0)	41
Lisinopril 20	10 (25.6)	29 (74.4)**†	39
HCTZ 25	23 (67.7)	11 (32.4)	34

** Lisinopril vs. losartan, $p \leq 0.01$; † = Lisinopril vs. HCTZ, $p \leq 0.01$;
Losartan vs. HCTZ: not statistically significant

Table 56.6b. Number and Percentage of Patients with Dry Cough By Treatment Per-Protocol Analysis. Medical Officer Analysis (Excludes patients with only one day between "yes" visits and patients with only one "yes" visit.)

Treatment	Dry Cough		Total No.
	No. (%)	Yes. (%)	
Losartan 50	30 (83.3)	6 (16.7)	36
Lisinopril 20	9 (31.0)	20 (69.0)	29
HCTZ 25	24 (75.0)	8 (25.0)	32

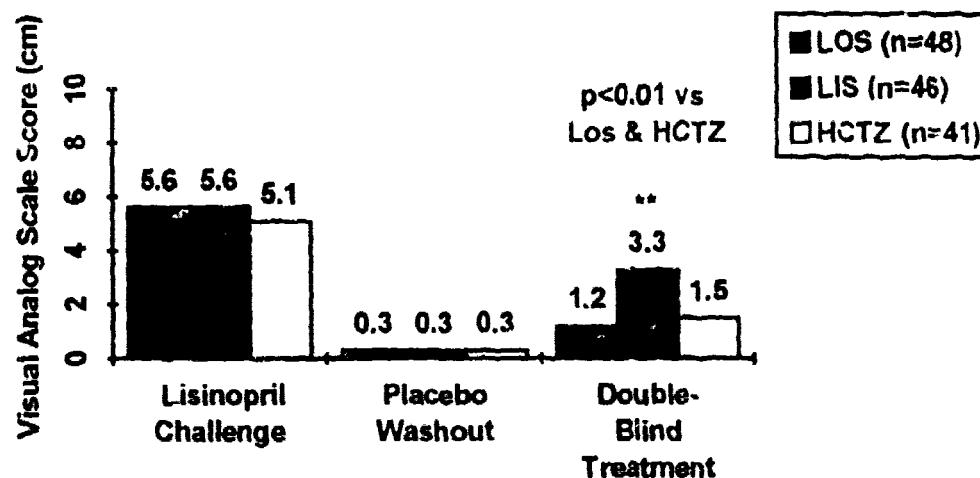
Table 56.7 lists the results based on the severity of cough for the all patients treated analysis. Most losartan patients with cough described the severity as "a little". Male and female patients had less cough with losartan than with lisinopril.

Table 56.7. Severity of Dry Cough, By Treatment (All-Patients-Treated Analysis)

Treatment	Not at All	A Little	Moderately	Quite a Bit	Extremely	Total
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No.
Losartan 50	34 (70.8)	9 (18.8)	4 (8.3)	1 (2.1)	0 (0.0)	48
Lisinopril 20	13 (28.3)	12 (26.1)	6 (13.0)	13 (28.3)	2 (4.4)	46
HCTZ 25	27 (65.9)	4 (9.8)	5 (12.2)	5 (12.2)	0 (0.0)	41

Figure 56.1 illustrates the difference in visual analog scores based on treatment group.

Figure 56.1 Visual Analog Scale Scores



The relationship between dry cough and all other symptom scores, in addition to treatment and gender, was analyzed with a multiple logistic regression analysis in order to determine if the presence of any of the other symptoms was related to the presence of dry cough, either independent of or dependent upon treatment. The results of this analysis indicated that the presence of both dry mouth and headache were associated with dry cough independently of treatment ($p < 0.01$). The relationship between treatment and the presence of dry cough was the same whether or not dry mouth was present, and reflected the relationship in the total population.

The mean changes for sitting systolic and diastolic blood pressure (mmHg) from the end of the placebo washout period to the end of the double-blind treatment period are presented in Tables 56.8 and 56.9. Presumably, this data represents the last double blind value carried forward. The change in blood pressure is better with lisinopril suggesting the doses of medication were not equipotent. The lowest recommended dose of lisinopril is 10 mg per day. The lowest dose recommended by the sponsor is 50 mg. If there is truly not a dose response for cough with ACE inhibitors, then this difference in potency may not be relevant. Obviously, had losartan 100 mg been used rather than 50 mg, these results would be more impressive.

Table 56.8. Mean Change in Sitting Systolic Blood Pressure (mmHg) From Placebo Washout

TREATMENT	N	PLACEBO WASHOUT		DOUBLE BLIND		CHANGE	
		Mean	S.D.	Mean	S.D.	Mean	S.D.
LOS 50	48	149.6	18.9	139.9	20.5	-9.6	14.6
LIS 20	46	154.5	19.1	140.6	21.3	-13.9	13.4
HCTZ 25	40	151.3	20.0	143.9	15.3	-7.4	13.2

Table 56.9 Mean Change in Sitting Diastolic Blood Pressure (mmHg) From Placebo Washout

TREATMENT	N	PLACEBO WASHOUT		DOUBLE BLIND		CHANGE	
		Mean	S.D.	Mean	S.D.	Mean	S.D.
LOS 50	48	94.8	10.1	89.6	9.3	-5.2	7.8
LIS 20	46	94.1	8.4	85.6	9.6	-8.5	8.2
HCTZ 25	40	95.8	9.1	91.1	7.5	-4.7	9.1

Conclusion:

The sponsor performed a specified interim analysis. They did not follow the protocol for the timing of the analysis (performed after 70 rather than 30 completed patients) and looked at the results of the losartan treated patients (should have looked only at the results of the lisinopril and HCTZ patients). The results of the trial are sufficiently robust so that any statistical adjustment still yields a significant outcome.

Although the definition of a positive cough response was not the same in the lisinopril treatment period and the double blind treatment period, it is apparent from table 56.7 that more lisinopril than losartan patients had cough defined as moderately severe or greater. The difference between therapies with regard to antihypertensive response suggest that lisinopril 20 mg had a greater antihypertensive effect compared to losartan 20 mg. If a more potent dose of lisinopril was used compared to losartan then an argument could be made that this study does not prove anything. A dose response for cough has not been defined for most ACE inhibitors. In general, the Cardio-Renal division has assumed that cough is not a dose dependent side effect. If this assumption is true, then the study does show something. If this assumption is false, then the study does not prove that the incidence of cough is less with losartan.

Study 64. A Double-blind, Randomized, Parallel, Active-controlled Study to Evaluate the Antihypertensive Efficacy and Safety of Losartan (MK-954, DuP 753) in Patients With Severe Hypertension.

Protocol

This is a randomized, double blind, parallel, enalapril controlled trial in patients with severe hypertension (siDBP = 115 - 130 mmHg). Eligible patients with severe hypertension whose previous antihypertensive medications could be safely discontinued, whose mean siDBP was 115 to 130 mmHg (on two readings, 30 minutes apart, with the 2 consecutive means being no more than 7 mmHg different) at least 24 hours and no more than 7 days off previous antihypertensive medications, and whose sitting systolic blood pressure was ≤ 220 mmHg, were stratified according to race (black or non-black) and were randomly assigned to one of two treatment groups. Patients were randomized in a ratio of 2:1 to receive once-daily therapy of either losartan 50 mg or enalapril 20 mg. Patients received double-blind therapy for 12 weeks. If siDBP remained ≥ 90 mmHg, losartan or enalapril doses were doubled. Over the course of therapy, HCTZ 25 mg, atenolol 100 mg and a dihydropyridine calcium channel blocker were added sequentially if siDBP remained ≥ 90 mmHg. A study outline of procedures and measurements performed is outlined in table 64.1.

Table 64.1. Procedures Performed During Trial.

Visit:	Double-Blind Period								
	Prestudy	1	2	3	4	5	6	7 ^a	8 ^b
Days:		1	8	15	29	43	57	71	85
Week:		0	1	2	4	6	8	10	12
Signed Informed Consent	X								
Medical History	X								
Complete Physical Examination	X								X
Clinic Visit ^c	X	X	X	X	X	X	X	X	X
BP and HR (trough [T] and peak [P] sitting and standing) ^d	X	T,P	T	T	T,P ^h	T	T	T	T,P
Routine Laboratory Examinations	X				X	X ^g			X
Electrocardiogram (12-lead)	X								X
Chest X-ray ^e	X								
AE Evaluation		X	X	X	X	X	X	X	X
Count/Dispense Double-Blind Medication ^f		X	X	X	X	X	X	X	X

^a Follow Visit 7 schedule for additional visits.; ^b Complete all procedures scheduled for Visit 8 if patient discontinues study for any reason prior to Visit 8.

^c Clinic visits will occur as indicated between 0630 and 1000 hours. Patients are to be in the fasted state at all clinic visits (i.e., no food is to be taken during the 8 hours prior to each clinic visit).

^d Measurements must be taken between 0630 and 1000 hours, 24 hours (range 22 to 26 hours) after last dose of study medication (for Visits 2 through 8) and prior to medication taken at the clinic visit. Peak measurements must be taken 6 hours (range 5 to 8 hours) after last dose.

^e If none available within past 6 months; ^f According to titration schedule.; ^g Complete abbreviated panel.

^h Peak blood pressure measurements obtained at end of monotherapy.

Results

Seventy five (75) patients were entered into the study. Fifty (50) patients were randomized to the losartan group and 25 were randomized to the enalapril group. The distribution of patients by treatment group for each investigator is presented in Table 64.2.

Table 64.2 Baseline Patient Demographic Characteristics

		Losartan (N=50)	Enalapril (N=25)	Total (N=75)
Sex	Female	19 (38%)	11 (44%)	30 (40%)
	Male	31 (62%)	14 (56%)	45 (60%)
Age (years)	Mean	49.8	53	50.9
	S.D.	11.6	11.5	11.6
	Range	23-74	34-72	23-74
Racial Origin	Caucasian	25 (50%)	15 (60%)	40 (53%)
	Black	22 (44%)	10 (40%)	32 (43%)
	Hispanic	2 (4%)	0	2 (3%)
	Native Amer.	1 (2%)	0	1 (1%)
Duration of Primary Diagnosis (years)	Mean	10.7	11.9	11.1
	S.D.	9.3	9.3	9.2
	Median	6.5	11	10
	Range	0.5-34	0.5-36	0.5-36
Baseline Blood Pressures (SiSBP/SiDBP)	Mean	173.7/118.5	176.5/119.3	

Six losartan patients and two enalapril patients discontinued therapy prior to completion of 12 weeks of therapy. Table 64.2a. lists the patients who did not complete the 12 week double-blind period of treatment.

Table 64.2a.

Patient #	Treatment	Day Discontinued	Reason Discontinued
4518	losartan	39	lost to follow-up
4559	losartan	69	lost to follow-up
4617	losartan	8	lost to follow-up
4573	losartan	51	protocol deviation
4577	losartan	97	protocol deviation
4601	losartan	46	uncooperative
4613	enalapril	29	lost to follow-up
4560	enalapril	25	laboratory adverse experience Increased creatinine (1.1 --> 2.2 mg/dl) and BUN (15 --> 62 mg/dl) compared to baseline.

Table 64.3 and 64.4 provide the mean change in trough siDBP and trough siSBP at weeks 4 and 12.

Table 64.3 Mean Change in Trough Sitting Diastolic Blood Pressure by Week All-Patients-Treated Approach(mmHg)

WEEK	TREATMENT GROUP	N	BASELINE		POST-TREATMENT		CHANGE		CHANGE Adj Mean	BETWEEN- GROUP COMPARISON
			Mean	S.D.	Mean	S.D.	Mean	S.D.		
4	Losartan	50	118.5	3.5	99.4	9.8	-19.1	9.7	-19.1	0.355
	Enalapril	25	119.3	3.1	98.2	8.5	-21.0	7.9	-21.0	--
12	Losartan	50	118.5	3.5	90.8	8.7	-27.7	8.0	-29.0	0.051
	Enalapril	25	119.3	3.1	88.4	5.1	-30.9	4.8	-32.4	--

Table 64.4 Mean Change in Trough Sitting Systolic Blood Pressure by Week All-Patients-Treated Approach (mmHg)

WEEK	TREATMENT GROUP	N	BASELINE		POST-TREATMENT		CHANGE		CHANGE Adj Mean	BETWEEN- GROUP COMPARISON
			Mean	S.D.	Mean	S.D.	Mean	S.D.		
4	Losartan	50	173.7	14.5	154.5	16.8	-19.2	17.9	-19.1	0.412
	Enalapril	25	176.5	14.9	152.7	16.4	-23.8	15.7	-22.0	--
12	Losartan	50	173.7	14.5	140.3	16.1	-33.4	17.8	-33.4	0.082
	Enalapril	25	176.5	14.9	133.8	14.5	-42.7	17.8	-39.6	--

At 12 weeks, all but one losartan treated patient were considered to be responders to therapy (siDBP < 90 mmHg or trough siDBP $\geq$ 90, reduction $\geq$ 10 mmHg). The significance of this definition of responder is suspect since patients could be markedly hypertensive but because they decreased their siDBP by 10 mmHg they are considered responders. The majority of losartan and enalapril patients required combination therapy. Sixty percent in each treatment group received 3 or more drugs to control blood pressure.

Table 64.5 lists the mean change in siDBP at week 4 and 12 based on racial subgroup. At week 4, most if not all patients should be on losartan monotherapy (50 or 100 mg). Although the mean change in siDBP in black patients at week 4 is impressive (-16.9 mmHg), it is not sufficient evidence that losartan is effective in black patients. There is no placebo group with which to compare. Since the pivotal studies (all placebo controlled) included in the NDA suggest that losartan is ineffective in black patients, nothing short of a placebo controlled trial can refute this observation. The week 12 results which suggest no difference between black and caucasian patients is not unexpected because other therapies contribute to the treatment effect.

Table 64.5 Summary Statistics for Trough Sitting Diastolic BP by Treatment Group and Race

WEEK	TREATMENT	RACE	N	Baseline		Post-Treatment		Change	
				Mean	S.D.	Mean	S.D.	Mean	S.D.
4	Losartan	BLACK	22	118.9	3.9	102	9.2	-16.9	9.7
		NON-BLACK	28	118.2	3.2	97.4	10	-20.8	9.5
	Enalapril	BLACK	10	120.3	3.7	102.6	7.9	-17.7	6.2
		NON-BLACK	15	118.6	2.5	95.3	7.8	-23.3	8.2
12	Losartan	BLACK	22	118.9	3.9	90.5	6.9	-28.4	6.8
		NON-BLACK	28	118.2	3.2	91.1	10	-27.1	8.9
	Enalapril	BLACK	10	120.3	3.7	88.7	6.2	-31.6	5
		NON-BLACK	15	118.6	2.5	88.2	4.4	-30.4	4.9

The incidence of adverse experiences is quite similar between treatment groups. There were no serious adverse events reported. A detailed summary of the results is not warranted since most patients were on multiple drug therapy to control blood pressure. As a consequence, adverse events could not be attributed to any one therapy. One enalapril patient (#4560) withdrew due to elevated creatinine.

The mean glucose in losartan treated patients increased from 102.8 mg/dl at baseline to 124.0 mg/dl at week 12. Two patients had marked increases in glucose. Patient #4551 a day 1 blood glucose of 197 mg/dl and a day 102 glucose of 417 mg/dl. Patient #4611 had a day -21 glucose of 166 and a day 92 glucose of 262.

Patient # 4551 had elevations in the ALT and AST during treatment. ALT increased from 57 U/L at baseline to 170 U/L at day 92. AST increased from 51 U/L at baseline to 101 U/L at day 92.

Open Label - Hypertensives						
Study #	Design/ Patient Population	Treatment Groups	N	Primary Endpoint	Other Measures	Page
012	- ol, nc, 2 center, 7 day Rx period - hypertensives with renal insufficiency - includes hemodialysis patients	- losartan 100 mg daily		pharmacokinetic parameters (losartan and E-3174)	- plasma renin - plasma aldosterone - urine creatinine clearance - urine sodium, urea nitrogen - hemodynamics	165
014	- sb, ol, nc, single center, 8 week Rx - hypertensives with renal nephropathy, proteinuria, non-black	- losartan 50 mg x 4 wks then 100 mg x 4 wks	13	Change in 24 hour protein excretion	- GFR, Renal Plasma Flow - plasma renin	170
058	Preliminary results included in NDA were not reviewed at this time. Enrollment is ongoing					
059	- ol, nc, 12 week treatment period - severe hypertensives - International Trial (U.S., S. Amer., Europe) - 50% have sDBP 115 - 125 mmHg	one treatment group; medication titrated based on response; losartan 50 - 100 mg +/- HCTZ 12.5 - 25 mg +/- atenolol 50 - 100 mg or felodipine 5 - 10 mg	180	no primary endpoint defined		173
L21 L11 L50 L49 L54	- ol extensions of db trials	- losartan +/- combination	659	Safety	- Change in DBP	178

wk = week, db = double-blind, ol = open label, od = once a day, bid = twice a day, r = randomized, ac = active control, pc = placebo control, nc = no control, p = parallel, co = crossover, hx = history, HTN = hypertension, ACEI = angiotensin converting enzyme inhibitor, NE = norepinephrine, Epi = epinephrine, PRA = plasma renin activity

Study 012. An Open, Multicenter Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Losartan after Chronic Dosing in Patients with Various Degrees of Renal Insufficiency

Objective: To determine the pharmacokinetics of losartan and E-3174 and hemodynamic in patients with various degrees of renal insufficiency

Design: open label, multicenter (2 centers), multi-dose; 1 week baseline washout period, 1 week treatment period.

Treatment Regimens: Losartan 100mg daily for 7 days

Population Studied: 24 patients with renal insufficiency defined by the creatinine clearance of two 24 hour urines obtained during baseline. The patients were subdivided based on the severity of renal insufficiency into 4 groups.

- Group I: Creatinine clearance 75 mL/min or higher
- Group II: Creatinine clearance 30-74 mL/min
- Group III: Creatinine clearance 10-29 mL/min
- Group IV: Creatinine clearance <10 mL/min (hemodialysis)

Six patients per renal clearance group completing the trial provided 80% power to detect a 114% difference in the AUC₂₄ of (LOSARTAN) between the normal group of subjects and any of the other three groups. The power to detect a 100% difference (2 fold) between the normal renal function group and any one of the other groups was 73%. Power estimates were based on two-sided t-test, with alpha=0.05.

Inclusion/Exclusion Criteria: Untreated DBP 95 - 115 mmHg, male or non-pregnant female, renal insufficiency as defined by creatinine clearance, no other relevant medical problems, not > 30% of ideal body weight.

Trial Description: All patients discontinued any prior antihypertensive medications (except diuretics in patients who required them) for a 1-week washout period (2 weeks if on prior angiotensin-converting enzyme inhibitor), during which their clinical status was closely monitored. Following the washout period, patients in Groups I, II, and III received losartan 100 mg for 7 days. Hemodialysis patients (Group IV) followed a similar pattern as patients in Groups I-III. Patients took 100 mg losartan at 8:00 a.m. at the clinic for 7 days, with the dose being taken 4 hours before dialysis on dialysis days. Dialysis was performed on a three-times-per-week schedule (Days 2, 4, 6, 9 of the study).

Endpoints/Parameters Measured:

- 1) Pharmacokinetic Parameters for losartan and E-3174 [the study is powered based on a difference between the AUC between creatinine clearance groups]
- 2) Table 12.1 and 12.2 list the parameters measured during the clinical trial.

Table 12.1. Clinical and Laboratory Measurements. Group I, II, and III (Non-hemodialysis Patients)

Study Day	Washout							Chronic Treatment/Pharmacokinetics								
	-7	-6	-5	-4	-3	-2	-1	1	2	3	4	5	6	7	8	9
Physical Examination	x															x
Medical History	x															
Inpatient														x	x	
Losartan 100 mg								x	x	x	x	x	x	x		
Plasma Losartan/E-3174 ***								x					x	x	x	
Vital Signs	x	x			x			x	x	x	x	x	x		x	
Laboratory Evaluation*		x			x			x						x		x
24 hr Urine**	x	x		x	x									x	x	
Creatinine Clearance	x	x		x	x									x	x	
Electrocardiogram	x															x

*Laboratory Evaluation:

Hematology: hemoglobin, hematocrit, RBC count, WBC count, WBC differential, platelet count

Serum Chemistry: AST (SGOT), ALT (SGPT), alkaline phosphatase, GGT, LDH, creatinine, total bilirubin, BUN, fasting serum glucose, uric acid, sodium, potassium chloride, calcium, phosphates, total protein, albumin, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides

Urinalysis: pH, glucose, microscopic (RBC, WBC, casts, epithelial); drug abuse screen (Days -6, 1)

Renin-Angiotensin System: plasma renin activity, aldosterone

Miscellaneous: HIV antibody (Day -6), pregnancy test (females of childbearing potential, Days -6 and 9)

**24 hr Urine: creatinine (creatinine clearance), sodium, urea nitrogen, total protein. Urine was collected 0-4, 4-8, 8-12, and 12-24 hours postdose on Day 7

*** On Day 6, a trough blood specimen was taken, and on Day 7, the patient was admitted to the study clinic for 30 to 60 hours. Blood specimens were collected predose and at 10, 20, 30, 45, 60, 75, and 90 minutes, and 2, 3, 4, 6, 8, 10, 12, 15, and 18 hours postdose on Day 7, then on Days 8-9 at timepoints 24, 30, 36, 48, and 60 hours after the Day 7 dose.

Table 12.2. Clinical and Laboratory Measurements. Group IV (Hemodialysis Patients)

Study Day	Washout							Chronic Treatment/Pharmacokinetics								
	-7	-6	-5	-4	-3	-2	-1	1	2	3	4	5	6	7	8	9
Physical Examination	x															x
Medical History	x															
Hemodialysis		x		x		x			x		x		x			x
Inpatient														x	x	
Losartan 100 mg (pre-dialysis)								x	x	x	x	x	x	x		
Plasma Losartan/E-3174***																
Peripheral Venous Pre-/Postdialyzer****								x						x		
Vital Signs	x	x		x		x		x	x	x	x	x	x	x	x	
Laboratory Evaluation*		x			x			x						x		x
Electrocardiogram	x															x

*Laboratory Evaluation:

Hematology: hemoglobin, hematocrit, RBC count, WBC count, WBC differential, platelet count

Serum Chemistry: AST (SGOT), ALT (SGPT), alkaline phosphatase, GGT, LDH, creatinine, total bilirubin, BUN, fasting serum glucose, uric acid, sodium, potassium chloride, calcium, phosphates, total protein, albumin, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides

Renin-Angiotensin System: plasma renin activity, aldosterone

Miscellaneous: HIV antibody (Day -6), pregnancy test (females of childbearing potential, Days -6 and 9), serum drug abuse screen (Days -6, 1)

*** On Day 6, a trough blood specimen was taken, and on Day 7, the patient was admitted to the study clinic for 30 to 60 hours. Blood specimens were collected predose and at 10, 20, 30, 45, 60, 75, and 90 minutes, and 2, 3, 4, 6, 8, 10, 12, 15, and 18 hours postdose on Day 7, then on Days 8-9 at timepoints 24, 30, 36, 48, and 60 hours after the Day 7 dose.

**** Pre- and post-dialysis blood specimens were taken from the dialysis shunt circuit at Hours 0, 1, 2, 3, and 4 of dialysis on Day 6 to evaluate the clearance of losartan and E-3174 by hemodialysis.

Enrolled/Randomized: 24 patients with 6 in each creatinine clearance classification group# **Demographics/Disposition:** All patients completed the study.

Group	Male/Female	Black/White	Mean Age (Years)	Mean Baseline Cr. Cl. (ml/min)	Range Baseline Creatinine Clearance (ml/min)
I	4/2	0/6	48.7	112	81 - 167
II	2/4	1/5	45.0	58.8	47.6 - 74.5
III	4/2	2/4	58.8	16.6	12 - 28.5
IV	2/4	4/2	38.5		

Efficacy Results:

Two patients had incomplete urine collection (# 113 and # 123). In addition, half-lives could not be calculated for 5 patients; Losartan : #231 and #143; E-3174: #222, #241 and #242.

Table 12.3 lists the pharmacokinetic parameters calculated for losartan. AUC tended to increase with increasing dose. C_{max} increased in hemodialysis patients. Elimination half-life was similar in all groups. Urinary recovery of losartan was less than 40% of the dose.

Table 12.3. Summary Pharmacokinetics Parameters for Losartan

Parameter	I (>75)			II (30-74)		
	n	Mean	Std	n	Mean	Std
C_{max}^1 (ng/mL)	6	854.22	315.23	6	1164.63	748.03
T_{max} (hr)	6	0.79	0.37	6	0.68	0.23
AUC ² (ng hr/mL)	6	1108.90	265.05	6	1212.20	755.06
$t_{1/2}$ (hr) ^A	6	2.13	0.68	6	2.17	0.97
CLr ³ (mL/min)	6	50.24	19.36	6	16.51	8.46
Urinary Recovery ⁴ (% Dose)	5	3.25	1.23	5	1.33	1.03
Parameter	III (10-29)			IV (Dialysis)		
	n	Mean	Std	n	Mean	Std
C_{max}^1 (ng/mL)	6	801.00	445.41	6	1615.05	117.36
T_{max} (hr)	6	0.88	0.41	6	0.68	0.32
AUC ² (ng hr/mL)	6	1760.61	1389.75	6	2065.63	551.01
$t_{1/2}$ (hr) ^A	5	3.22	2.19	5	2.64	1.02
CLr ³ (mL/min)	6	2.31	0.89		NA	
Urinary Recovery ⁴ (% Dose)	6	0.27	0.32		NA	

A Harmonic mean and pseudo-standard deviation used for half life.

1 C_{max} was significantly higher in Group IV than in Group I ($p=0.020$) and Group III ($p=0.013$). There was a notable trend ($p=0.072$).

2 AUC₂₄ was significantly higher in Group IV than in Group I ($p=0.008$) and notably higher in Group IV than Group II ($p=0.066$). There was a significant trend, $p=0.021$.

3 Renal clearance was significantly greater in Group I than in Groups II and III, $p=0.008$ and $p=0.005$, and significantly higher in Group II than in Group III, $p=0.005$.

There was a highly significant trend, $p<0.001$.

4 Urinary Recovery was significantly greater in Group I than in Groups II and III, $p=0.037$ and $p=0.008$, and significantly higher in Group II than in Group III, $p=0.035$.

There was a highly significant trend, $p<0.001$.

Figure 12.1 plots the mean losartan concentration on day 7. Group IV does not have a value at any time after 16 hours and, as a consequence, it is not clear that the elimination $t_{1/2}$ has been accurately determined.

Figure 12.1 LOSARTAN Mean Plasma Concentrations After Dose Day 7

Mean: MK, 954 Plasma Concentration (ng/ml)

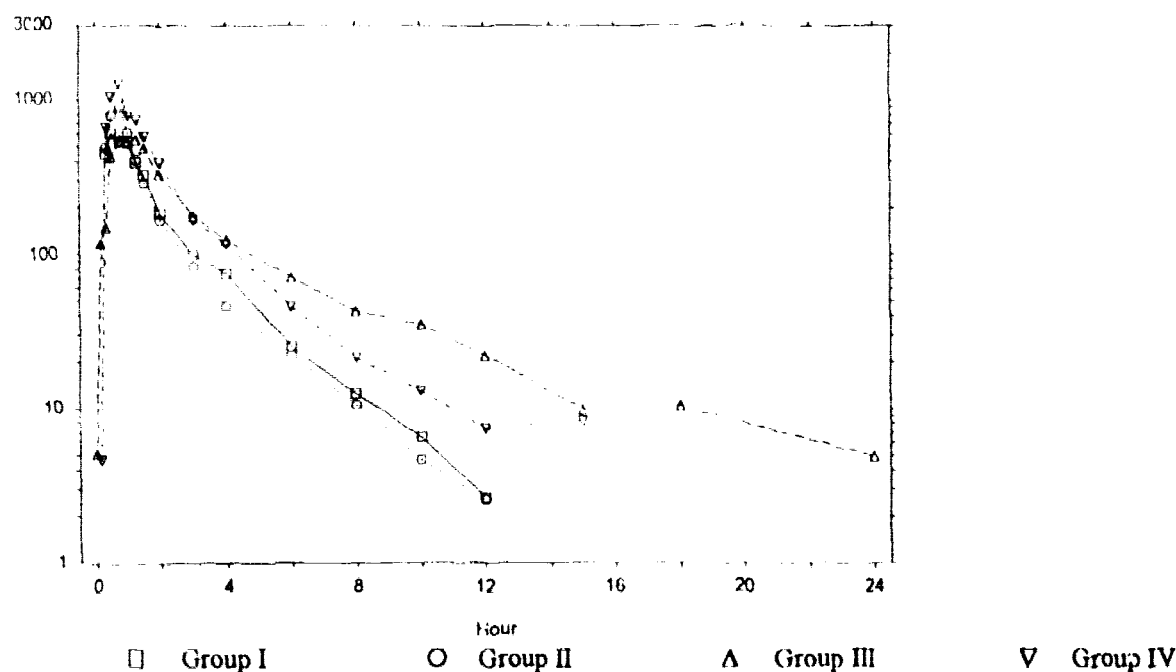


Table 12.4. Summary Pharmacokinetics Parameters for E-3174. Group (Creatinine Clearance - mL/min)

Parameter	I (>75)			II (30-74)		
	n	Mean	Std	n	Mean	Std
C_{max} (ng/mL)	6	681.28	210.49	6	622.98	214.06
T_{max} (hr)	6	2.42	0.92	6	2.08	0.49
AUC (ng hr/mL)	6	4362.15	1143.24	6	3694.26	953.12
$t_{1/2}$ (hr) ^A	6	9.55	3.47	5	11.04	5.44
CL_{cr} (mL/min)	6	16.10	4.14	6	6.92	2.55
Urinary Recovery ³ (% Dose)	5	4.44	1.34	5	1.85	0.92
Parameter	III (10-29)			IV (Dialysis)		
	n	Mean	Std	n	Mean	Std
C_{max} (ng/mL)	6	402.60	344.18	6	715.28	579.02
T_{max} (hr)	6	4.17	1.60	6	2.50	1.00
AUC (ng hr/mL)	6	3912.44	2766.13	6	5011.61	4037.50
$t_{1/2}$ (hr) ^A	6	13.45	5.78	4	11.25	9.00
CL_{cr} (mL/min)	6	1.29	0.78		NA	
Urinary Recovery ³ (% Dose)	6	0.24	0.08		NA	

A. Harmonic mean and pseudo-standard deviation used for half life

- T_{max} was significantly later in Group III than in Group II, $p=0.019$ and notably later in Group III than in Group I ($p=0.058$) and Group IV ($p=0.072$). There was no significant trend.
- Renal clearance was significantly greater in Group I than in Groups II and III, $p=0.006$ and $p=0.005$, and significantly higher in Group II than in Group III, $p=0.008$. There was a highly significant trend, $p<0.001$.
- Urinary Recovery was significantly greater in Group I than in Groups II and III, $p=0.012$ and $p=0.008$, and significantly higher in Group II than in Group III, $p=0.008$. There was a highly significant trend, $p<0.001$.

Figure 12.2. E-3174 Mean Plasma Concentrations After Dose Day 7

Mean E-3174 Plasma Concentration (ng/ml)

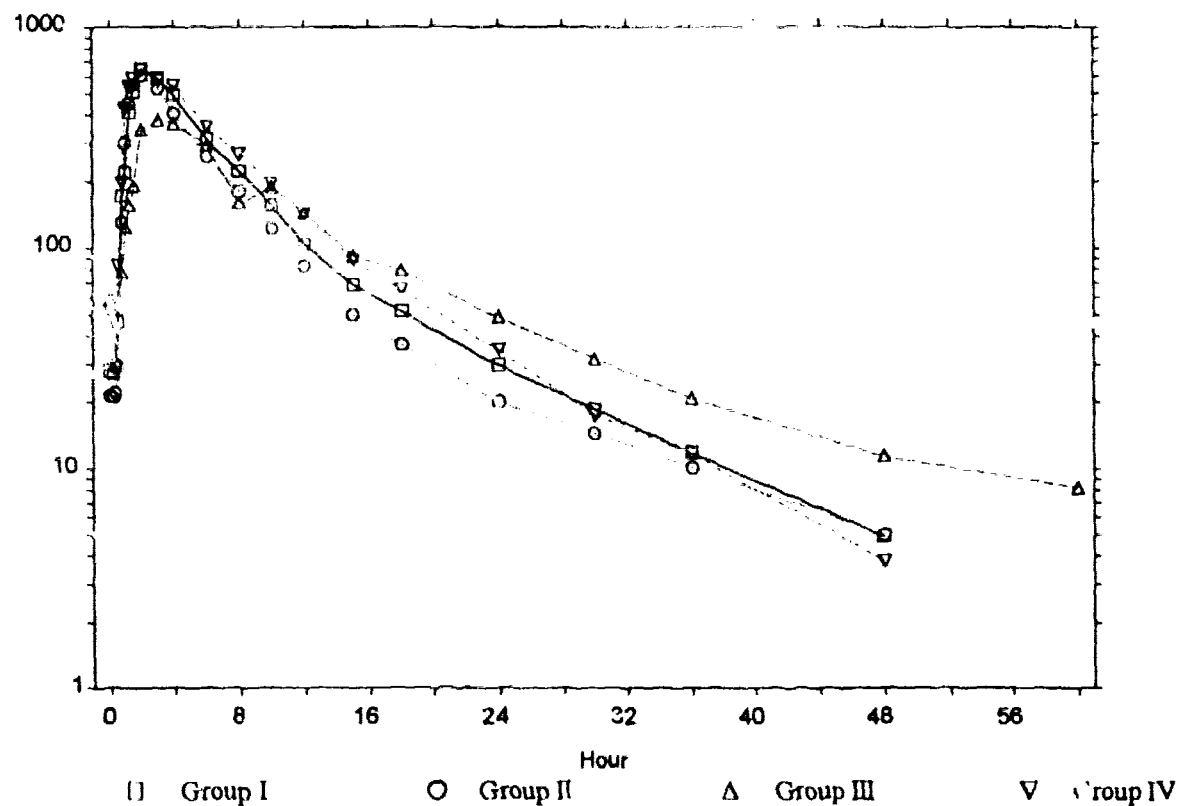


Table 12.5 list the mean losartan and E-3174 concentration during dialysis. Dialysis does not remove losartan or active drug.

Table 12.5. Plasma Concentrations Across Dialyzer - Hemodialysis Patients (Day 6)

Hour Post-Dose	Sampling Location	Mean (S.D.) Plasma Concentrations			
		n	LOSARTAN	n	E-3174
4 ^a	Predialyzer	6	193.0 (191.2)	6	469.4 (419.0)
	Postdialyzer	6	142.7 (151.2)	6	404.5 (422.5)
5	Predialyzer	6	133.5 (152.5)	6	497.4 (466.9)
	Postdialyzer	6	131.8 (141.3)	6	530.4 (508.6)
6	Predialyzer	6	79.4 (83.7)	6	499.1 (496.5)
	Postdialyzer	6	85.1 (88.4)	6	543.6 (569.7)
7	Predialyzer	6	53.6 (56.3)	6	518.3 (592.8)
	Postdialyzer	6	54.4 (54.5)	6	509.7 (549.6)
8	Predialyzer	4	62.7 (59.2)	4	625.0 (681.8)
	Postdialyzer	4	57.8 (59.9)	4	549.9 (558.7)

^a Beginning of dialysis

Table 12.6 Correlation of Pharmacokinetics Parameters with Creatinine Clearance. For Renal Function Groups I, II and III. Day 7 Correlation with Creatinine Clearance

Parameter	LOSARTAN			E-3174		
	n	Corr	p-value	n	Corr	p-value
C _{max} (ng/mL)	17	0.064	0.808	17	0.407	0.105
T _{max} (hr)	7	-0.123	0.637	17	-0.601	0.011
AUC (ng*hr/mL)	17	-0.164	0.529	17	0.252	0.328
t _{1/2} (hr)	16	-0.153	0.572	16	-0.212	0.431
Cl _r (mL/min)	17	0.892**	<0.001	17	0.958**	<0.001
Urinary Recovery (% Dose)	15	0.792**	<0.001	15	0.913**	<0.001

*, ** Correlation coefficient significantly different from zero, p<0.050, p<0.01, respectively.

For all patient groups, SBP and DBP declined with losartan therapy compared to baseline. There was no correlation between change in blood pressure and plasma concentration of losartan or E-3174 on day 7 (for 12 hours post drug administration).

Table 12.7. PRA, Aldosterone and 24-Hour Urine Tests. Day 7.

Parameter	Group I				Group II			
	Baseline		Day 7		Baseline		Day 7	
	n	Mean	Mean	Mean Change	n	Mean	Mean	Mean Change
Aldosterone (ng/mL)	6	12.15	9.57	-2.58	6	17.58	17.97	0.38
PRA (ng/mL/hr)	6	0.81	2.59	1.78*	6	1.45	3.46	2.01*
U 24 hr Protein (mg/24 hr)	6	117.2	43.83	-73.33	6	621.5	363.17	-258.3
U Urea Nitrogen (gm/24 hr)	6	12.04	12.27	0.22	6	9.05	9.58	0.53
Protein/Creatinine	5	0.06	0.02	-0.03	6	0.32	0.21	-0.11
U 24 hr Sodium (mEq/24 hr)	6	159.2	161.67	2.50	6	151.8	165.17	13.33
U 24 hr Creat. (mg/24 hr)	6	1888	1732	-156	6	1327	1361	34.00
Creat. Clearance (mL/min)	6	110.3	117.33	7.03	5	55.07	61.72	6.65
Parameter	Group III				Group IV			
	Baseline		Day 7		Baseline		Day 7	
	n	Mean	Mean	Mean Change	n	Mean	Mean	Mean Change
Aldosterone (ng/mL)	6	38.93	28.72	-10.22	6	48.42	16.98	-31.43
PRA (ng/mL/hr)	6	2.79	6.20	3.41*	6	1.26	3.55	2.29
U 24 hr Protein (mg/24 hr)	6	2092	1607.6	-484.0			N/A	
U Urea Nitrogen (gm/24 hr)	6	7.52	8.05	0.53			N/A	
Protein/Creatinine	6	2.30	1.39	-0.91			N/A	
U 24 hr Sodium (mEq/24 hr)	6	133.7	164.50	30.83			N/A	
U 24 hr Creat. (mg/24 hr)	6	1328	1282	-45.67			N/A	
Creat. Clearance (mL/min)	6	17.13	17.21	0.10			N/A	

Within Group Test Is Signed Rank Test

p<0.05*

p<0.01**

Note: Baseline 24-hour urine was collected on Day -3. Collection began Day 7 for on treatment 24-hour urine values.

PRA/aldosterone measured immediately prior to first dose for baseline and immediately prior to Day 7 dose or on treatment assessment.

Safety Results:

Seven patients experienced adverse events. Table 12.8 lists the adverse experiences.

Table 12.8. Clinical Adverse Experiences

Patient No	Adverse Experience	Renal Group	Study Day of Onset	Intensity
Investigator: Keane (#012001)				
111	Pharyngitis	I	4	Mild
	Laryngitis		4	Moderate
112	Headache	I	1	Mild
121	Stiffness	II	1	Moderate
	Neck Pain		2	Moderate
122	Somnolence	II	3	Moderate
	Somnolence		3	Mild
	Somnolence		7	Mild
131	Flatulence	III	2	Mild
	Muscle Cramp		3	Mild
	Headache		6	Mild
	Dizziness		7	Mild
	Contusion		7	Mild
	Fever		8	Mild
			(Off Drug)	
	Epistaxis		9	Mild
			(Off Drug)	
142	Somnolence	IV	1	Mild
Investigator: Sica (#012002)				
231	Dizziness	III	7	Unknown
	Orthostatic Hypotension		7	Unknown

Study 014. A Single-blind, Longitudinal, Pilot Study to Investigate the Effects of Losartan (DuP 753) on Urinary Protein Excretion in Nondiabetic Patients with Proteinuria

Protocol

Objective: To evaluate the effect of losartan on total urinary protein excretion in nondiabetic patients with ≥ 2.0 gms/24 hours total urinary protein excretion, and mild to moderate hypertension; To evaluate the effect of losartan on the fractional urinary clearance of albumin and IgG.

Design: single-blind, longitudinal, pilot clinical trial, single center (Holland); 4 week placebo baseline period, 8 week treatment period, 4 week washout period.

Population Studied: hypertensive patients with renal nephropathy and proteinuria

Inclusion/Exclusion Criteria: (This is not a comprehensive list.)

To be included in the trial, patients fulfilled the following criteria:

- (1) mild to moderate hypertension [untreated supine diastolic blood pressure (suDBP) of 90-115 mmHg, based upon the mean of the last two baseline determinations of suDBP (i.e., end of Weeks -2 and -1)] and historically documented or renal-biopsy-proven nephropathy;
- (2) non-black;
- (3) at least 21 years of age but <70 years;
- (4) stable proteinuria defined as total urinary protein excretion ≥ 2.0 gms/24 hours based upon the mean of three single 24-hour urine results taken at the end of study weeks -4, -3, and -2. None of the three 24-hour urine results should have been < 1.0 gms/24 hours. [NOTE: Entry eligibility was based on the mean of the Week -4, -3, and -2 results; however, the mean of three 24-hour urine results at the end of Week -1 was used as the baseline value.];
- (5) creatinine clearance of ≥ 60 mL/min based upon the mean of the Week -4, -3, and -2 baseline values [NOTE: Entry eligibility was based upon the mean of Week -4, -3, and -2 creatinine clearances; however, the creatinine clearance calculated based upon the mean of the three collections at the end of Week -1 was used as the baseline value];
- (6) No history of diabetes mellitus.

Treatments: losartan 50 mg daily for the first four weeks and 100 mg daily for the second four weeks.

Trial Description: The trial consisted of a 4 week placebo baseline period, an 8 week treatment period and a 4 week placebo washout period.

Endpoints/Parameters Measured:

Primary efficacy evaluation was based on the effect of losartan on total 24-hour urinary protein excretion in nondiabetic patients with ≥ 2.0 gm/24-hour total urinary protein excretion and mild to moderate hypertension.

Table 14.1. Clinical and Laboratory Evaluation Flowchart

	Day Week -28	Baseline				Treatment								Maintenance			
		-4	-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12
Clinical Evaluations																	
1.	HX/PE	X															
2.	BP/Pulse	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Evaluations																	
3.	Hematology:	X			X	X							X				X
4.	Chemistry																
	Creatinine	X	X	X	X	X							X				X
	Albumin	X			X	X							X				X
	IgG	X			X	X							X				X
	Total Protein	X			X	X							X				X
	Uric Acid	X			X	X							X				X
	Fasting Glucose*	X				X							X				X
	LFTs	X			X	X							X				X
	Lipids*				X	X							X				X

* NOTE: Fasting glucose and lipid profiles were done at the end of Week -1, and on days of the renal function tests (at the end of Weeks 4, 8, and 12). All other labs during the study were nonfasting.

Table 14.2. Clinical and Laboratory Evaluation Flowchart

	Day Week -28	Baseline				Treatment								Maintenance			
		-4	-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12
Clinical Evaluation:																	
5.	24-Hour Urine:																
	Sodium	X	XX	X	X#		X#		X	X#			X			X#	
	Urea Nitrogen	X	X	X	X#		X		X			X	X			X	X
	Tot. Protein	X	X	X	X#		X		X			X	X			X	X
	Creatinine	X		X			X		X			X	X			X	X
6.	Fractional Clearances				X				X				X				X
	Albumin and IgG																
7.	GFR*				X				X				X				X
8.	RBF (PAID)				X				X				X				X
9.	Plasma Renin Activity (PRA) (Supine)		X		X				X				X				X
10.	Creatinine Clearance	X		X	X#				X				X				X
11.	Pregnancy Test				X**				X				X**				X*
12.	Urine Drug Screen (See pg. 41)	X							**								*

NOTE: At the end of Weeks -1, 4, 8 and 12, patients will collect three consecutive daily 24-hour urine collections, the mean of which will be used for baseline (Week -1), and efficacy (Weeks 4, 8 and 12).

* Iothalamate, inulin, or DTPA may be used to determine GFR; however, the method used must be consistent within institution and patient.

** A pregnancy test must be done and negative results obtained within 72 hours prior to the GFRs done at the end of Weeks -1, 4, 8, and 12. Results must be obtained prior to the start of the GFR procedure.

GFR and ERPF were analyzed after adjusting for body surface area (BSA). BSA was calculated using the following formula:

$$BSA (m^2) = (wt. \text{ in kg})^{0.425} \times (ht. \text{ in cm})^{0.725} \times 0.007184$$

GFR and ERPF were both adjusted for the BSA by the following formula: Measurement $\times 1.73/BSA$.

In order to detect a 33% change from baseline in total 24-hour urinary protein excretion (a change of 0.40 on the log scale) with 80% power, 14 patients needed to be enrolled.

Results**Demographics/Disposition:**

Thirteen patients (11 male, 2 female) were enrolled. One patient (# 0001) discontinued following the completion of Week 8 due to a clinical adverse experience. The average age of subjects was 43.3 years (range: 20 - 62). All subjects were caucasian.

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FIRM:

MERCK

4 OF 10

TRADE NAME:

COZAAR (LOSARTAN POTASSIUM) 25/50 MG TAB

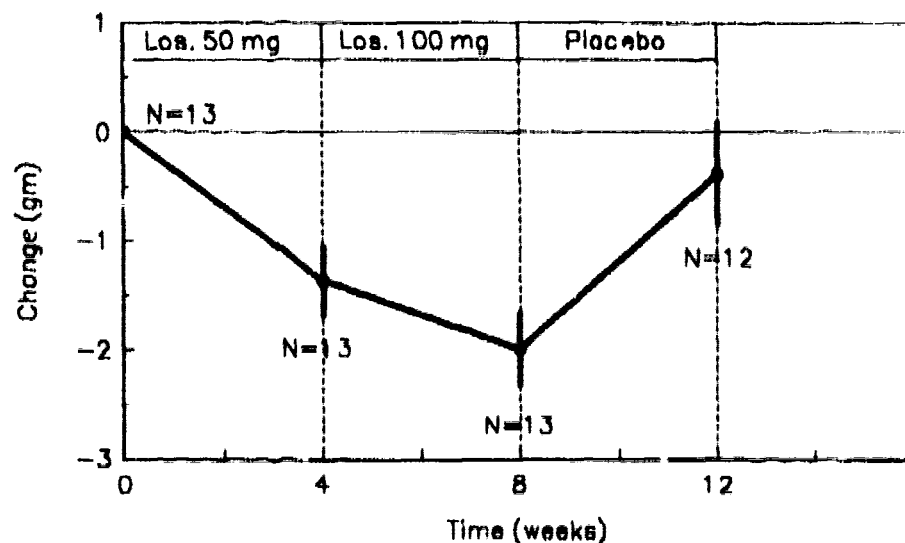
GENERIC NAME:

LOSARTAN POTASSIUM

Efficacy Results:**Table 14.4. Mean 24-Hour Urine Protein (gm) Changes from Baseline.**

Week	N	Baseline			Weekly Response			Change from Baseline			WITHIN GRP COMPARISON
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	
4	13	5.82	4.40	4.23	4.45	3.30	4.27	-1.37	-1.10	1.11	0.000
8	13	5.82	4.40	4.23	3.83	2.80	4.14	-1.99	-1.70	1.18	0.000
12	12	5.99	4.55	4.37	5.61	4.00	4.86	-0.38	-0.80	1.59	0.424

ANALYSIS SPECS: WITHIN GROUP = SIGN RANK, BASED ON RANKS

Figure 14.1.Average ($\pm$ Standard Error) Changes from Baseline of Mean 24 Hr. Urine Protein by Time(Weeks)

Note: All Patients Received Losartan 50 mg for 4 Weeks and 100 mg through Week 8

Table 14.5. Mean Creatinine Clearance (mL/min) Changes from Baseline

Week	N	Baseline			Weekly Response			Change from Baseline			WITHIN GRP COMPARISON
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	
4	13	94.95	90.30	24.76	89.54	90.00	21.22	-5.41	-5.00	13.05	0.174
8	13	94.95	90.30	24.76	90.15	93.00	20.51	-4.79	-7.00	15.70	0.251
12	12	98.44	94.65	22.25	90.58	91.50	19.71	-7.86	-1.00	21.76	0.377

ANALYSIS SPECS: WITHIN GROUP = SIGN RANK, BASED ON RANKS

Table 14.6. ERPF (mL/1.73m²) Change from Baseline

Week	N	Baseline			Weekly Response			Change from Baseline			WITHIN GRP COMPARISON
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	
4	13	271.47	280.84	70.19	296.66	278.43	72.64	25.19	12.00	71.80	0.340
8	13	271.47	280.84	70.19	307.99	287.22	62.33	36.52	22.98	106.11	0.127
12	12	276.50	292.85	70.83	291.96	296.48	40.17	15.46	-0.45	94.44	0.850

ANALYSIS SPECS: WITHIN GROUP = SIGN RANK, BASED ON RANKS

Table 14.7. Filtration Fraction (%) Changes from Baseline

Week	N	Baseline			Weekly Response			Change from Baseline			WITHIN GRP COMPARISON
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	
4	13	21.321	23.707	4.774	19.119	19.641	3.570	-2.201	-2.443	1.927	0.005
8	13	21.321	23.707	4.774	18.584	19.304	3.214	-2.736	-2.775	2.365	0.003
12	12	21.470	23.831	4.955	21.632	23.496	4.605	0.162	-0.037	1.631	0.970

ANALYSIS SPECS: WITHIN GROUP = SIGN RANK, BASED ON RANKS

Table 14.8. Blood Pressure Diastolic, Supine (mmHg) Changes from Baseline

Week	N	Baseline			Weekly Response			Change from Baseline			WITHIN GRP COMPARISON
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	
4	13	94.31	96.00	6.73	81.08	80.00	7.40	-13.23	-15.00	6.30	0.000
8	13	94.31	96.00	6.73	78.00	77.00	8.35	-16.31	-15.00	7.16	0.000
12	12	94.67	96.00	6.89	90.08	90.50	7.88	-4.59	-6.50	4.78	0.016

ANALYSIS SPECS: WITHIN GROUP = SIGN RANK, BASED ON RANKS

Table 14.9. Blood Pressure Systolic, Supine (mmHg) Changes from Baseline

Week	N	Baseline			Weekly Response			Change from Baseline			WITHIN GRP COMPARISON
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	
4	13	152.77	154.00	13.41	135.69	133.00	15.31	-17.08	-18.00	13.51	0.001
8	13	152.77	154.00	13.41	133.62	129.00	13.81	-19.15	-17.00	12.19	0.001
12	12	154.00	155.50	13.22	155.00	154.00	17.76	1.00	1.00	13.26	0.984

ANALYSIS SPECS: WITHIN GROUP = SIGN RANK, BASED ON RANKS

Table 14.10. PRA (nmol/L/h) Changes from Baseline

Week	N	Baseline			Weekly Response			Change from Baseline			WITHIN GRP COMPARISON
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	
4	13	1.71	1.10	1.59	5.59	4.70	4.21	3.88	3.50	3.20	0.001
8	13	1.71	1.10	1.59	9.02	5.90	7.39	7.32	5.10	7.02	0.002
12	12	1.78	1.15	1.64	2.17	2.10	1.72	0.38	0.75	1.62	0.258

ANALYSIS SPECS: WITHIN GROUP = SIGN RANK, BASED ON RANKS

Safety Results

Patient #0001 withdrew after eight weeks of therapy due to adverse experience. It is not clear what adverse events caused patient #0001 to withdraw.

Six patients experienced clinical adverse events. Patient #0005 experienced a syncopal episode on day 38 which lasted for 10 minutes. Two patients (#0003 and #0008) had edema/swelling while receiving losartan which apparently resolved after approximately 1 week despite continued losartan therapy. Seven patients had laboratory values outside of pre-defined parameters. Only one patient (#0003) had lab abnormalities of clinical relevance. Patient #0003 had decreases in hemoglobin/hematocrit and increases in transaminases while receiving losartan. On day 54, ALT = 112 U/L (baseline ALT = 38 U/L), AST = 105 U/L (baseline AST = 30 U/L) and hemoglobin 10.8 Gm/dl (baseline hgb. = 13.8 gm/dl). ALT and AST returned to baseline on placebo. Hemoglobin remained stable (10.3 Gm/dl) on placebo.

Study 059. A Multicenter Study to Investigate the Safety and Antihypertensive Efficacy of Losartan (MK-954, DuP 753) in Patients with Severe Hypertension

This is an open label, uncontrolled multi-center, international (U.S., Europe and S. America) trial in patients with a history of severe hypertension (defined as DBP $\geq$ 115 mmHg). For enrollment, patients had to have either an untreated sIDBP 115 - 125 mmHg or a documented history of severe hypertension (sIDBP $\geq$ 115 mmHg) with a currently treated sIDBP of 96-125 mmHg (measured at the trough of the dosing interval) while receiving at least one antihypertensive agent. After discontinuing medications for at least 48 hours, the sIDBP must have remained 96-125 mmHg and not have increased by more than 15 mmHg from the sIDBP on therapy. Fifty percent (50%) of the patients enrolled must have sIDBP 115-125 mmHg

immediately prior to the first dose of losartan. Patients qualified for the study based on medical history, the results of a complete physical examination, routine laboratory evaluation, electrocardiogram (ECG), chest x-ray, and blood-pressure measurement (Visit 1). Patients were seen in the clinic after 1 week of treatment with losartan 50 mg once-daily (Visit 2) for a safety evaluation. Dosage adjustment was not planned at Visit 2 unless the patient's SiDBP was ≥ 105 mmHg and it was clinically indicated. At Visit 3, after 2 weeks of losartan therapy, the dose of losartan was increased to 100 mg once daily, if SiDBP ≥ 95 mmHg. At Visit 4, after 4 weeks of losartan therapy, hydrochlorothiazide (HCTZ) 12.5 mg once daily was added, if SiDBP ≥ 95 mmHg. At Visit 5 (Week 6), HCTZ was increased to 25 mg once daily, if SiDBP ≥ 95 mmHg. Atenolol 50 mg or a calcium channel blocker (felodipine ER 5 mg at U.S. study sites) once daily was added at Visit 6 (Week 8), if SiDBP ≥ 95 mmHg. The final dosage adjustment was made at Visit 7 (Week 10) at which time atenolol was increased to 100 mg (or the calcium channel blocker was increased to the next higher dose, felodipine ER was 10 mg) once daily, if SiDBP ≥ 95 mmHg. Patients were treated for a total of 12 weeks. Table 59.1 lists the procedures performed during the study.

Table 59.1. Clinical and Laboratory Measurements

Visit Week	Screening ¹	Treatment							
		2 1	3 2	4 4	5 6	6 8	7 10	8 12	
Medical History	X								
Physical Examination	X								X
Sign Informed Consent	X								
Medication:									
Withdrawal ²	X								
Losartan		X	X	X	X	X	X	X	X
Clinical Evaluation ³	X ^{1a}	X	X	X	X	X	X	X	X
Laboratory Evaluation ⁴	X		•	•	•	•	•	•	X
ECG	X								X
Chest X-ray ⁵	X								
Dose Titration ⁶			X	X	X	X	X	X	
AE Evaluation		X	X	X	X	X	X	X	X

¹ Visit 1 - Treated patients may have required more than one actual visit to the clinic to complete all of the evaluations.
^{1a} Visit 1 - If the patient discontinued prior to completion of this visit, all evaluations were performed.
² Medication Withdrawal - patients were instructed to stop all existing antihypertensive therapy for at least 48 hours prior to the first dose of losartan.
³ Clinical Evaluation - included measurement of blood pressure, heart rate, and body weight at trough (22 to 26 hours after the previous dose of losartan).
^{3a} At Visit 1, blood pressure was measured at one hour intervals until 2 consecutive measurements of SiDBP at one-hour intervals were within 7 mmHg. The patient then entered the treatment period and received the first dose of losartan. The baseline blood-pressure margin measurement was obtained immediately prior to the first dose of losartan.
⁴ Laboratory Evaluation - included hematology, blood chemistry and urinalysis. A laboratory evaluation was performed at the end of the losartan monotherapy period (*). An additional laboratory evaluation was required at the next visit after addition of HCTZ (*), after an increase in dose of HCTZ (*), at the end of the study (Visit 8), or at the time of premature discontinuation.
⁵ Chest X-ray - was performed if one was not available from within the previous 6-month period.
⁶ * if SiDBP ≥ 95 mmHg. Visit 3 - losartan 100 mg. Visit 4 - add HCTZ 12.5 mg. Visit 5 - increase to HCTZ 25 mg. Visit 6 - add atenolol 50 mg or calcium channel blocker. Visit 7 - Double Dose of atenolol or calcium channel blocker.

There was no primary endpoint listed in the protocol of this trial. The primary objective of the study was to determine whether losartan is safe and effective in controlling blood pressure either alone or in combination with other agents. Blood pressure changes after 4 and 12 weeks treatment were used to assess efficacy.

Results

Demographics and Disposition

One hundred eighty (180) patients entered at 21 centers. The number of patient entered per center ranged from 0 - 20 with a median of 10. Table 59.2 lists the demographic characteristics of the enrolled patients.

Table 59.2. Demographic Data

		N	%
TOTAL PATIENTS		180	
SEX	MALE	96	-53%
	FEMALE	84	-47%
AGE (YRS.)	MEAN +/- (STD)	51.3 +/- (10.122)	
	RANGE	23.0 - 72.0	
ORIGIN	CAUCASIAN	122	-68%
	BLACK	34	-19%
	ASIAN	3	-2%
	HISPANIC	13	-7%
	SPANISH	1	-1%
	MESTIZO	7	-4%

The number of patients on multi-drug therapy for hypertension is not readily accessible. Table 59.3 lists the disposition of patients in the trial. Nine patients withdrew prematurely from therapy. The majority of patients completed the study and continued into an extension period.

Table 59.3. Patient Disposition

TOTAL PATIENTS ENTERED	180
PATIENTS COMPLETED ACUTE PHASE CONTINUING INTO EXTENSION	159
PATIENTS COMPLETED ACUTE PHASE NOT CONTINUING INTO EXTENSION	12
TOTAL DISCONTINUED	9
CLINICAL ADVERSE EXPERIENCE	5
LOST TO FOLLOW-UP	1
THERAPY INEFFECTIVE	1
CLINICAL AE & ECG AE	1
PATIENT WITHDREW	1

Table 59.4 lists the patients withdrawn and the reason for withdrawal.

Table 59.4. Patient Withdrawals

Number	Reason Discontinued	Day Discontinued
5673	Clinical AE	8
5729	Clinical AE	12
5501	Clinical AE	29
5708	Clinical AE	42
5523	Clinical AE	73
5528	Lost To Follow-up	21
5680	Therapy Ineffective	9
5725	Clinical AE & ECG AE	50
5517	Patient Withdrew	3

Efficacy

Table 59.5 shows the mean change in siDBP and siSBP over the treatment period.

Table 59.5. Trough siDBP and siSBP. (All Patients Treated Analysis)

Trough siDBP	WEEK	N	Baseline		Treatment		Change	
			Mean	S.D.	Mean	S.D.	Mean	S.D.
	2	177	112	7.7	104.8	10	-7.3	8.7
	4	172	111.9	7.7	102.6	11.1	-9.3	10.2
	8	170	111.8	7.7	95.9	9	-15.9	7
	Final Visit	179	112	7.7	93.1	9.4	-18.9	10.3
Trough siSBP								
	2	177	171.4	16.6	164.5	21.9	-6.9	16.4
	4	172	171.6	16.7	160.3	20.9	-11.3	17.5
	8	170	171.6	16.6	149.1	18	-22.5	17.4
	Final Visit	179	171.5	16.6	145.8	20.1	-25.7	20.2

Table 59.6 lists the number of patients at each visit by the treatment received at that visit. Since titration was not required unless sDBP was ≥ 95 mmHg, the number of patients requiring triple drug therapy at the end of 12 weeks may be underestimated if a "normal blood pressure" (sDBP < 90 mmHg) had been the goal.

Table 59.6. Number of patients on each treatment by week.

Week	L	L/H	L/A/A	L/L/F	L/L/A/F	other	Total
2	174	3	0	0	0	0	177
4	135	37	0	1	0	0	173
8	42	100	4	22	0	L/F = 2	170
Final	39	54	19	56	8	H = 1 L/F = 1 L/A = 1	179

L = losartan, H = hydrochlorothiazide, A = atenolol, F = felodipine

Subgroup analysis were performed by the sponsor based demographic variables. It is difficult to interpret this data due to the open label design of this trial.

Safety

Fifty-eight percent of the patients experienced a event; but less than 2% were considered serious. Table 59.7 compares the possible treatment regimens with regard to the incidence of adverse events.

Table 59.7. Incidence of Adverse Events Based on Treatment Regimen

	Losartan N=180	Losartan/HCTZ N=142	Losartan/HCTZ/ Other N=85	Other N=24	Combined N=180
Number of Patients (%)					
With One or More Adverse Experiences	79 (43.9%)	46 (32.4%)	27 (31.8%)	4 (16.7%)	105 (58.3%)
With Serious Adverse Experiences	1 (0.6%)	1 (0.7%)	0	1 (4.2%)	3 (1.7%)
Withdrawn Due to Adverse Experiences	3 (1.7%)	2 (1.4%)	0	1 (4.2%)	6 (3.3%)
Who Died	0	0	0	0	0
With Drug-Related Adverse Experiences	28 (15.6%)	17 (12.0%)	11 (12.9%)	2 (8.3%)	45 (25.0%)
Note: The number of adverse experiences in the treatment groups does not sum up to the number in all patients combined because the same patient may have received different treatments at different times and thus could be counted more than once.					
Other: The "Other" group includes all reports of adverse experiences when the patient was not on a regimen defined in the protocol.					

The most common adverse experiences for these treatment regimens are outlined in table 59.8.

Table 59.8. Adverse Experiences Based on Treatment Regimen

	Losartan N=180 (%)	Losartan/HCTZ N=142 (%)	Losartan/HCTZ/ Other N=85 (%)	Other N=24 (%)	Combined N=180 (%)
Nervous System					
Headache	37 (20.6)	13 (9.2)	6 (7.1)	0	47 (26.1)
Dizziness	7 (3.9)	8 (5.6)	5 (5.9)	1 (4.2)	18 (10.0)
Body as a Whole					
Asthenia/Fatigue	5 (2.8)	5 (3.5)	2 (2.4)	0	12 (6.7)
Septicemia	0	0	0	1 (4.2)	1 (0.6)
Syncope	0	0	0	1 (4.2)	1 (0.6)
Respiratory System					
Cough	4 (2.2)	4 (2.8)	0	0	8 (4.4)
Hemoptysis	0	0	0	1 (4.2)	1 (0.6)
Infection, Upper Respiratory	6 (3.3)	2 (1.4)	2 (2.4)	0	10 (5.6)
Digestive System					
Diarrhea	5 (2.8)	3 (2.1)	2 (2.4)	0	9 (5.0)
Musculoskeletal System					
Pain, Knee	2 (1.1)	1 (0.7)	1 (1.2)	1 (4.2)	3 (1.7)
Arthralgia	0	0	0	1 (4.2)	1 (0.6)
Cardiovascular System					
Palpitation	2 (1.1)	2 (1.4)	1 (1.2)	1 (4.2)	6 (3.3)
Premature Beat	0	0	0	1 (4.2)	1 (0.6)
Pulse Abnormality	0	0	0	1 (4.2)	1 (0.6)

Note: The number of adverse experiences in the treatment groups does not add up to the number in all patients combined because the same patient received different treatments at different times and thus could be counted more than once

Other: The "Other" group includes all reports of adverse experiences when the patient was not on a regimen defined in the protocol

Six patients were withdrawn from therapy for adverse events. Table 59.9 lists the patients and the adverse events that they experienced during therapy.

Table 59.9. Patients Withdrawn due to Adverse Events

Number	Adverse Experience	Therapy	Start Day	Stop Day
5501	SEIZURE DISORDER	losartan	29	29
5525	DIARRHEA	losartan	11	12
	ACNE		11	16
	DIARRHEA	Los/H	60	64
	PNEUMONIA		70	76
	ACNE		71	76
	RASH		74	76
	HYPOTENSION		75	76
	HYPOCALCEMIA		76	
	HYPOKALEMIA		76	
	HYPONATREMIA		76	
	HYPOPHOSPHATEMIA		76	
	HYPOPROTEINEMIA		76	
	LEUKOCYTE COUNT INCREASED		76	
	SERUM CREATININE INCREASED		76	
	SINUS TACHYCARDIA		76	
	TOTAL SERUM BILIRUBIN INCREASED		76	
5675	DIZZINESS	losartan	1	8
	HEADACHE		1	8
	ANXIETY		8	9
	VERTIGO		8	9
5708	PROTEINURIA	Los/H	29	
	PARESTHESIA		32	43
	WEAKNESS, MUSCLE		32	43
	FASTING BLOOD GLUCOSE INCREASED		43	
	GLYCOSURIA		43	
5725	HEADACHE	losartan	1	2
	GLYCOSURIA		29	
	HEMATURIA		29	
	PREMATURE VENTRICULAR CONTRACTION	Los/H	48	
	PALPITATION		48	48
	SYNCOPE		48	48
	PREMATURE BEAT		48	55
	PULSE ABNORMALITY		48	55
	PALPITATION		49	55
5729	DEPRESSION	losartan	10	15
	PAIN, ABDOMINAL		12	12
	PAIN, BACK		12	12

Patient 5501 is a 38-year-old male patient with severe hypertension, hypothyroidism and a history of epilepsy and recent weight loss (350 lbs to 336 lbs) was treated with losartan 50 to 100 mg for 29 days during the acute phase of the study when he experienced a grand mal seizure while at home upon rising from the dinner table. The patient reported that he had epilepsy in the past and that he had not had any grand mal seizures for the last 20 years although he had not taken any antiepileptic medications for the past 20 years. The patient recovered completely within 3 minutes, sustained no injury and did not seek medical help. He was seen in the clinic the day after the event at which time he reported feeling well and was observed to be neurologically intact. The patient was discontinued at this time. The patient stated that he was on an aggressive weight-reduction diet which led to 14 pound weight loss in the previous 2 weeks.

Patient 5725 is a 57-year-old female patient with severe hypertension had been treated with losartan 50 to 100 mg alone for 28 days and then concurrently with HCTZ 12.5 mg for an additional 20 days (study Day 48) when she experienced palpitations and syncope; blood pressure was 187/115 mmHg. Pulse abnormality (irregular pulse) and premature beats were noted on physical examination. An ECG revealed left ventricular hypertrophy with ventricular extrasystoles (PVCs). The patient was hospitalized. Routine blood chemistry showed serum chloride and potassium to be normal. Therapy with losartan and HCTZ was continued with atenolol 25 mg once-daily added to treat the pulse abnormality. Two days later, a repeat ECG revealed an increased number of extrasystoles of more than 30/min. Study therapy with losartan and HCTZ was discontinued as was therapy with atenolol. Therapy with verapamil 240 mg daily and amiodarone 600 mg daily was commenced. Three days after discontinuation, a follow-up ECG revealed no arrhythmia.

Patient 5525 is a 44-year-old male patient with severe hypertension and a history of shortness of breath had been treated with losartan 50 to 100 mg alone for 11 days and then concurrently with HCTZ 12.5 to 25 mg for an additional 49 days (study day 60) when he experienced diarrhea. Ten days later, study day 70, he developed pneumonia. On study day 71, he noticed acne around his mouth followed three days later by a red spotty rash around his neck. On study day 75, the patient experienced hypotension, tachycardia, and gross hematuria followed the next day by hemoptysis. The patient was seen in the

clinic on study day 76 at which time he was observed to be short of breath, pale with a blood pressure of 100/68, pulse 110 and rales and rhonchi over the middle lobe of the right lung. An x-ray showed right middle lobe infiltrate. He was diagnosed with pneumonia and possible sepsis and was hospitalized. Therapy with losartan and HCTZ was discontinued. The patient recovered.

Forty-one patients were noted to have experienced laboratory adverse experiences. Table 59.10 lists some patients with clinically relevant lab abnormalities.

Table 59.10.

Patient #	Test	Baseline Test	Abnormal Test	Day of Test	Comment
5525	creatinine	1.1 mg/dl	1.7 mg/dl	76	Patient on L/H. For most labs, returned to normal off drug. Patient septic.
	phosphorus	4.2 mg/dl	1.7 mg/dl	76	
	potassium	4.8 Meq/L	2.8 Meq/L	76	
	sodium	134 Meq/L	127 Meq/L	76	
	WBC	9,200 /mm ³	22,600 /mm ³	76	
	total Bilirubin				Increased, but not in CANADA
5565	creatinine	1.0 mg/dl	1.8 mg/dl	80	On L/H/I; remained elevated on therapy
5561	eosinophils	2%	9%	89	
5604	total bilirubin				Increased, but not in CANADA. Other LFT not abnormal. On L/H
5605	total bilirubin				Increased, but not in CANADA. ALT and AST mildly elevated.
5606	eosinophil	2%	10%	106	WBC = 5,500/mm ³
	total bilirubin				Increased, but not in CANADA
5703	total bilirubin				Increased, but not in CANADA
5607	BUN	29 mg/dl	57 mg/dl	92	
	creatinine	.8 mg/dl	1.2 mg/dl	92	On L/H/A/N
5614	hemoglobin	12.7 g/dl	10.0 g/dl	103	On L/H/AM
5712	potassium	3.8 Meq/L	3.0 Meq/L	87	On L/H
5724	potassium	4.6 Meq/L	3.0 Meq/L	71	On L/H, K up to 3.6 at day 83.

L = losartan, H = HCTZ, F = felodipine, A = atenolol, I = isradipine, N = nifedipine, AM = amlodipine

Long Term Therapy Studies. Protocols 011, 021, 049, 050 and 054 Open Label Follow-Up.

The sponsor has summarized the long term open label follow-up studies of protocols 011, 021, 049, 050 and 054 in a single clinical summary report. The data presentation in this report was divided according to duration of treatment with losartan in the following categories: (1) experience in patients treated with losartan for less than 6 months, (2) experience in patients treated with losartan for at least 6 months but less than a year, and (3) experience in patients treated with losartan for a year or more. The double-blind portion of protocols 011, 021 and 050 are summarized separately in the review of NDA 20-386. Protocols 049 and 054 are reviewed separately in Dr. Knudson's review of NDA 20-387.

At the beginning of the open-label extensions, patients were transferred from their double-blind therapy (either losartan, losartan/HCTZ, placebo, or active control agent) to open-label losartan or losartan/HCTZ. Clinical assessments varied between protocol and are outlined in table LTF 1.

Table LTF 1. Clinical and Laboratory Measurements in Extensions

Parameter	Protocol	Frequency
Clinic visit, Vital signs (trough)	011	Monthly
	021	Every 2 months
	049	Every 2 months (every 3 months after first year)
	050	Every 3 months
	054	First month, then every 2 months
Adverse Experience Assessment	011	Monthly
	021	Every 2 months
	049	Every 2 months (every 3 months after the first year)
	050	Every 3 months
	054	First month, then every 2 months
Laboratory Evaluation	011	First month, then every 2 months
	021	Every 6 months
	049	Month 4, then every 6 months (every 6 months after the first year)
	050	Month 4, then every 6 months
	054	Month 4, then every 6 months
Electrocardiogram	011	Every 3 months
	021	Every 6 months
	049	Month 4, then every 6 months (annually after the first year)
	050	Month 12
	054	Month 4, then every 6 months
Physical Examination	All	Annually

The dosage titrations employed in the extension protocols are shown in table LTF 2

Table LTF 2. Dosage Titration Steps in Study Extensions

Protocol	Titration Steps (All dosages in mg)
011	Los 50 → Los 100 → Los 150 → Los 100/HCTZ 12.5 → Los 150/HCTZ 12.5 → Los 150/HCTZ 25 → Los 150/HCTZ 50
021	Los 50 → Los 50/HCTZ 12.5 → Los 50/HCTZ 25 → Los 50/HCTZ 25 + calcium channel blocker
049	Los 50 → Los 50/HCTZ 6.25 → Los 50/HCTZ 12.5 → Los 50/HCTZ 25 → Los 50/HCTZ 25 + Felodipine 5 → Los 50/HCTZ 25 + Felodipine 10
050	Los 50 → Los 50/HCTZ 6.25 → Los 50/HCTZ 12.5 → Los 50/HCTZ 12.5 + Felodipine 5 → Los 50/HCTZ 12.5 + Felodipine 10
054	Los 50/HCTZ 6.25 → Los 50/HCTZ 12.5 → Los 50/HCTZ 12.5 + Felodipine 5 → Los 50/HCTZ 12.5 + Felodipine 10
Los = losartan	HCTZ = Hydrochlorothiazide

In Protocol 011, all dosage titrations could be made at 2-week intervals. In the other protocols, the initial step was to last 4 weeks, then the remaining steps could be made at 2-week intervals. In Protocols 021, 049, 050, and 054, dosage titrations were to be performed if the trough sitting diastolic blood pressure was ≥ 90 mmHg. In Protocol 011, dosage titrations could be performed if the trough supine diastolic blood pressure was > 90 mmHg.

Results

Demographics and Disposition

Six-hundred and fifty-nine of the original 2071 patients randomized in these trials continued into open label studies. Table LTF 3 lists the number of patients contributed from each study.

Table LTF 3.

Protocol #	# of patients randomized into double blind period	# of patients continuing into open label
011	576	307
021	122	9
049	304	102
050	366	193
054	703	48
Total	2071	659

The demographics of the patients in the long term open label studies is listed in table LTF 4. This table includes all patients receiving any dose of losartan +/- combination therapy. Losartan treatment exposure (< 6 months, 6 - 12 months, >12 months) includes double blind exposure for those randomized to losartan therapy in the double blind portion of the trials. Six hundred and thirteen of the 659 patients received losartan alone at some time point during the open label extension period. Forty-six of 48 patients in study 054 started on losartan/HCTZ at the beginning of the open label period (see table LTF 2 for the titration scheme for study 054).

Table LTF 4. Demographic Data - Patients Treated with Losartan (with or without HCTZ or other therapy) in Extensions.
[Time of Follow-up determined as of 3/31/93]

		Losartan for <6 Months	Losartan for >6 Months but <1 Year	Losartan for 1 Year or More	Total
Total Patients		127	226	306	659
Sex	Male	98	150	195	433
	Female	39	76	111	226
Age (yrs)	< 36	9	11	22	42
	36-45	34	42	53	129
	46-55	43	71	97	211
	56-64	25	66	85	176
	65-74	13	35	43	91
	>75	3	1	6	10
	Mean (SD)	51.0 (10.8)	53.6 (10.8)	53.1 (11.1)	52.9 (11.0)
	Median	50	54	53	53
Range	28-77	26-77	25-88	25-88	
Race	Black	13	29	33	75
	Non-Black	114	197	273	584
Duration of Disease (yrs)	<1	1	7	13	21
	1 to 5	35	77	89	201
	>5 to 10	39	47	80	166
	>10	52	95	124	271
	Mean (SD)	10.9 (8.2)	10.7 (8.9)	10.1 (7.5)	10.4 (8.1)
	Median	9	9	9	9
	Range	0.5-46.0	0.08-44.0	0.08-38.0	0.08-46.0
Reasons Discontinued*	Total	81	71	17	169
	Clinical AE	20	26	7	53
	Laboratory AE	2	2	0	4
	Therapy Ineffective	32	23	2	57
	Protocol Deviation	2	1	0	3
	Lost to Follow-up	8	7	1	16
	Patient Withdrew	14	7	6	27
	Other/Pt Uncooperative	3	5	1	9

*Note: Some patients had adverse experiences that began in the double-blind study, continued during the extension, and resulted in the patient being discontinued during the extension. These patients were not counted in this report. The time of exposure included the double blind treatment period in those who were randomized to losartan.

The exposure to losartan therapy in the extension phase either alone or of any combination is presented in table LTF 4a.

LTF 4a.

Patient Exposure to Losartan +/- other anti-hypertensive therapy. N = 659. [Does not include double-blind exposure]

Total Days on losartan in Extension	166,127
Mean # of Days on Losartan	252
Median # of Days on Losartan	272
Range of Days exposed to Losartan	6 - 635

It is of interest to separate those out who were exposed to losartan alone at some time in the open label extension. Six-hundred and thirteen patients were on losartan therapy alone for at least part of the extension period. Table LTF 4b lists the exposure to losartan alone.

LTF 4b.

Patient Exposure to Losartan Alone. N = 613. [Does not include double-blind exposure]

Total Days on losartan Alone in Extension	75,725
Mean # of Days on Losartan Alone	123
Median # of Days on Losartan Alone	Not able to compute in CANDA
Range of Days exposed to Losartan Alone	Not able to compute in CANDA

The WMA CANDA database lists 170 patients (from the Merck clinical summary the number is 169) discontinuing the study prematurely. Table LTF 4c lists the number of withdrawals from each study and the reason for withdrawal. The additional patient in the WMA database (compared to the clinical summary report) was a clinical adverse experience. A complete list of premature withdrawals and the reason for withdrawal can be found in the appendix.

Table LTF 4c. Reason for Withdrawal from Open Label Extensions.

Reason Discontinued	Study 011	Study 021	Study 049	Study 050	Study 054	Total
Clinical AE	28	.	9	16	1	54
Lab AE	2	.	.	2	.	4
Lost to Follow-up	11	1	2	2	.	16
Protocol Deviation	1	.	2	.	.	3
Patient Uncooperative	5	.	.	1	.	6
Therapy Ineffective	29	.	16	12	.	57
PATIENT WITHDREW	13	.	6	7	1	27
OTHER	1	.	1	1	.	3
TOTAL	90	1	36	41	2	170

Efficacy

The mean changes in DBP and the response rates at 6 and 12 months of therapy suggest that losartan +/- combination therapy lowers blood pressure. The sponsor's clinical summary reports the changes in mean DBP from baseline and from the end of the double blind treatment period for each study. The summary tables for changes in DBP from baseline can be found in the appendix.

Safety (from WMA database)

Two patients died during the long term open label portions of the trials. Table LTF 5 lists the patients who died

Table LTF 5. Serious Fatal Clinical Adverse Experiences (Patients Treated with Losartan in Extensions)

Study #	Patient #	Sex/Age	Treatment	Daily Dose (mg)	Study Day of Onset	Adverse Experience
011-009	0174	M70	L	100	89	CVA
					89	Corn
050-023	2414	M46	L/H	50/6.25	244	Cerebral aneurysm

Patient #0174 in study 011 was a 70 year old hypertensive male was hospitalized on 4/30/91 for what appeared to be a stroke. A CT scan of the brain showed a hemorrhagic infarct of the mid-brain. The patient did not recover consciousness and was kept alive via life-support (respirator) until 5/1/91. An EEG done on 5/1/91 showed extremely depressed brain function. It was the opinion of the consulting neurologist that the patient was beyond recovery and advised the family accordingly. The family chose to discontinue life-support at that time. No spontaneous respiratory activity was noted, and the patient died at 7:45 PM on 5/1/91. The patient had been treated for moderately severe hypertension since 1975. He had no other known complications from hypertension; his only abnormal findings were an S4 on physical examination and a L.AHB and RBBB on EKG. At the time of the adverse event, the patient was taking losartan 100 mg q.d. and was last seen in the clinic on 22/APR91 (Supine BP = 167/100 mmHg, standing BP = 162/110 mmHg). The patient was taking no other concomitant medication. Patient #2414 in study 050 was a 46-year-old hypertensive male with ankylosing spondylitis, hypercholesterolemia, and back pain, and a history of cigarette smoking, who collapsed at home on 12/7/92. Despite medical intervention, he was pronounced dead. The cause of death was found to be a ruptured cerebral aneurysm. At the time of the event the patient was receiving losartan/LICTZ 50/6.25 mg, and ibuprofen.

Fifty-four patients withdrew from the study due to clinical adverse experiences and four patients for laboratory adverse experiences. Table LTF 6 lists the patients withdrawn due to clinical adverse experience. Table LTF 7 lists the patients withdrawn due to laboratory adverse experiences. Patient # 493 is listed in both tables. Patient #322 (protocol 011; losartan 100 mg) is a 51 year old Caucasian male who experienced sloughing of the skin (eschar) on day 265 which resulted in

withdrawal. In the sponsor's clinical summary (table 87a in CSR), this patient is listed as withdrawing due to impotence. Further clarification is provided by the sponsor. On study day 265, the patient requested withdrawal due to decreased libido. On examination, the patient had "eschar" on the lower extremities. It is unclear whether the eschar was related to losartan therapy. Patient #0493 (study 011; losartan 100 mg/HCTZ 12.5 mg) appears to have withdrawn due to an acute attack of gout. Patient #8815 (study 054; losartan 50 mg/HCTZ 12.5 mg/felodipine 5 mg) experienced flushing in addition to depression. Patient #648 (Study 011; losartan 50 mg/100mg) withdrew due to weight of loss of 30 pounds. This patient was not included in table 87a. The evaluation for weight loss was ongoing. Patient #2248 (Study 050; Losartan 50 mg) was discontinued because of muscle aches and joint swelling. This patient was not included in table 87a.

Table LTF 6. Patients Withdrawn Due to Adverse Experiences (from table 87a of sponsor's clinical summary report)

Protocol #	Patient #	Sex/ Age	Treatment	Daily Dose (mg)	Study Day of Onset	Relative Day Discontinued	Adverse Experience	Serious	Resolved
011-004	0068	F62	L	100	114	117	Arthralgia	No	Yes
011-005	0095	M51	L	100	108	108	Angina pectoris Supraventricular tachycardia	Yes Yes	Yes Yes
011-005	0097	M67	L	100	269	269	Atrial fibrillation	No	Yes
011-009	0170	F53	L/H	100/12.5	160	164	Rash	No	Yes
011-009	0172	M60	L	50	581	589	Rash	No	No
011-009	0174	M70	L	100	89	89	CVA Coma	Yes Yes	Yes Yes
011-013	0260	F71	L	50	108	150	Arrhythmia Dyspnea	No No	No No
011-014	0276	F53	L/H	100/12.5	291	296	Dizziness Nausea	No No	No No
011-016	0322	M51	L	50	97	265	Libido decreased	No	No
011-017	0339	F53	L	150	111	132	Asthenia/fatigue	No	Yes
011-018	0365	M60	L	100	86	90	Depression	No	Yes
011-020	0402	M48	L/H	100/12.5	176	178	Myalgia	No	Yes
011-020	0406	F48	L	150	113	114	Rash	No	No
011-020	0407	M50	L/H	150/25	155	162	Impotence	No	Yes
011-024	0493	M71	L/H	100/12.5	175	181	Edema/swelling Erythema Toe pain	No No No	Yes Yes Yes
011-025	0510	M40	L	50	534	553	Hearing loss	Yes	No
011-025	0519	M63	L	50	561	563	Rash	No	No
011-028	0579	M70	L/H	150/12.5	350	364	Chest pain	No	No
011-	0648	M44	L	50/100	7	88	Weight loss		No
011-031	0644	M51	L/H	100/12.5	323	383	Exertional dyspnea Chest pain	No No	No No
011-031	0646	M34	L/H	150/12.5	128	133	Nocturia Urinary frequency	No No	Yes Yes
011-032	0666	F58	L	100	66	72	Neoplasm, skin, malignant	Yes	No
011-036	0740	F39	L	50	70	79	Chest pain Dyspnea	No No	Yes Yes
011-037	0764	M44	L	150	206	266	Impotence	No	No
011-037	0766	M53	L	100	206	218	Prostate disorder	No	No
011-038	0783	M61	L/H	100/12.5	218	280	Diarrhea	Yes	Yes
011-039	0818	M53	L	50	419	419	Dyspnea Atrial fibrillation	Yes Yes	No
011-032	0882	F53	L	50	453	454	Aneurysm	Yes	No
050-003	2042	M62	L	50	217	222	Obstruction, carotid artery	Yes	No
050-011	2187	M52	L/H/F	50/12.5/10	238	245	Edema/swelling	No	Yes
050-012	2212	M70	L/H	50/6.25	184	193	Asthma	No	No
050-013	2217	F52	L/H	50/12.5	317	317	Dyspnea Chest pain Atrial tachycardia	No No No	Yes Yes Yes
050-013	2226	M32	--	OFF	323	--	Suicide attempt	Yes	Yes
050-014	2241	M46	L/H	50/6.25	119	126	Agitation Malaise	No No	Yes Yes
050-0	2246	M54	L/H/F	12.5/5	166	228	Edema/swelling	No	No
050-	2248	M53	L	50	1	216	Muscle Aches Joint Swelling		Unk.
050-015	2255	M48	L/H/F	50/12.5/10	216	273	Edema/swelling	No	Yes
050-016	2283	M44	L	50	206	206	Asthenia/fatigue Orthostatic hypotension	No No	No No
050-019	2325	M42	L	50	99	153	Impotence	No	Yes
050-019	2336	M61	L/H/F	50/12.5/10	172	202	Edema/swelling	No	No

Table LTF 6. (continued)

Protocol #	Patient #	Sex/ Age	Treatment	Daily Dose (mg)	Study Day of Onset	Relative Day Discontinued	Adverse Experience	Serious	Resolved
050-021	2365	M61	L	50	59	59	Facial edema Rash	No No	No No
050-021	2371	F50	L/H/F	50/12.5/10	304 304 304	332	Tachycardia Muscle weakness Flushing	No No No	No No No
050-021	2373	M59	L/H/F	50/12.5/5	197	197	Myocardial infarction	Yes	Yes
050-023	2414	M46	L/H	50/6.25	244	244	Cerebral aneurysm	Yes	No
049-001	7016	M52	L/H/F	50/25/10	292	326	Impotence	No	No
049-012	7199	M41	L/H/F	50/25/10	307	307	Gastroenteritis	No	Yes
049-014	7236	M48	L/H/F	50/12.5/10	133	139	Edema/swelling	Yes	No
049-016	7264	F68	L i L/F	50 50 50/5	85 203 259	267	Abdominal pain Rash Asthenia/fatigue	No No No	Yes Yes Yes
049-017	7279	M52	L	50	267	338	Neoplasm, tongue, malignant	Yes	No
049-027	7361	M45	L/H/F	50/12.5/5	147	159	Headache	No	Yes
049-023	7411	M61	---	OHF	291	286	Neoplasm, kidney, malignant	Yes	Yes
049-023	7414	M56	L	50	98	114	Myalgia	No	No
049-023	7453	M52	L/H/F	50/25/5	168	181	Tachycardia	No	Yes
054-039	8815	F55	L/H/F	50/12.5/5	162	205	Depression	No	No

Treatment L=losartan, H=HCTZ, F=felodipine

Table LTF 7. Laboratory Adverse Experiences Causing Discontinuation

Protocol #	Patient #	Sex/ Age	Treatment	Study Day of Onset	Relative Day Discontinued	Adverse Experience	Serious
011-004	0064	M47	L/H 100/12.5	97	103	Hematuria	No
011-024	0493	M71	L 100	182	181	Hyperuricemia	No
011-031	0638	M66	L/H 50/50	322 332 352	351	ALT increased ALT increased ALT increased	No No No
050-013	2230	M54	L/H 50/12.5	233 233	232	AST increased ALT increased	No No
050-017	2305	M51	L/H 50/6.25	134 134 134 134	154	Alk. Phos. increased Hemoglobin increased Leukocyte count increased Hematocrit increased	No No No No

Treatment L=losartan, H=HCTZ

Patient #64 had urine blood reported for the first time on day 90 as 15 RBC/HPF and on day 97 as 100 RBC/HPF. Urine WBC, up to 15 WBC/HPF, were reported throughout treatment

Patient #493 had a baseline serum uric acid of 9.6 mg/dl. On day 105 and 154, serum uric acid was 10.8 and 10.6 mg/dl respectively.

Patient #638, # 473 and #2230 had increases in ALT and AST as outlined in table LTF 7a

LTF 7a. Transaminases for patients #638, #473 and #2230.

Patient #	Day	ALT (U/L)	AST (U/L)
638	Baseline	39	26
	203	38	31
	266	79	47
	322	138	67
	332	109	55
	352	123	73
473	Baseline	19	23
	410	60	45
	484	175	188
	489	156	68
	533	139	110
	540	101	52
	568	23	25
2230	Baseline	44	44
	107	93	65
	122	81	65
	136	96	62
	211	219	171
	233	152	116

Three additional patients had simultaneous increases in AST and ALT > 100 U/L. Patient # 2097 had an increase in ALT 197 U/L (baseline ALT = 96 U/L) and AST to 112 U/L (baseline AST = 60 U/L) on day 203. The next value was obtained on day 408. AST was within normal limits but ALT remained elevated. Patient # 319 had a AST of 151 U/L (baseline = 29 U/L) and a ALT of 179 (baseline = 26 U/L) on day 582. AST and ALT on day 590 were normal. Patient # 530 had a ALT of 167 U/L and AST of 109 on day 204. On day 217, AST and ALT were normal.

Several patients had elevations of serum creatinine that were clinically relevant. Patient # 594 had an increase in creatinine to a maximum of 2.4 mg/dl (baseline = 1.2 mg/dl) on losartan 150 mg/HCTZ 25 mg (day 377). The dose of HCTZ was eliminated and the creatinine returned to baseline values. Patient # 646 had an increase in creatinine to 2.4 mg/dl (baseline = 1.2 mg/dl) on losartan 150 mg/HCTZ 25 mg (day 134). Patient #834 had an increase in creatinine to 1.8 mg/dl (baseline = .7 mg/dl) on losartan 150 mg/HCTZ 25 mg (day 405). Patient #2212 (study 50) had an increase in creatinine to 2.8 mg/dl (baseline = 1.2 mg/dl) and BUN to 35 mg/dl (baseline = 13 mg/dl) on losartan/HCTZ (day 198; it appears that therapy was stopped on day 194 for reasons that are unclear). Creatinine on day 209 (off drug) was 1.4 mg/dl.

Patient #2305 had elevations of hemoglobin values to a maximum of 19.9 Gm/dl (baseline = 17.9 Gm/dl) and WBC of $13.9 \times 10^3/\text{MM}^3$.

Thirteen of the patients withdrawn due to adverse experience had adverse experiences described as serious. Twenty patients had serious adverse events that did not result in withdrawal. Table LTF 8 list the patients who experienced serious adverse events in the open label extension.

Table LTF 8. Serious Non-Fatal Clinical Adverse Experiences (Patients Treated with Losartan in Extensions)

Protocol #	Patient #	Sex/ Age	Treatment	Daily Dose (mg)	Day of Onset	Adverse Experience	Outcome
011-002	0027	M57	L/H	150/25	403	Neoplasm, skin, malignant (melanoma)	Still Present
011-003	0048	M36	L/H	100/12.5	185	Pneumonia	Recovered
011-004	0070	M53	L	50	289	Bone pain	Recovered
011-004	0071	M49	L	50	237	Neoplasm, skin, malignant (melanoma)	Recovered
			L/H	150/12.5	362	Blindness	Recovered
021-004	0072	F63	L	50	363	Pneumonia	Recovered
					363	Sinusitis	Recovered
011-005	0095	M51	L	100	108	Angina pectoris*	Recovered
					108	Supraventricular tachycardia*	Recovered
011-022	0442	F64	L	100	293	Depression	Recovered
			L	50	399	Depression	Recovered
			L	50	452	Depression	Recovered
			L	50	467	Depression	Recovered
011-022	0444	F73	L	150	357	CVA	Recovered
					357	Paresis	Still Present
011-025	0508	M66	L/H	150/12.5	498	Melanoma	Still Present
011-025	0510	M40	L	50	534	Hearing loss* (Sensory Neural)	Still Present
011-025	0517	M57	L	100	333	Traumatic arthropathy	Recovered
011-026	0527	M53	---	OFF	322	Pericardial effusion	Recovered
011-026	0530	F52	L/H	100/25	247	Cholelithiasis	Recovered
011-032	0652	M33	L	100	101	Tear, ligament	Recovered
011-032	0655	M29	L	50	101	Chest pain	Recovered
					102	T-wave abnormality (ECG)	
011-032	0656	M51	L/H	150/25	369	Atrial fibrillation	Recovered
011-032	0666	F58	L	100	66	Neoplasm, skin, malignant* (melanoma)	Still Present
011-032	0668	M49	L/H	150/12.5	338	Retinal detachment	Recovered
011-038	0783	M61	L/H	100/12.5	218	Diarrhea* (rectal bleeding, rectal cancer)	Recovered
011-039	0818	M53	L	50	419	Dyspnea*	Still Present
					399	Atrial Fibrillation*	
011-040	0828	M65	---	OFF	133	Neoplasm, skin, malignant (melanoma)	Recovered
011-040	0832	F59	L/H	100/12.5	274	Leg pain	Still Present
011-032	0882	F53	L	50	453	Aneurysm* (ruptured cerebral)	Still Present
050-002	2022	M66	L/H/F	50/12.5/5	336	Neoplasm, prostate, malignant	Still Present
050-003	2042	M62	L	50	217	Obstruction, carotid artery*	Still Present
050-013	2226	M32	---	OFF	323	Suicide attempt*	Recovered
050-014	2246	M54	L	50	127	Urolithiasis	Recovered
050-021	2371	M59	L/H/F	50/12.5/5	197	Myocardial infarction*	Recovered
049-010	7172	M58	---	OFF ¹	209	Hemiplegia	Still Present
049-014	7236	M48	L	50	59	Urolithiasis	Recovered
049-017	7279	M52	L	50	267	Neoplasm, tongue, malignant*	Still Present
049-023	7411	M61	---	OFF ²	293	Neoplasm, kidney, malignant*	Recovered
054-039	8804	M68	L/H	50/6.25	85	Strain (muscle)	Recovered

Treatment L=losartan, H=HCTZ, F=felodipine. *Caused Discontinuation from Study. 1 = withdrew on day 189, 2 = discontinued med on day 286

The following narrative summaries describe the serious adverse experiences which occurred in the study extensions.

Study 011-002/AN 0027: This 57-year-old hypertensive male had a biopsy which identified a melanoma on the right shoulder. In addition to losartan 150 mg, the patient was receiving HCTZ 25 mg and a potassium supplement at the time of this experience.

Study 011-003/AN 0048: This 36-year-old hypertensive male reported having "flu-like" symptoms. He was admitted to the hospital with a diagnosis of pneumonia. In addition to losartan 100 mg, at the time of this experience the patient was receiving HCTZ 12.5 mg. At the time of the hospitalization, he was also taking a variety of over-the-counter products for his flu-like symptoms.

Study 011-004/AN 0070: This 53-year-old male was hospitalized for an elective coccygectomy. The patient had a history of coccyx pain which worsened during the time he participated in the study. At the time of the incident, the patient was taking losartan 50 mg once daily. Study drug was not interrupted. The patient recovered.

Study 011-004/AN 0071: This 49-year-old hypertensive male presented at the study site with an irregular looking mole on his back. This mole had been present prior to the patient's participation in the double-blind and open-label extension phases of the study. The study investigator biopsied the mole and the pathological examination classified the specimen as a melanoma. Study drug (losartan 50 mg once daily) was continued. The investigator considered this event to be definitely not study drug related. This same patient was hospitalized for surgical removal of the bursa sack in his elbow. He had injured the elbow at work, and it subsequently became infected. The patient was discharged, and fully recovered. At the time of the event the patient was receiving losartan 150 mg and HCTZ 12.5 mg.

Study 021-04/AN 0072: This 63-year-old hypertensive female was admitted to the hospital with a severe sinus infection. While in the hospital, a chest x-ray indicated that the patient also had pneumonia. She was discharged four days

later. Losartan therapy was interrupted while the patient was hospitalized. At the time of the hospitalization she was receiving losartan 50 mg once daily.

Study 011-005/AN 0095: This 51-year-old hypertensive male was admitted to the hospital with angina and supraventricular tachycardia. Study medication (losartan 100 mg) was discontinued, and the patient was started on verapamil and digoxin.

Study 011-022/AN 0442: This 64-year-old hypertensive female reported feeling depressed. She went to the emergency room and was subsequently admitted to the psychiatric ward. Therapy with losartan 100 mg was continued. She is considered to have chronic intermittent depression, which is considered to be a permanent/substantial disability.

Study 011-022/AN 0444: This 73-year-old hypertensive female presented at the clinic for a regularly scheduled visit with symptoms of a TIA. The patient was subsequently scheduled for outpatient diagnostic testing at the local hospital. It was discovered during the testing that there had been a rapid change in her vascular lab study and ultrasound of her carotid, and she was hospitalized. She underwent angiograms which showed a 90% occlusion of the right carotid which was surgically corrected. About 24 hours after surgery, she developed a weakness of the right leg and her brain scan at that time showed a lesion in the left side which was opposite the side of the surgery. She continued to take her medications (losartan 150 mg) throughout the hospitalization.

Study 011-025/AN 0508: This 66-year-old hypertensive male had a melanoma removed from his right arm. At the time of this event he was receiving losartan/HCTZ 150/12.5 mg, which was continued.

Study 011-025/AN 0510: This 40-year-old hypertensive male noted right sided deafness. The patient requested that the study drug (losartan 50 mg) be discontinued. An otologic exam revealed sensory neural hearing loss in the right ear. This was considered to be a permanent disability.

Study 011-025/AN 0517: This 57-year-old hypertensive male was hospitalized for repair of a torn rotator cuff. At the time of the incident, the patient was taking losartan 100 mg once daily. Study drug was not interrupted. The patient recovered and continued in the study.

Study 011-026/AN 0527: This 53-year-old hypertensive male was admitted to the hospital with pericardial effusion, without signs of myocardial infarction or congestive heart failure. Study drug (100 mg losartan) was interrupted.

Study 011-026/AN 0530: This 52-year-old hypertensive female was admitted to the hospital for an elective cholecystectomy. The patient had a history of abdominal pain prior to entry into the acute phase of the study, but it increased in intensity. The pain was diagnosed to be cholecystolithiasis, and the patient then elected to have the surgery. At the time of the cholecystectomy, the patient was controlled on losartan 100 mg and HCTZ 25 mg, and she was also receiving estrogen replacement, antacid, and potassium chloride.

Study 011-032/AN 0652: This 33-year-old hypertensive male was hospitalized for repair of a cruciate ligament tear. At the time of the incident, the patient was taking losartan 100 mg once daily. Study drug was not interrupted. The patient recovered and continued with the study.

Study 011-032/AN 0655: This 29-year-old hypertensive male was admitted to the hospital with chest pressure and left arm numbness; a T-wave abnormality was also noted. A cardiac catheterization suggested the pain was due to angina; myocardial infarction was ruled out. Losartan therapy was interrupted during the hospitalization. In addition to losartan 50 mg, the patient was receiving antacid at the time of the experience.

Study 011-032/AN 0656: This 51-year-old hypertensive male experienced palpitations. The patient was hospitalized and found to have atrial fibrillation and hypokalemia. Laboratory analysis revealed serum potassium 3.2 and serum CPK 192. The patient was treated with heparin, digoxin, and intravenous potassium. In addition to losartan 150 mg, at the time of this experience the patient was receiving hydrochlorothiazide 25 mg daily, simvastatin, and aspirin. Therapy with hydrochlorothiazide was discontinued and therapy with losartan continued.

Study 011-032/AN 0666: This 58-year-old non-black hypertensive female (with a history of prior melanoma which was surgically removed) noted a lump on her left groin (original melanoma on right side). A biopsy was positive for malignant melanoma. At the time of the experience she was receiving losartan 100 mg which was discontinued.

Study 011-032/AN 0668: This 49-year-old hypertensive male presented at his ophthalmologist's office complaining of blurred vision and irritation to his left eye. Upon examination, it was discovered that the patient had suffered a retinal detachment. He was admitted to the hospital and the retina was surgically reattached; the patient was subsequently discharged. At the time of the incident, the patient was taking losartan 150 mg and HCTZ 12.5 mg. Drug was continued.

Study 011-038/AN 0783: This 61-year-old hypertensive male developed diarrhea and hemorrhoid bleeding. He was found to have a "large, fungating mass in the rectal vault". He was admitted to the hospital and underwent resection of an adenocarcinoma of the rectum, and a small liver nodule was also resected. At the time of the event, the patient was receiving losartan 100 mg and HCTZ 12.5 mg.

Study 011-039/AN 0818: This 53-year-old hypertensive male was admitted to the hospital for atrial fibrillation and shortness of breath. He was treated with digoxin and procainamide HCl. At the time of the adverse experience, the patient was receiving losartan 50 mg which was discontinued.

Study 011-040/AN 0828: This 65-year-old hypertensive male had a mole removed from his left arm by his private physician. The mole was biopsied and diagnosed as malignant melanoma. The patient was admitted to the hospital and underwent radical dissection of left upper arm with complete lymph node removal of left axilla. According to the patient, all nodes and surrounding tissues were biopsied; none were found to be cancerous.

Study 011-040/AN 0832: This 59-year-old hypertensive female suffered a fractured patella in a car accident. The patient was hospitalized for surgery; the patella was repaired with a pin. At the time of the accident, the patient was taking losartan 100 mg/HCTZ 12.5 once daily.

Study 011-032/AN 0882: This 53-year-old black hypertensive female patient was hospitalized for what was diagnosed as a rupture of a posterior communicating artery aneurysm. The patient remains hospitalized on a ventilator, is responsive to some verbal stimuli and exhibits small amounts of leg and eye movement. At the time of the incident, the patient was taking losartan 50 mg. The patient was discontinued from the clinical trial.

Study 050-002/AN 2022: This 66-year-old male was diagnosed with prostate cancer. He was receiving losartan 50 mg, HCTZ 12.5 mg, and felodipine 5 mg, which were continued.

Study 050-003/AN 2042: This is a 62-year-old Caucasian male with diabetes mellitus, hypothyroidism and arthritis and who had a history of right leg claudication, portacaval shunt and splenorenal shunt. An ultrasound and subsequent arteriography revealed occlusion of the right internal carotid artery and bilateral stenosis. Therapy with losartan was discontinued. The patient underwent right carotid endarterectomy with saphenous vein patch angioplasty. At the time of this event the patient was receiving losartan 50 mg daily, glipizide, sodium levothyroxine, acetaminophen, zinc, multivitamin, vitamin E, potassium, vitamin B and beta-carotene. Aspirin was added to his treatment regimen.

Study 050-013/AN 2226: This 32-year-old black male with a history of untreated depression and alcohol abuse had been treated with losartan 50 mg. Concomitant medication included hydrochlorothiazide 6.25 mg daily and captopril. After drinking heavily, the patient reportedly had an altercation with his ex-wife and then took overdoses of his medications including approximately 150 mg of hydrochlorothiazide, 3750 mg of losartan and approximately 750 mg of captopril. He was hospitalized and placed in intensive care. He was treated with intravenous fluids to prevent hypotension and monitored overnight. All medications were discontinued. It was reported that the patient did not develop hypotension.

Study 050-014/AN 2246: This 54-year-old hypertensive male, with a prior history of kidney stone, reported low back pain and abdominal pain, and was hospitalized. Laboratory evaluation revealed urine RBC and bacteria. An intravenous pyelogram confirmed the diagnosis of nephrolithiasis. The patient improved with treatment and was discharged. At the time of the event, the patient was receiving losartan 50 mg daily.

Study 050-021/AN 2373: This 59-year-old male with diabetes mellitus, psoriasis and rosacea, and a history of pneumococcal pneumonia, began to experience arm, upper back and chest pain. The chest pain continued and the patient was hospitalized with an anterolateral myocardial infarction. Therapy with study drug and felodipine ER was discontinued, and the patient was placed on therapy with an ACE inhibitor and hydrochlorothiazide. At the time of the event, the patient was receiving losartan 50 mg daily, glyburide, tetracycline, anthralin ointment and flucronide, hydrochlorothiazide 12.5 mg, and felodipine ER 5 mg.

Study 049-010/AN 7172: This 58-year-old hypertensive male did not return to the clinic and several attempts were made to contact him. The patient reportedly had a stroke while in Argentina. The exact dose, if any, at the time of the experience was unknown.

Study 049-014/AN 7236: This 48-year-old male with diabetes mellitus developed severe lower back pain. An intravenous pyelogram revealed a large kidney stone and the patient was hospitalized. Study drug therapy (losartan 50 mg) was continued. The calculus was of calcium oxalate composition. The patient subsequently recovered.

Study 049-017/AN 7279: This 52-year-old hypertensive male noticed a lump on the left side of his tongue. He was diagnosed as having a malignant tumor. The patient was sent for surgical resection and radiation. Study drug therapy was discontinued. At the time of the event, the patient was receiving losartan 50 mg daily.

Study 049-023/AN 7411: This 61-year-old male, with an existing left kidney cyst (evaluated previously for renal carcinoma, but not surgically excised), was hospitalized for removal of his left kidney. The final pathology report revealed multifocal papillary renal cell carcinoma. All nodes were negative. The patient developed pneumonia and hepatitis after surgery, but was subsequently discharged. The patient had a negative prostate biopsy. Losartan was discontinued.

Study 054-039/AN 8804: This 68-year-old hypertensive male suffered a fall and was hospitalized with gluteal pain. He was diagnosed as having strained his gluteal muscle; he subsequently recovered. The patient continued study drug throughout the hospitalization. At the time of this event, he was taking losartan 50 mg and HCTZ 6.25 mg daily.

Clinical Adverse Events

Table LTF 9 lists the incidence of adverse events in patients on any combination of losartan or losartan alone. Of the 659 patients exposed to losartan with or without combination therapy, 477 (72%) experienced at least one adverse event during the open label extension. There was no difference in incidence rates within subgroups.

LTF 9. Incidence of Patients with at Least One Adverse Event on Losartan +/- combination therapy

	total	male	female	caucasian	black	other	≥ 65	< 65
exposed to losartan	659	433	226	548	75	36	101	558
at least 1 ae on losartan	477 (72%)	300 (69%)	177 (78%)	394 (72%)	57 (76%)	26 (72%)	70 (69%)	407 (73%)

Table LTF 10 lists incidences of clinical adverse events in patient on losartan. The list is not comprehensive in that it includes adverse events that occurred in > 1% of patients, have potential serious clinical implications, are characteristic with ACE Inhibitors or have clinical relevance based on the mechanism of action of losartan. There were 226 females and 433 males. Myalgia, decreased hematocrit, gout, hyperuricemia, dental pain and trauma occurred at greater than double the incidence in males verses females. Urinary tract infections and abdominal pain occurred at greater than double the incidence in females verses males. Impotence was reported in 13 males. Subgroup comparisons based on race and age are difficult to interpret since the open label extension only included 11.3 % black and 15.3 % ≥ 65 years of age.

Table LTF 10. Listing of Adverse Events Based on Gender on Losartan +/- Combination Therapy. [Includes adverse events that have a total incidence > 1%, have potential serious clinical implications, are characteristic in ACE Inhibitors or may have clinical relevance based on the mechanism of action of losartan.]

Adverse Experience	Female N=226	Male N=433	Total N=659	Adverse Experience	Female N=226	Male N=433	Total N=659
ALKALINE PHOSPHATASE INCREASED	2	6	8	HYPONATREMIA		1	1
ALT INCREASED	5	18	23	IMPOTENCE		13	13
ANXIETY	4	5	9	INFECTION, DENTAL PROCESS	2	6	8
AST INCREASED	2	11	13	URI	42	73	115
BRONCHITIS	7	8	15	INFLUENZA	3	8	11
CONGESTION, NASAL	7	15	22	INSOMNIA	5	9	14
CONGESTION, RESPIRATORY	3	4	7	MYALGIA	1	8	9
COUGH	15	18	33	NAUSEA	13	9	22
CRAMP, MUSCLE	5	5	10	ORTHOSTATIC EFFECTS	2	8	10
DIARRHEA	15	13	28	PAIN, ABDOMINAL	19	9	28
DIZZINESS	16	31	47	PAIN, BACK	15	13	28
DYSPEPSIA	5	9	14	PAIN, CHEST	12	20	32
DYSPNEA	6	6	12	PAIN, DENTAL	1	7	8
EDEMA, FACIAL		1	1	PAIN, FLANK	2	6	8
EDEMA, ORBITAL		1	1	PAIN, KNEE	4	5	9
EDEMA/SWELLING	13	13	26	PAIN, LEG	4	3	7
EFFUSION, PERICARDIAL		1	1	PAIN, SHOULDER	5	8	13
FALLING	1		1	PAIN, TOE		6	6
FECAL OCCULT BLOOD		3	3	PAIN, WRIST	1	2	3
FLU LIKE ILLNESS	4	7	11	PALPITATION	1	2	3
FLUID OVERLOAD		1	1	PARSIS	1		1
GOUT	1	7	8	PARESTHESIA	5	8	13
HEADACHE	39	53	92	PHARYNGITIS	13	14	27
HEARING LOSS	1	1	2	PYURIA	12	7	19
HEMATOCRIT DECREASED	1	6	7	RASH	12	11	23
HEMATURIA	8	15	23	SERUM CREATININE INCREASED	1	4	5
HEMOGLOBIN DECREASED	3	6	9	SINUS DISORDER	7	7	14
HYPERGLYCEMIA	7	11	18	SINUSITIS	9	10	19
HYPERKALEMIA		1	1	SLOUGHING SKIN		1	1
HYPERNATREMIA		1	1	STRAIN	2	8	10
HYPERURICEMIA	1	7	8	INCREASED TOTAL BILIRUBIN	1	1	2
HYPERTHESIA	4	7	11	TRAUMA	2	9	11
HYPOKALEMIA	6	11	17	UROLITHIASIS		4	4

Table LTF 11 lists the incidence of adverse events in patients while on losartan alone. Of the 613 patients who were on losartan alone for some period during the extension phase, 315 (51%) had an adverse experience while on losartan alone. In subgroups, the percentage of patients with at least one adverse event is similar. Subgroup comparisons was only reviewed based on gender. Subgroup comparisons based on race and age are difficult to interpret since the open label extension only included 12% black and 14.5% ≥ 65 years of age.

LTF 11. Incidence of Patients with at Least One Adverse Event on Losartan Alone.

	total	male	female	caucasian	black	other	> 65	< 65
exposed to losartan alone*	613	402	211	504	73	36	89	524
at least 1 ae on losartan alone	315 (51%)	200 (50%)	115 (55%)	270 (54%)	32 (44%)	13 (36%)	44 (40%)	271 (52%)
at least 1 ae on any losartan combination	458 (75%)							

*may have received additional therapy at some time in extension

Table LTF 12 lists incidences of clinical adverse events in patients on losartan alone. The list is not comprehensive in that it includes adverse events that occurred in > 1% of patients, have potential serious clinical implications, are characteristic with ACE Inhibitors or have clinical relevance based on the mechanism of action of losartan. The time of exposure to losartan alone in this database is approximately 50% the time of exposure to losartan +/- combination. The most common adverse experiences (occurring in greater than 3% of patients) are asthenia/fatigue, diarrhea, dizziness, headache and upper respiratory infection. Cough was reported in 2.7% of patients. Gout was reported in four patients. [Reviewer's Note: This is important to know since the sponsor has touted losartan for lowering uric acid levels. Although that observation may be true it is unclear whether it is clinically relevant.] Patient #2365 (protocol 011; losartan 50 mg) was a 61 year old male who developed facial edema on day 59 of the extension which resulted in withdrawal from the study.

Table LTF 12. Listing of Adverse Events Based on Gender on Losartan Alone. [Includes adverse events that have a total incidence > 1%, have potential serious clinical implications, are characteristic in ACE Inhibitors or may have clinical relevance based on the mechanism of action of losartan.]

Adverse Experience	Female	Male	Total
ALT INCREASED	3	11	14
AST INCREASED	.	5	5
ASTHENIA/FATIGUE	10	13	23
COMA	.	1	1
CONGESTION, NASAL	1	7	8
COUGH	6	11	17
CVA	1	1	2
CVA, HEMORRHAGIC	.	1	1
DIARRHEA	11	9	20
DIZZINESS	5	15	20
EDEMA, FACIAL	.	1	1
EDEMA, ORBITAL	.	1	1
EDEMA/SWELLING	8	4	12
FALLING	1	.	1
GOUT	1	3	4
HEADACHE	27	30	57
HEMATURIA	4	5	9
HEMOGLOBIN DECREASED	1	1	2
HYPERURICEMIA	.	3	3
HYPOTENSION	1	.	1
URI	25	45	70
UTI	9	2	11
INSOMNIA	3	7	10
NAUSEA	7	7	14
ORTHOSTATIC EFFECTS	2	3	5
PAIN, ABDOMINAL	9	7	16
PAIN, BACK	8	6	14
PAIN, CHEST	8	8	16
PHARYNGITIS	6	9	15
PYURIA	5	2	7
RASH	9	8	17
SINUS DISORDER	5	4	9
SINUSITIS	8	6	14
SLOUGHING SKIN	.	1	1
STRAIN	2	5	7
SWELLING, EYE	.	1	1
SWELLING, JOINT	4	1	5
SYNCOPE	.	1	1
UROLITHIASIS	.	4	4
URTICARIA	.	1	1
VERTIGO	.	3	3

Heart Failure Trials						
Study #	Design/Patient Population	Treatment Groups	N	Primary Endpoint	Other Measures	Page
016	- r, db, pc, single dose - Heart Failure patients	- placebo - losartan 5, 10, 25, 75, 150 mg	12 54	Intracardiac Hemodynamics		190
047	- r, db, pc, 12 wk Rx period - CHF patients	- placebo - losartan 2.5 mg - losartan 10 mg - losartan 25 mg - losartan 50 mg	29 31 33 34 27	Intracardiac hemodynamics	- neurohormones - plasma losartan and E-3174	190

wk = week, db = double-blind, ol = open label, od = once a day, bid = twice a day, r = randomized, ac = active control, pc = placebo control, nc = no control, p = parallel, co = crossover, hx = history, HTN = hypertension, ACEI = angiotensin converting enzyme inhibitor, NE = norepinephrine, Epi = epinephrine, PRA = plasma renin activity

Study 016. Randomized, Double-blind, Placebo-controlled, Multicenter Study of the Hemodynamic Responses to a Single Oral Dose of MK-954 (DuP 753) in Patients with Heart Failure.

This was a randomized, double blind, placebo controlled trial designed to measure changes in intracardiac hemodynamics after a single dose of placebo or losartan (5, 10, 25, 75, 150 mg) in patients with congestive heart failure. Since the efficacy information collected in this study is not pertinent to the proposed indication of this NDA, only safety data will be reviewed. Patients with a history of CHF (NYHA Class II - IV), off of vasodilators and ejection fractions less than 40% were enrolled. Sixty-six patients, 10 - 12 per treatment group, received double-blind therapy. Eighty-four percent were men.

Two deaths occurred (#154, #512) seven and twelve days after the single oral dose of losartan and another two patients (#107 cholelithiasis, #256 pulmonary edema) had non-fatal serious adverse events 9 and 12 days after the single oral dose of losartan. Patient #154 was a 66 year-old Caucasian male with an ejection fraction of 29%, NYHA Class II heart failure and a history of myocardial infarction. He was randomized and received a single oral dose of losartan 5 mg on 4/7/91. On April 11, 1991, he had a myocardial infarction and suffered cardiogenic shock with bradycardia. He was admitted to the hospital and treated with atropine, dopamine, and streptokinase and his heart rate was maintained with a pacemaker. The patient was stable for 48 hours then subsequently had episodes of ventricular tachycardia which were followed by ventricular fibrillation. On April 13, 1991 the patient died. Autopsy demonstrated left ventricular myocardial infarction and extensive sclerosis of the coronary arteries. A thrombus was found in the circumflex artery. The investigator felt the myocardial infarction and ventricular fibrillation were not related to study drug. Patient #512 was a 62 year-old Caucasian male with an ejection fraction of 16% and NYHA Class III heart failure. The etiology of heart failure in this patient was ischemic cardiomyopathy. The patient had a myocardial infarction in 1977. The patient was randomized and received a single oral dose of losartan 150 mg on 6/19/91. On 6/20/91, prestudy therapy of furosemide, quinidine, isosorbide dinitrate, diltiazem, aspirin, and enalapril was reinstated. On 6/30/91, the patient was found dead in bed.

There was no significant difference in non-serious adverse events between treatments.

Study 047. Multicenter, Double-blind, Randomized, Parallel, Multiple-dose, Placebo-controlled Study of the Hemodynamic and Clinical Effects of Losartan in Patients with Heart Failure (U.S. and International Centers)

Protocol

This was a randomized, double-blind, placebo controlled trial designed to test the hypothesis that oral administration of losartan for 12 weeks would produce sustained hemodynamic and clinical improvement in patients with heart failure. The primary endpoint of the trial was the change in hemodynamics after the initial dose and after 12 weeks of therapy. Patients of either sex with evidence of left ventricular failure were eligible for inclusion if they:

- were New York Heart Association (NYHA) Functional Class II, III, or IV.
- had a resting left ventricular ejection fraction $\leq 40\%$ as measured by radionuclide ventriculography or contrast angiography within 6 weeks prior to the study.
- were ≥ 18 years of age.
- had not received vasodilators (including angiotensin-converting enzyme [ACE] inhibitors) and antihypertensive agents (excluding diuretics) for at least 14 days prior to randomization and inotropic agents (except digitalis) for at least 7 days prior to randomization.
- if the patient was receiving digitalis and/or diuretics, had received doses stable for 14 and 7 days, respectively, prior to randomization.

Patients were excluded if they experienced CABG surgery, coronary angioplasty, CVA or TIA in the previous 3 months, had uncontrolled angina pectoris or had uncontrolled cardiac arrhythmia or required anti-arrhythmic therapy. Patients with severe pulmonary disease or with a history of clinically important renal, hepatic, hematological, or neurological disorders were excluded.

Patients entered a baseline period of unspecified duration during which they underwent a history and physical exam, symptom review, laboratory evaluation and radionuclide ventriculogram (if not performed within the previous 6 weeks). On day -1, patients were hospitalized to undergo insertion of a swan ganz catheter. In order to be randomized into the trial, the mean pulmonary capillary wedge pressure was ≥ 13 mmHg. Patients were randomized to either placebo, losartan 2.5 mg, losartan 10 mg, losartan 25 mg or losartan 50 mg on day 1 for 12 weeks of double blind treatment. Hemodynamic measurements were measured repeatedly after the first and last doses of randomized therapy. The procedures performed during the study are outlined in table 47.1 and 47.2.

Table 47.1. Clinical Observations and Laboratory Measurements

	Baseline		Double-Blind						
	Day -1	Day 1	Week 1	Week 2	Week 4	Week 8	Week 12 Pre-HD ^a	Week 12 Post-HD ^a	
Complete Physical Exam	X							X	
Abbreviated Physical Exam ^b	X	X	X	X	X	X	X		
Laboratory Screen ^c	X	X	X		X	X	X		
Chest Roentgenogram including CT Ratio ^d	X						X		
Electrocardiogram (12-Lead)	X	X	X		X	X	X		
Hospitalization		X	X				X	X	
Resting radionuclide Left Ventricular Ejection Fraction	X								
Dyspnea-Fatigue Index	X	X			X	X	X		
Invasive Hemodynamics			X				X ^f		
Neurohormonal Blood Samples			X				X ^f		
Drug Level Blood Samples			X				X ^f		

^a Pre-hemodynamic and post-hemodynamic (HD) study

^b Includes evaluation of the signs and symptoms of heart failure (presence of third heart sound, jugular venous pulsation at 45°, pulmonary rales, peripheral edema, orthopnea, paroxysmal nocturnal dyspnea, exertional dyspnea, and New York Heart Association Functional Class)

^c Laboratory evaluation included standard urinalysis (specific gravity, pH, protein, glucose, and microscopic exam), hematology (hemoglobin, hematocrit, WBC differential count, platelet count), serum chemistry (BUN, creatinine, total bilirubin, AST, ALT, glucose, LDH, uric acid, sodium, potassium, magnesium, chloride, alkaline phosphatase, carbon dioxide content, total protein, albumin, calcium, phosphorus, total cholesterol, triglycerides), and trough digoxin or digitoxin level at Day -1 and Week 12 for those patients receiving these agents

^d The cardiothoracic (CT) ratio is the ratio of the widest transverse diameter of the cardiac silhouette to the widest thoracic diameter

^e If not performed within 6 weeks prior to the hemodynamic study.

^f During the second hemodynamic study.

Table 47.2. Schedule of Acute and Chronic Hemodynamic Periods

	Baseline	Hour(s) After Oral Dose of Losartan										
		0.5	1	2	3	4	5	6	10	12	24	
Hemodynamics	X	X	X	X	X	X	X	X	X	X	X	X
Plasma Angiotensin II	X						X					X
Serum Aldosterone	X						X					X
Plasma Norepinephrine	X						X					X
Plasma Renin Activity	X						X					X
Drug Levels ^a	X						X				X	X
Light Meal ^b								X			X	

^a Plasma drug samples were collected from all patients but concentrations (losartan and its metabolite E-3174) were determined for the 25 mg dose only.

^b Fluid intake of 200 mL was allowed with each meal.

Results

The hemodynamic data will not be reviewed. Only safety data will be presented. One hundred and fifty-four patients were randomized and given double-blind therapy. The numbers of patients entered into the study by investigator are shown in Table 47.3. Most patients were white males with ischemic heart disease or cardiomyopathy as the etiology of heart failure. The mean age was 61 years, the mean duration of the diagnosis was 4 years, the mean ejection fraction 25% and 68% of the patients were NYHA class II. Demographic and heart failure characteristics are summarized in Table 47.3.

Table 47.3. Demographics

	Placebo (N=29)	2.5 mg (N=31)	10 mg (N=33)	25 mg (N=34)	50 mg (N=27)	Total (N=154)
Sex						
Female	1 (3%)	8 (26%) ^a	3 (9%)	8 (24%)	3 (11%)	23 (15%)
Male	28 (97%)	23 (74%)	30 (91%)	26 (76%)	24 (89%)	131 (85%)
Age (years)						
Mean	60.5	61.2	60.6	60.1	59.9	60.5
S.D.	11.4	11.7	11.1	10.3	10.6	10.9
Range	34-80	28-77	40-76	36-77	28-74	28-80
Racial Origin						
Caucasian	25 (86%)	22 (71%)	28 (85%)	26 (76%)	25 (93%) ^b	126 (82%)
Black	2 (7%)	3 (10%)	3 (9%)	3 (9%)	0	11 (7%)
Other	2 (7%)	6 (19%)	2 (6%)	5 (15%)	2 (8%)	17 (11%)

a: Statistically significant difference against the placebo group, $p \leq 0.05$

b: Statistically significant difference against the 2.5 mg group, $p \leq 0.05$

c: Statistically significant difference against the 10 mg group, $p \leq 0.05$

d: Statistically significant difference against the 25 mg group, $p \leq 0.05$

Baseline intracardiac pressure measurements were similar between treatment groups except for baseline pulmonary capillary wedge pressures (PCWP). Table 47.4 lists the baseline PCWP. The minimum value for all losartan groups is < 13 mmHg. Thus, some patients in all losartan treatment groups do not fulfill the criteria for enrollment that the mean PCWP be > 13 mmHg.

Table 47.4. Pulmonary Capillary Wedge Pressure (mmHg)

	N	Baseline					Comparison			
		Mean	S.D.	Median	Min.	Max	vs. B	vs. c	vs. D	vs. E
PBO	29	21.6	7.9	19	10.5	38.5	NS	NS	*	*
losartan 2.5 mg	30	18.4	5.3	17	12.5	33	--	NS	NS	NS
losartan 10 mg	32	21.5	8.1	19.5	7.5	37	--	--	*	*
losartan 25 mg	34	17.7	6.3	16.3	8.5	41.5	--	--	--	NS
losartan 50 mg	27	17.6	6.2	16.5	9	39.5	--	--	--	--

NS -- NOT STATISTICALLY SIGNIFICANT

* -- TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, $P < 0.05$

** -- TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, $P < 0.01$

Nineteen patients did not complete the double blind portion of the study. Table 47.5 list the reasons for discontinuation. The majority were discontinued due to adverse events. Only one patient (#1067) discontinued due to ineffective therapy. Three patients receiving losartan therapy died. Three deaths were reported for the double-blind period of the study. Two deaths (# 1128, 1133) were in the losartan 2.5 mg group, and one (# 1139) was in the losartan 10 mg group. Additionally, one death (# 1195) occurred 30 days following the completion of the double-blind period and discontinuation of losartan in a patient that received losartan 10 mg during the double-blind period. A summary of the events surrounding the deaths is presented in table 47.5a.

Table 47.5. Patient Disposition

	PBO (N=29)	2.5 mg (N=31)	10 mg (N=33)	25 mg (N=34)	50 mg (N=27)
Completed Double-Blind/ Not Continuing Into Extension	7	5	8	9	7
Completed Double-Blind/ Continuing Into Extension	18	24	20	20	17
Discontinued Double-blind Phase	4	2	5	5	3
Clinical Adverse Experience	4	2	4	5	3
Therapy Ineffective	0	0	1	0	0

Table 47.4a Deaths

Patient Number	Summary
1128	This 68-year-old Caucasian male with an ejection fraction of 29%, NYHA functional class IIa heart failure, angina, peripheral vascular disease and a history of 2 myocardial infarctions and coronary artery bypass graft was randomized to receive single daily doses of losartan 2.5 mg. The etiology of heart failure in this patient was ischemic heart disease. His last dose of study drug was on Day 84. He was concomitantly treated with dipyridamole. On Day 85, he experienced a cardiac arrest and was hospitalized. On admission, the patient was found to be in ventricular fibrillation and died that day.
1123	This 71-year-old Caucasian male with an ejection fraction of 14%, NYHA Class IIb heart failure, atrial fibrillation, diabetes, and a history of 3 myocardial infarctions was randomized to receive single daily doses of losartan 2.5 mg. The etiology of heart failure in this patient was ischemic heart disease. Concomitant medications included digoxin, furosemide, spironolactone, glyburide, and warfarin. On Day 21, the patient died suddenly - attempts at resuscitation failed. The investigator identified the cause of death as ventricular fibrillation.
1139	This 65-year-old Caucasian male with an ejection fraction of 23%, NYHA Class IIb heart failure, atrial fibrillation and a history of myocardial infarction and coronary artery bypass graft surgery was randomized to receive single daily doses of losartan 10 mg. The etiology of heart failure in this patient was ischemic heart disease. Concomitant medications included digoxin, furosemide, spironolactone, dipyridamole, and aspirin. On Day 10, the patient suffered ventricular fibrillation and cardiac arrest. He was resuscitated and was hospitalized, but remained unconscious. On Day 15, the patient developed pneumonia. On Day 17 life-sustaining measures were withdrawn. On Day 18, the patient died. Autopsy confirmed pneumonia as the cause of death.
1195	This 67-year-old Caucasian male with an ejection fraction of 22%, NYHA Class IIb heart failure, angina, and a history of myocardial infarction, and ventricular tachycardia was randomized to receive single daily doses of losartan 10 mg. The etiology of heart failure in this patient was ischemic heart disease. The patient completed the study and losartan was discontinued on Day 85. Twelve days following completion of the study, the patient suffered cardiac arrest and was resuscitated. He was hospitalized and was found to have suffered a myocardial infarction. These episodes caused serious cerebral degeneration which led to the patient's death thirty days after completion of the study.

Table 47.6 lists the patients withdrawn from therapy prematurely. Eighteen patients withdrew due to adverse events.

Table 47.6. Patients Withdrawn from Therapy.

Patient Number	Treatment	Age	Gender	Race	Reason Discontinued	Stop Day	Adverse Event	AE start day	AE stop day
1005	Losartan 25 mg	73	M	Caucasian	Clinical AE	2	HYPOTENSION, ORTHOSTATIC	2	2
							VOMITING	2	2
1020	Losartan 10 mg	54	F	Caucasian	Clinical AE	58	DIZZINESS	4	4
							DIZZINESS	7	7
							DIZZINESS	9	9
							INSOMNIA	13	18
							DYSPNEA	17	58
							HEART FAILURE	30	35
							WEAKNESS, MUSCLE	30	35
							HEART FAILURE	53	54
1060	Losartan 50 mg	69	M	Caucasian	Clinical AE	2	HYPOTENSION	1	3
1070	Losartan 25 mg	47	M	Caucasian	Clinical AE	16	BRONCHITIS	3	9
							DIARRHEA	14	18
							HEADACHE	14	18
							NAUSEA	14	18
							PRURITUS	14	18
							SWEATING	14	18
							ALT INCREASED	17	
							AST INCREASED	17	
							LDH INCREASED	17	
							PLATELET COUNT INCREASED	17	
1072	Losartan 25 mg	67	M	Caucasian	Clinical AE	73	HYPOTENSION	11	11
							DIARRHEA	11	17
							NAUSEA	11	17
							ASTHENIA/FATIGUE	43	73
							MEMORY IMPAIRMENT	43	73
							DYSPNEA	59	73
1073	Placebo	67	M	Caucasian	Clinical AE	74	ATRIAL FIBRILLATION	2	2
							HEART FAILURE	74	80

Table 47.6. Patients Withdrawn from Therapy (continued)

Patient Number	Treatment	Age	Gender	Race	Reason Discontinued	Stop Day	Adverse Event	AE start day	AE stop day
1082	Losartan 25 mg	77	M	Caucasian	Clinical AE	7	HYPOTENSION	2	2
1090	Losartan 10 mg	73	M	Caucasian	Clinical AE	23	EDEMA, PULMONARY	23	24
							HEART FAILURE	23	24
1101	Losartan 50 mg	67	M	Caucasian	Clinical AE	9	BLURRED VISION	4	4
							ASTHENIA/FATIGUE	4	13
							DIZZINESS	4	13
							BLURRED VISION	5	5
							BLURRED VISION	6	5
							BLURRED VISION	8	8
							HYPOTENSION, ORTHOSTATIC	9	9
1112	Placebo	65	M	Negro	Clinical AE	43	FEVER	1	1
							PAIN, CATHETER, CARDIAC	1	.
							HEART FAILURE	9	56
1123	Placebo	71	M	Negro	Clinical AE	61	SEPTICEMIA	1	1
							EDEMA/SWELLING	16	70
							OBSTRUCTION, URINARY TRACT	30	34
							HEPATOMEGALY	60	61
1128	Losartan 2.5 mg	68	M	Caucasian	Clinical AE	85	DYSPNEA	8	21
							WHEEZING	8	21
							CARDIAC ARREST	85	85
							DEATH	85	85
							VENTRICULAR FIBRILLATION	85	85
1133	Losartan 2.5 mg	71	M	Caucasian	Clinical AE	21	CONSTIPATION	1	1
							MYALGIA	1	1
							DEATH	21	21
							VENTRICULAR FIBRILLATION	21	21
1139	Losartan 10 mg	65	M	Caucasian	Clinical AE	10	CARDIAC ARREST	10	10
							VENTRICULAR FIBRILLATION	10	10
1174	Losartan 50 mg	28	F	Caucasian	Clinical AE/Continuing	1	HYPOTENSION	1	1
1176	Losartan 25 mg	73	M	Caucasian	Clinical AE	2	RASH	1	5
							DIARRHEA	2	2
							HYPOTENSION, ORTHOSTATIC	2	2
1188	Losartan 10 mg	70	M	MESTIZO	Clinical AE	45	DEPRESSION	2	45
							PHLEBITIS/THROMBOPHLEBITIS	6	16
							ABSCESS	13	16
							AV BLOCK, SECOND DEGREE	30	37
							EDEMA, PULMONARY	44	47
1206	Placebo	69	M	Caucasian	Clinical AE	71	DYSPNEA	32	72
							HEART FAILURE	71	72

As table 47.7 illustrates, there was no difference in the number of patients with at least one adverse event.

Table 47.7. Incidence of Patients With At Least One Adverse Experience

	PBO (N=29)	2.5 MG (N=31)	10 MG (N=33)	25 MG (N=34)	50 MG (N=27)
Number (%) of Patients	n (%)	n (%)	n (%)	n (%)	n (%)
With One Or More Adverse Experiences	19 (65.5)	18 (58.1)	18 (54.5)	19 (55.9)	16 (59.3)

Table 47.8 lists the patients who experienced a serious adverse event.

Table 47.8. Listing of Information for Serious Clinical Adverse Experiences

Patient Number	Sex/Age/ NYHA	Total Daily Dosage	Onset Day	Adverse Experience	Duration	Intensity
PLACEBO GROUP						
1054	M/76/IV	OFFDRUG	44	Ventricular Tachycardia	5 days	Severe
1211	M/34/IIa	PBO	82	Ventricular Tachycardia	1 min	Severe
1206	M/69/IIa	PBO	71	Heart Failure	2 days	Severe
1235	M/57/IIb	PBO	69	Dyspnea	12 hrs	Severe
1123	M/71/IIa	PBO	1	Septicemia	1 day	Mild
			30	Obstruction, Urinary Tract	55 days	Moderate
1136	M/68/IIIb	PBO	71	Pneumonia	5 days	Moderate
1192	M/45/III	PBO	58	Heart Failure	28 days	Severe
		OFFDRUG	88	Pneumonia	6 days	
1186	M/59/III	PBO	2	Embolism/Pulmonary Infarction	14 days	Moderate
			43	Dyspnea	18 days	Severe
LOSARTAN 2.5 mg GROUP						
1004	F/64/III	2.5 mg	14	Chest Pain	2 hrs	Moderate
1051	M/69/IIa	OFFDRUG	8	Cardiac Arrest	1 hr	Severe
		2.5 mg	14	Ventricular Tachycardia	1 hr	Severe
1071	F/73/III	2.5 mg	58	Atrial Fibrillation	35 days	Severe
1194	M/72/IIb	2.5 mg	9	Pneumonia	20 days	Severe
1189	F/69/IIb	2.5 mg	59	CVA	26 days	Moderate
LOSARTAN 10 mg GROUP						
1020	F/54/III	10 mg	30	Heart Failure	6 days	Severe
			53	Heart Failure	2 days	Severe
1047	M/58/III	10 mg	77	Heart Failure	60 days	Severe
1185	M/71/III	10 mg	55	Hepatobiliary Pain	12 days	Moderate
1188	M/70/III	10 mg	44	Pulmonary Edema	4 days	Severe
1195 [†]	M/67/IIb	OFFDRUG	97	Cardiac Arrest	1 day	
			97	Myocardial Infarction	1 day	
			97	Cerebral Degeneration	19 days	
			115	Death		
LOSARTAN 25 mg GROUP						
1025	M/62/III	25 mg	8	Pneumonia	7 days	Severe
1072	M/67/IIa	25 mg	59	Dyspnea	15 days	Severe
1080	M/60/III	25 mg	92	Bacteremia	1 day ^{††}	Moderate
LOSARTAN 50 mg GROUP						
1174	F/28/III	50 mg	1	Hypotension	9 hrs	Severe

[†] This patient died 30 days following completion of the double-blind period and discontinuation of losartan therapy.

^{††} This adverse experience occurred on the last day of double-blind therapy and continued into the open-label extension period.

Patient #1031 (losartan 2.5 mg) who was on warfarin 5.0 mg daily had an elevated prothrombin time on day 33. Additional information was presented in the submission of 10/7/94. This patient experienced gingival bleeding with a prothrombin time of 29.4 seconds.

For both supine and standing heart rate, the placebo levels at the end of the study had increased by 7 to 8 beats/min above baseline levels, while the 25 mg and 50 mg groups maintained baseline levels. There was not a consistent pattern of change in blood pressure compared to placebo.

Neurohormone levels (aldosterone, renin activity, angiotensin II, norepinephrine, epinephrine and dopamine) were measured during both hemodynamic periods at Hours 0, 5 and 24 postdose. The neurohormone concentrations were provided as log transformed means. Significant differences between treatment groups are discussed as fold changes from baseline, that is, the geometric mean of the original measurements, which translates to the geometric mean of ratios (posttreatment value/pre-treatment value). The geometric mean is calculated from the logarithmic mean (Table 95) after exponentiation (geometric mean = exp(mean of logarithmic values)). In this form, this data is uninterpretable from a clinical perspective. The sponsor will need to supply the means and range of values for the various neurohormones.

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Patients Discontinued in Study 011.

Patient #	Treatment	Reason Discontinued	Day Discontinued
33	Losartan 150 mg	Clinical AE	17
488	Losartan 150 mg	Clinical AE	20
489	Losartan 10 mg	Clinical AE	24
85	Losartan 50 mg	Clinical AE	34
294	Losartan 100 mg	Clinical AE	36
399	Losartan 10 mg	Clinical AE	36
684	Losartan 25 mg	Clinical AE	41
649	Placebo	Lab AE	28
115	Losartan 25 mg	Lab AE	32
321	Enalapril	Lab AE	41
802	Placebo	Lab AE	43
376	Losartan 50 mg	Lost to Followup	1
698	Placebo	Lost to Followup	16
496	Losartan 100 mg	Lost to Followup	29
808	Placebo	Lost to Followup	31
192	Losartan 25 mg	Lost to Followup	42
466	Enalapril	Lost to Followup	62
190	Losartan 100 mg	Protocol Deviation	1
743	Losartan 50 mg	Protocol Deviation	8
210	Losartan 25 mg	Protocol Deviation	10
475	Placebo	Patient Uncooperative	56
480	Placebo	Patient Uncooperative	56
469	Losartan 100 mg	Patient Uncooperative	57
359	Placebo	Therapy Ineffective	6
761	Losartan 150 mg	Therapy Ineffective	12
680	Placebo	Therapy Ineffective	13
419	Losartan 150 mg	Therapy Ineffective	14
706	Losartan 25 mg	Therapy Ineffective	14
447	Losartan 10 mg	Therapy Ineffective	22
837	Losartan 25 mg	Therapy Ineffective	28
632	Losartan 150 mg	Therapy Ineffective	39
613	Placebo	Therapy Ineffective	51
799	Losartan 10 mg	Therapy Ineffective	54
505	Losartan 10 mg	Therapy Ineffective	56
699	Losartan 10 mg	Therapy Ineffective	64
548	Losartan 150 mg	Clinical and Lab AE	34
119	Losartan 100 mg	Patient Withdrew	6
124	Enalapril	Patient Withdrew	10
498	Losartan 100 mg	Patient Withdrew	12
552	Losartan 100 mg	Patient Withdrew	14
805	Losartan 100 mg	Patient Withdrew	35
651	Losartan 100 mg	Patient Withdrew	49
452	Placebo	Patient Withdrew	50
49	Placebo	Patient Withdrew	52
485	Losartan 25 mg	Patient Withdrew	55
494	Losartan 10 mg	Patient Withdrew	56
490	Losartan 100 mg	Patient Withdrew	59
617	Losartan 150 mg	Clinical AE/Cont.	28
667	Enalapril	Clinical AE/Cont.	47
659	Losartan 10 mg	Therapy Ineffective/Cont.	49

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Patients Discontinued from Double-Blind Phase of Study 050.

Patient Number	Treatment Regimen	Reason Discontinued	Day Discontinued
2170	Losartan 50mg/100mg	Clinical Adverse Experience	1
2397	Losartan 50mg/100mg	Clinical Adverse Experience	9
2160	Losartan 50mg/100mg	Clinical Adverse Experience	11
2386	Losartan 50mg/100mg	Clinical Adverse Experience	21
2028	Placebo	Clinical Adverse Experience	23
2266	Losartan 50mg/100mg	Clinical Adverse Experience	32
2020	Losartan 50mg/100mg	Clinical Adverse Experience	36
2149	Placebo	Clinical Adverse Experience	39
2271	Losartan 50mg/100mg	Clinical Adverse Experience	47
2292	Placebo	Clinical Adverse Experience	72
2394	Losartan 50mg/100mg	Lost To Followup	6
2282	Losartan 50 mg	Lost To Followup	9
2291	Losartan 50 mg	Lost To Followup	29
2314	Placebo	Lost To Followup	54
2110	Losartan 50 mg	Lost To Followup	64
2396	Placebo	Lost To Followup	68
2385	Placebo	Protocol Deviation	5
2436	Losartan 50 mg	Protocol Deviation	13
2383	Losartan 50 mg	Protocol Deviation	35
2278	Losartan 50mg/100mg	Protocol Deviation	84
2285	Placebo	Protocol Deviation	87
2243	Losartan 50mg/100mg	Patient Uncooperative	89
2228	Losartan 50 mg	Therapy Ineffective	10
2378	Placebo	Therapy Ineffective	21
2232	Placebo	Therapy Ineffective	22
2227	Placebo	Therapy Ineffective	35
2072	Losartan 50 mg	Therapy Ineffective	48
2158	Placebo	Therapy Ineffective	51
2063	Placebo	Therapy Ineffective	62
2284	Losartan 50 mg	Patient Withdrew	3
2235	Placebo	Patient Withdrew	14
2328	Losartan 50mg/100mg	Patient Withdrew	42
2205	Placebo	Patient Withdrew	64
2119	Losartan 50mg/100mg	Patient Withdrew	84
2247	Losartan 50mg/100mg	Therapy Ineffective*	5
2376	Losartan 50mg/100mg	Therapy Ineffective*	15
2412	Placebo	Therapy Ineffective*	19
2372	Losartan 50 mg	Therapy Ineffective*	24
2423	Losartan 50 mg	Therapy Ineffective*	29
2365	Placebo	Therapy Ineffective*	48
2209	Losartan 50 mg	Therapy Ineffective*	65
2253	Placebo	Therapy Ineffective*	71
2408	Placebo	Protocol Violator*	18
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Patient #	Treatment	Reason Discontinued	Day Discontinued
1301	Losartan 50 mg	Clinical AE	4
1373	Placebo	Clinical AE	4
1308	Placebo	Clinical AE	5
1145	Placebo	Clinical AE	10
1415	Losartan 25mg BID	Clinical AE	16
1607	Losartan 25mg BID	Clinical AE	16
1623	Placebo	Clinical AE	27
1272	Placebo	Clinical AE	33
1153	Placebo	Clinical AE	39
1596	Losartan 25mg BID	Clinical AE	41
1421	Placebo	Clinical AE	43
1560	Placebo	Clinical AE	52
1246	Placebo	Clinical AE	84
1330	Placebo	Clinical AE	85
1599	Losartan 50 mg	Lab AE	84
1730	Losartan 50 mg	Lab AE	90
1628	Losartan 50 mg	Lost to Followup	1
1685	Losartan 25 mg	Lost to Followup	1
1407	Losartan 50 mg	Lost to Followup	30
1676	Losartan 25 mg	Lost to Followup	57
1655	Placebo	Protocol Deviation	12
1417	Placebo	Protocol Deviation	18
1692	Losartan 25 mg	Protocol Deviation	27
1290	Losartan 50 mg	Protocol Deviation	36
1631	Losartan 25mg BID	Protocol Deviation	60
1674	Losartan 25mg BID	Protocol Deviation	60
1668	Losartan 25 mg	Protocol Deviation	85
1669	Placebo	Protocol Deviation	85
1219	Placebo	Therapy Ineffective	7
1161	Losartan 50 mg	Therapy Ineffective	13
1288	Losartan 25mg BID	Therapy Ineffective	15
1273	Losartan 25 mg	Therapy Ineffective	16
1280	Placebo	Therapy Ineffective	21
1164	Placebo	Therapy Ineffective	27
1168	Losartan 50 mg	Therapy Ineffective	28
1170	Placebo	Therapy Ineffective	28
1175	Losartan 25 mg	Therapy Ineffective	28
1464	Placebo	Therapy Ineffective	28
1174	Losartan 50 mg	Therapy Ineffective	35
1691	Placebo	Therapy Ineffective	35
1768	Placebo	Therapy Ineffective	55
1228	Losartan 25mg BID	Therapy Ineffective	58
1249	Losartan 50 mg	Therapy Ineffective	58
1603	Placebo	Therapy Ineffective	60
1126	Placebo	Therapy Ineffective	61
1411	Losartan 50 mg	Therapy Ineffective	62
1310	Losartan 25mg BID	Patient Withdrew	7
1267	Losartan 25mg BID	Patient Withdrew	27
1420	Losartan 25 mg	Patient Withdrew	28
1386	Losartan 25 mg	Patient Withdrew	29
1127	Losartan 25 mg	Patient Withdrew	50
1418	Losartan 25mg BID	Patient Withdrew	51
1351	Losartan 50 mg	Patient Withdrew	56

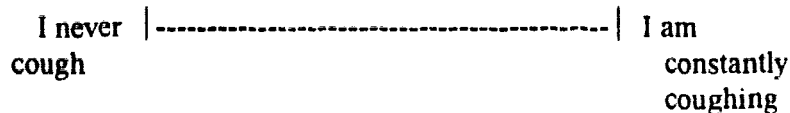
Study 56. Questionnaire and Visual Analog scale.

On this page is a list of words that describe symptoms people have. Please read each one carefully, then mark the box under the answer which describes whether you have experienced the symptom in the last week, and, if so, the extent to which it has bothered you.

	Not at All	A Little	Moderately	Quite a Bit	Extremely
Dry mouth					
Cramps in legs					
Dry cough					
Racing Heart					
Heartburn					
Headache					
Sore throat					
Getting up at night to pass urine					
Flushing of face					

Visual Analog Scale

Please make a vertical line to show how often you cough.



Study L11. Open Label Mean Change in suDBP
Mean Reduction at Months 6 and 12 in Supine Blood Pressure (Trough, mmHg) From Baseline

MEASUREMENT	MONTH	LOS-HCTZ-CCB-OTHER	N	BASE		FINAL		CHANGE			
				Mean	S.D.	Mean	S.D.	Mean	S.D.		
Supine Diast	6	50- 0 -NO -NO	75	101.4	2.0	84.2	5.3	-17.3	5.7		
		50-12.5-NO -NO	4	105.0	5.7	91.5	11.1	-13.5	5.7		
		50-25 -NO -NO									
		100- 0 -NO -NO	47	102.0	2.6	86.3	4.9	-15.7	4.9		
		100-12.5-NO -NO	48	103.3	3.2	87.4	5.4	-15.9	5.9		
		100-25 -NO -NO	4	103.8	2.5	83.3	2.9	-20.5	2.6		
		100-50 -NO -NO									
		150- 0 -NO -NO	17	102.2	3.8	88.2	6.3	-14.0	6.2		
		150-12.5-NO -NO	15	105.0	3.8	88.5	5.1	-16.5	6.8		
		150-25 -NO -NO	33	103.9	3.8	88.4	5.1	-15.5	5.7		
		150-50 -NO -NO	33	105.1	4.5	91.6	7.7	-13.5	8.2		
		12	50- 0 -NO -NO	48	101.6	2.4	83.7	4.4	-17.9	4.5	
	50-12.5-NO -NO		3	101.0	0.0	87.0	8.7	-14.0	8.7		
	50-25 -NO -NO										
	100- 0 -NO -NO		36	101.5	1.5	86.9	7.8	-14.6	7.7		
	100-12.5-NO -NO		27	103.7	3.3	87.3	4.0	-16.4	4.8		
	100-25 -NO -NO		8	103.3	2.9	88.3	3.0	-15.0	4.1		
	150- 0 -NO -NO		12	102.9	3.7	88.3	4.7	-14.6	5.8		
	150-12.5-NO -NO		12	103.8	4.0	88.3	4.7	-15.6	4.2		
	150-25 -NO -NO		25	103.6	3.1	87.8	5.5	-15.8	5.5		
	150-50 -NO -NO		27	105.8	4.8	87.6	4.8	-18.2	6.8		
	Supine Syst		6	50- 0 -NO -NO	75	152.8	14.7	136.5	15.3	-16.3	14.6
				50-12.5-NO -NO	4	152.3	7.4	132.8	8.4	-19.5	11.0
		50-25 -NO -NO									
100- 0 -NO -NO		47		152.3	14.9	137.3	14.1	-15.0	13.4		
100-12.5-NO -NO		48		163.0	14.8	141.4	16.6	-21.6	15.8		
100-25 -NO -NO		4		162.8	14.1	132.5	3.7	-30.3	13.8		
100-50 -NO -NO											
150- 0 -NO -NO		17		160.1	18.6	144.8	15.9	-15.4	13.8		
150-12.5-NO -NO		15		154.7	10.4	134.4	13.0	-20.3	17.6		
150-25 -NO -NO		33		158.4	14.5	139.4	15.7	-19.0	16.5		
150-50 -NO -NO		33		169.3	14.5	144.0	15.5	-25.3	13.2		
12		50- 0 -NO -NO		48	150.3	14.2	133.9	14.1	-16.4	13.7	
		50-12.5-NO -NO	3	151.0	8.7	128.7	8.7	-22.3	10.0		
		50-25 -NO -NO									
		100- 0 -NO -NO	36	154.6	14.5	137.7	12.4	-16.9	14.2		
		100-12.5-NO -NO	27	163.7	15.2	138.4	16.3	-25.3	17.5		
		100-25 -NO -NO	8	150.0	11.6	133.0	9.7	-17.0	16.5		
		150- 0 -NO -NO	12	157.4	10.2	135.9	9.4	-21.5	14.3		
		150-12.5-NO -NO	12	162.8	12.6	145.7	11.3	-17.1	12.6		
		150-25 -NO -NO	25	160.8	13.6	138.4	15.2	-22.4	16.0		
		150-50 -NO -NO	27	166.1	15.1	136.6	14.1	-29.4	13.6		

Study L21. Open Label Mean Change in siDBP.

Mean Reduction at Months 6 and 12 in Sitting Blood Pressure (Trough, mmHg) From Baseline

MEASUREMENT	MONTH	LOS-HCTZ-CCB-OTHER	N	BASE		FINAL		CHANGE	
				Mean	S.D.	Mean	S.D.	Mean	S.D.
Sitting Diast	6	50- 0 -NO -NO	5	99.6	2.9	82.8	5.5	-16.8	8.0
		50-12.5-NO -NO	3	99.7	1.2	84.7	4.0	-15.0	5.0
		50-25 -NO -NO							
	12	50- 0 -NO -NO	5	99.6	2.9	81.6	6.3	-18.0	8.1
		50-12.5-NO -NO							
		50-25 -NO -NO							
Sitting Syst	6	50- 0 -NO -NO	5	144.4	15.7	128.8	14.6	-15.6	11.0
		50-12.5-NO -NO	3	158.3	23.0	134.7	3.8	-23.7	23.0
		50-25 -NO -NO							
	12	50- 0 -NO -NO	5	144.4	15.7	129.2	14.7	-15.2	16.1
		50-12.5-NO -NO	1						
		50-25 -NO -NO	1						

Study L49. Open Label Mean Change in siDBP.

Mean Reduction at Months 6 and 12 in Sitting Blood Pressure (Trough, mmHg) From Baseline

MEASUREMENT	MONTH	LOS-HCTZ-CCB-OTHER	N	BASE		FINAL		CHANGE		
				Mean	S.D.	Mean	S.D.	Mean	S.D.	
Sitting Diast	6	0-6.25-NO -NO	1							
		50- 0 -NO -NO	19	100.1	4.7	86.8	6.7	-13.3	7.1	
		50- 0 -YES-NO	1							
		50-6.25-NO -NO	12	104.9	7.3	87.5	5.4	-17.4	8.7	
		50-12.5-NO -NO	13	104.2	4.7	89.4	7.0	-14.8	8.1	
		50-12.5-YES-NO	22	107.8	7.2	92.3	8.0	-15.5	7.5	
		50-25 -NO -NO	2	101.0	0.0	93.0	8.5	-8.0	8.5	
		50-25 -YES-NO	7	107.1	8.7	93.4	4.4	-13.7	8.6	
		12	50- 0 -NO -NO	5	99.0	3.9	85.4	9.1	-13.6	10.6
			50- 0 -YES-NO	1						
			50-6.25-NO -NO	4	101.0	8.2	85.3	3.1	-15.8	7.2
			50-12.5-NO -NO	5	100.8	1.8	87.2	3.9	-13.6	4.4
			50-12.5-YES-NO	3	110.0	3.5	91.0	2.0	-19.0	5.3
			50-25 -NO -NO	2	109.5	2.1	97.0	2.8	-12.5	4.9
			50-25 -YES-NO	7	104.4	5.7	87.7	8.9	-16.7	11.6
Sitting Syst	6	0-6.25-NO -NO								
		50- 0 -NO -NO	19	151.8	14.6	137.1	12.8	-14.7	15.3	
		50- 0 -YES-NO								
		50-6.25-NO -NO	12	159.4	14.7	142.3	14.2	-17.2	11.8	
		50-12.5-NO -NO	13	152.2	16.9	134.6	14.9	-17.5	12.2	
		50-12.5-YES-NO	22	166.4	17.8	139.5	13.7	-27.0	18.6	
		50-25 -NO -NO	2	159.0	9.9	123.0	1.4	-36.0	8.5	
		50-25 -YES-NO	7	166.3	21.8	143.4	13.7	-22.9	14.7	
		12	50- 0 -NO -NO	5	154.6	11.5	135.8	11.9	-18.8	5.8
			50- 0 -YES-NO							
			50-6.25-NO -NO	4	153.5	12.7	131.3	8.4	-27.3	10.6
			50-12.5-NO -NO	5	153.4	19.6	136.4	19.3	-17.0	7.6
			50-12.5-YES-NO	3	165.0	17.3	137.3	3.5	-27.7	13.9
			50-25 -NO -NO	2	153.0	2.8	135.0	2.8	-18.0	0.0
			50-25 -YES-NO	7	163.9	21.1	141.4	18.4	-22.4	14.7

Study L50. Open Label Mean Change in siDBP.

Mean Reduction at Months 6 and 12 in Sitting Blood Pressure (Trough, mmHg) From Baseline

MEASUREMENT	MONTH	LOS-HCTZ-CCB-OTHER	N	BASE		FINAL		CHANGE	
				Mean	S.D.	Mean	S.D.	Mean	S.D.
Sitting Diast	6	50-0 -NO -NO	47	99.2	3.9	84.8	5.2	-14.4	5.4
		50-0 -YES-NO							
		50-6.25-NO -NO	23	101.2	4.3	88.3	4.0	-12.8	5.7
		50-12.5-NO -NO	42	102.5	4.6	88.7	4.6	-13.8	6.1
		50-12.5-YES-NO	46	104.5	5.0	89.6	5.7	-14.9	7.4
	50-25 -YES-NO	4	109.0	2.2	93.0	5.9	-16.0	5.0	
	12	50-0 -NO -NO	23	99.3	4.0	85.7	6.0	-13.7	4.5
		50-6.25-NO -NO	8	101.1	2.9	89.1	6.2	-12.0	5.2
		50-12.5-NO -NO	18	102.7	4.2	88.6	5.2	-14.1	7.4
		50-12.5-YES-NO	21	103.9	5.0	86.9	6.2	-17.0	7.4
50-25 -NO -NO									
50-25 -YES-NO									
Sitting Syst	6	50-0 -NO -NO	47	144.4	11.5	129.4	12.1	-15.0	9.1
		50-0 -YES-NO							
		50-6.25-NO -NO	23	151.3	12.6	136.4	13.9	-14.8	15.5
		50-12.5-NO -NO	42	156.0	15.2	136.5	12.6	-19.5	15.9
		50-12.5-YES-NO	46	161.5	20.4	141.3	14.8	-20.2	14.9
	50-25 -YES-NO	4	170.8	12.4	143.5	8.4	-27.3	19.2	
	12	50-0 -NO -NO	23	142.3	12.7	130.6	13.2	-11.7	11.3
		50-6.25-NO -NO	8	153.9	13.0	140.3	10.5	-13.6	13.2
		50-12.5-NO -NO	18	160.7	15.7	140.7	11.4	-20.1	15.5
		50-12.5-YES-NO	21	165.9	22.0	143.6	15.1	-22.3	17.3
50-25 -NO -NO		1							
50-25 -YES-NO	1								

Study L54. Open Label Mean Change in siDBP.

Mean Reduction at Month 6 in Sitting Blood Pressure (Trough, mmHg) From Baseline

MEASUREMENT	MONTH	LOS-HCTZ-CCB-OTHER	N	BASE		FINAL		CHANGE	
				Mean	S.D.	Mean	S.D.	Mean	S.D.
Sitting Diast	6	50-6.25-NO -NO	14	99.6	2.6	85.4	3.1	-14.1	3.4
		50-12.5-NO -NO	5	102.2	5.3	88.2	8.7	-14.0	4.4
		50-12.5-YES-NO	7	105.1	6.3	89.0	3.5	-16.1	4.7
Sitting Syst	6	50-6.25-NO -NO	14	150.7	14.5	134.5	13.7	-16.2	16.4
		50-12.5-NO -NO	5	149.4	7.3	131.4	7.9	-18.0	6.1
		50-12.5-YES-NO	7	159.7	27.2	141.6	15.1	-18.1	16.9

Patients Withdrawn from Open Label Extension of Protocols 011, 021, 049, 050 and 054.

Study	Patient #	Reason Discontinued	Day Discontinued
L11	68	Clinical AE	117
L11	95	Clinical AE	108
L11	97	Clinical AE	269
L11	170	Clinical AE	164
L11	172	Clinical AE	589
L11	174	Clinical AE	89
L11	260	Clinical AE	150
L11	276	Clinical AE	296
L11	322	Clinical AE	265
L11	339	Clinical AE	132
L11	365	Clinical AE	90
L11	402	Clinical AE	178
L11	406	Clinical AE	114
L11	407	Clinical AE	162
L11	493	Clinical AE	181
L11	510	Clinical AE	553
L11	519	Clinical AE	563
L11	579	Clinical AE	364
L11	644	Clinical AE	383
L11	646	Clinical AE	133
L11	648	Clinical AE	88
L11	666	Clinical AE	72
L11	740	Clinical AE	79
L11	764	Clinical AE	266
L11	766	Clinical AE	218
L11	783	Clinical AE	286
L11	818	Clinical AE	419
L11	882	Clinical AE	454
L11	64	Lab AE	103
L11	638	Lab AE	351
L11	178	Lost to Followup	92
L11	179	Lost to Followup	195
L11	186	Lost to Followup	137
L11	188	Lost to Followup	280
L11	378	Lost to Followup	301
L11	474	Lost to Followup	292
L11	596	Lost to Followup	513
L11	770	Lost to Followup	159
L11	809	Lost to Followup	92
L11	816	Lost to Followup	115
L11	817	Lost to Followup	216
L11	677	Protocol Deviation	163
L11	46	Patient Uncooperative	269
L11	355	Patient Uncooperative	217
L11	652	Patient Uncooperative	306
L11	682	Patient Uncooperative	133
L11	801	Patient Uncooperative	345
L11	52	Therapy Ineffective	294
L11	69	Therapy Ineffective	152
L11	91	Therapy Ineffective	300
L11	180	Therapy Ineffective	182
L11	211	Therapy Ineffective	197
L11	229	Therapy Ineffective	62
L11	231	Therapy Ineffective	195
L11	338	Therapy Ineffective	185
L11	364	Therapy Ineffective	252
L11	416	Therapy Ineffective	246
L11	417	Therapy Ineffective	132
L11	444	Therapy Ineffective	634

Patients Withdrawn from Open Label Extension of Protocols 011, 021, 049, 050 and 054. (con't)

Study	Patient #	Reason Discontinued	Day Discontinued
L11	467	Therapy Ineffective	669
L11	484	Therapy Ineffective	179
L11	486	Therapy Ineffective	167
L11	504	Therapy Ineffective	185
L11	568	Therapy Ineffective	183
L11	616	Therapy Ineffective	172
L11	647	Therapy Ineffective	216
L11	654	Therapy Ineffective	238
L11	659	Therapy Ineffective	144
L11	672	Therapy Ineffective	153
L11	674	Therapy Ineffective	167
L11	675	Therapy Ineffective	166
L11	756	Therapy Ineffective	185
L11	758	Therapy Ineffective	98
L11	760	Therapy Ineffective	140
L11	800	Therapy Ineffective	167
L11	875	Therapy Ineffective	186
L11	280	Patient Withdrew	218
L11	401	Patient Withdrew	222
L11	503	Patient Withdrew	342
L11	526	Patient Withdrew	565
L11	527	Patient Withdrew	515
L11	530	Patient Withdrew	472
L11	612	Patient Withdrew	137
L11	645	Patient Withdrew	149
L11	739	Patient Withdrew	133
L11	807	Patient Withdrew	504
L11	819	Patient Withdrew	570
L11	824	Patient Withdrew	118
L11	829	Patient Withdrew	314
L11	413	Other	96
L21	90	Lost to Followup	306
L49	7016	Clinical AE	326
L49	7199	Clinical AE	307
L49	7236	Clinical AE	139
L49	7264	Clinical AE	267
L49	7279	Clinical AE	338
L49	7361	Clinical AE	159
L49	7411	Clinical AE	286
L49	7414	Clinical AE	114
L49	7453	Clinical AE	181
L49	7146	Lost to Followup	113
L49	7172	Lost to Followup	186
L49	7004	Protocol Deviation	129
L49	7170	Protocol Deviation	211
L49	7173	Therapy Ineffective	254
L49	7217	Therapy Ineffective	161
L49	7230	Therapy Ineffective	166
L49	7232	Therapy Ineffective	190
L49	7233	Therapy Ineffective	203
L49	7234	Therapy Ineffective	149
L49	7235	Therapy Ineffective	172
L49	7237	Therapy Ineffective	168
L49	7238	Therapy Ineffective	140
L49	7239	Therapy Ineffective	110
L49	7270	Therapy Ineffective	191
L49	7304	Therapy Ineffective	188
L49	7410	Therapy Ineffective	179
L49	7436	Therapy Ineffective	134

Patients Withdrawn from Open Label Extension of Protocols 011, 021, 049, 050 and 054. (con't)

Study	Patient #	Reason Discontinued	Day Discontinued
L49	7449	Therapy Ineffective	81
L49	7451	Therapy Ineffective	134
L49	7156	Patient Withdrew	102
L49	7227	Patient Withdrew	143
L49	7240	Patient Withdrew	155
L49	7267	Patient Withdrew	109
L49	7433	Patient Withdrew	149
L49	7450	Patient Withdrew	124
L49	7011	Other	260
L50	2042	Clinical AE	222
L50	2187	Clinical AE	245
L50	2212	Clinical AE	193
L50	2217	Clinical AE	317
L50	2226	Clinical AE	323
L50	2241	Clinical AE	126
L50	2246	Clinical AE	228
L50	2248	Clinical AE	216
L50	2255	Clinical AE	273
L50	2283	Clinical AE	264
L50	2325	Clinical AE	153
L50	2336	Clinical AE	202
L50	2365	Clinical AE	59
L50	2371	Clinical AE	332
L50	2373	Clinical AE	197
L50	2414	Clinical AE	244
L50	2230	Lab AE	232
L50	2305	Lab AE	154
L50	2127	Lost to Followup	161
L50	2377	Lost to Followup	167
L50	2067	Patient Uncooperative	118
L50	2062	Therapy Ineffective	127
L50	2074	Therapy Ineffective	171
L50	2143	Therapy Ineffective	203
L50	2155	Therapy Ineffective	204
L50	2161	Therapy Ineffective	159
L50	2199	Therapy Ineffective	225
L50	2222	Therapy Ineffective	207
L50	2247	Therapy Ineffective	20
L50	2268	Therapy Ineffective	252
L50	2324	Therapy Ineffective	153
L50	2329	Therapy Ineffective	174
L50	2398	Therapy Ineffective	163
L50	2165	Patient Withdrew	161
L50	2169	Patient Withdrew	189
L50	2174	Patient Withdrew	189
L50	2188	Patient Withdrew	149
L50	2231	Patient Withdrew	209
L50	2281	Patient Withdrew	218
L50	2405	Patient Withdrew	304
L50	2404	Other	307
L54	8815	Clinical AE	205
L54	8263	Patient Withdrew	101

Listing of Losartan and Placebo Adverse Event Incidence Rates for Studies 011, 050 and 065 Combined.

	Losartan	Placebo	Total
Number Randomized	985	302	1287
Adverse Experience			
ABRASION, CORNEAL	0.1%	0.3%	0.2%
ACCOMMODATION DISORDER	0.1%	0.0%	0.1%
ACID REGURGITATION	0.1%	0.3%	0.2%
ACNE	0.1%	0.0%	0.1%
ALK. PHOS. INCREASED	0.3%	0.7%	0.4%
ALLERGY	0.2%	0.0%	0.2%
ALOPECIA	0.3%	0.0%	0.2%
ALT INCREASED	2.8%	1.7%	2.6%
ALTERATION, RETINAL PIGMENT	0.1%	0.0%	0.1%
ANGINA PECTORIS	0.3%	0.0%	0.2%
ANOREXIA	0.5%	0.3%	0.5%
ANOSMIA	0.1%	0.0%	0.1%
ANXIETY	0.6%	0.7%	0.6%
ANXIETY DISORDER	0.1%	0.0%	0.1%
APPETITE CHANGE	0.1%	0.0%	0.1%
APPETITE INCREASE	0.2%	0.0%	0.2%
ARCUS SENILIS	0.1%	0.0%	0.1%
ARRHYTHMIA	0.1%	0.0%	0.1%
ARTERIOLAR NARROWING	0.0%	0.3%	0.1%
ARTHRALGIA	0.1%	0.7%	0.2%
ARTHRITIS	0.1%	0.0%	0.1%
AST INCREASED	1.5%	0.7%	1.3%
ASTHENIA/FATIGUE	3.4%	5.0%	3.7%
ASTHMA	0.3%	0.0%	0.2%
ATAXIA	0.0%	0.7%	0.2%
AV BLOCK, FIRST DEGREE	0.2%	0.3%	0.2%
AV BLOCK, SECOND DEGREE	0.1%	0.0%	0.1%
AXIS DISTURBANCE	0.3%	0.0%	0.2%
BACTERIURIA	0.3%	0.0%	0.2%
BENIGN PROSTATIC HYPERTROPHY	0.1%	0.0%	0.1%
BICARBONATE DECREASED	0.1%	0.0%	0.1%
BLURRED VISION	0.3%	1.0%	0.5%
BONE FIXATION DEVICE	0.1%	0.0%	0.1%
BOWEL PATTERN CHANGE	0.1%	0.0%	0.1%
BRADYCARDIA	0.1%	0.0%	0.1%
BROMHYDROSIS	0.0%	0.3%	0.1%
BRONCHITIS	0.8%	0.7%	0.8%
BROWACHE	0.1%	0.0%	0.1%
BURN	0.1%	0.7%	0.2%
BURNING/STINGING, EYE	0.3%	0.0%	0.2%
BURSITIS	0.0%	0.3%	0.1%
CARDIOMEGALY	0.1%	0.0%	0.1%
CARPAL TUNNEL SYNDROME	0.1%	0.0%	0.1%
CELLULITIS	0.1%	0.0%	0.1%
CHILLS	0.4%	0.3%	0.4%
CHOLELITHIASIS	0.1%	0.0%	0.1%
CONFUSION	0.1%	0.3%	0.2%
CONGESTION, NASAL	2.0%	1.3%	1.9%
CONGESTION, PULMONARY	0.2%	0.0%	0.2%
CONGESTION, RESPIRATORY	0.6%	0.7%	0.6%
CONJUNCTIVITIS	0.1%	0.0%	0.1%
CONSTIPATION	0.5%	0.3%	0.5%
CONTUSION	0.2%	0.3%	0.2%
COSTOCHONDRITIS	0.1%	0.0%	0.1%
COUGH	3.6%	3.0%	3.4%
CRAMP, MUSCLE	1.0%	0.3%	0.9%

Listing of Losartan and Placebo Adverse Event Incidence Rates for Studies 011, 050 and 065 Combined.

	Losartan	Placebo	Total
Number randomized	985	302	1287
CVA	0.1%	0.3%	0.2%
DEATH	0.0%	0.3%	0.1%
DEFECT, RETINAL	0.1%	0.0%	0.1%
DENTAL CARIES	0.1%	0.3%	0.2%
DEPRESSION	0.5%	0.7%	0.5%
DERMATITIS	0.1%	0.0%	0.1%
DERMATITIS, CONTACT	0.2%	0.0%	0.2%
DERMATOMYCOSIS	0.2%	0.0%	0.2%
DIARRHEA	2.3%	2.0%	2.3%
DIPLOPIA	0.1%	0.0%	0.1%
DISCOMFORT, PHARYNGEAL	0.5%	0.3%	0.5%
DISCOMFORT, VISUAL	0.2%	0.0%	0.2%
DISTENTION, ABDOMINAL	0.1%	0.7%	0.2%
DIZZINESS	3.2%	2.0%	3.0%
DRUSEN, MACULAR	0.0%	0.3%	0.1%
DRY EYES	0.1%	0.0%	0.1%
DRY MOUTH	0.2%	0.7%	0.3%
DYSARTHRIA	0.0%	0.3%	0.1%
DYSCHIZIA	0.1%	0.0%	0.1%
DYSPEPSIA	1.1%	1.0%	1.1%
DYSPHASIA	0.1%	0.0%	0.1%
DYSPNEA	0.6%	1.7%	0.9%
DYSPNEA, EXERTIONAL	0.2%	0.0%	0.2%
ECCHYMOSIS	0.0%	0.3%	0.1%
ECZEMA	0.0%	0.3%	0.1%
EDEMA, EYELID	0.1%	0.0%	0.1%
EDEMA, FACIAL	0.1%	0.0%	0.1%
EDEMA/SWELLING	1.8%	2.0%	1.9%
EMOTIONAL CHANGES	0.2%	0.0%	0.2%
ENTRAPMENT, NERVE	0.1%	0.0%	0.1%
EPISTAXIS	0.7%	0.0%	0.5%
ERYTHEMA	0.1%	0.0%	0.1%
ESOPHAGITIS	0.1%	0.3%	0.2%
EUSTACHIAN TUBE DISORDER	0.1%	0.0%	0.1%
EXCORIATION	0.1%	0.0%	0.1%
EXTRAOCULAR MUSCLE IMBALANCE	0.1%	0.0%	0.1%
EYE MOVEMENT DISORDER	0.1%	0.0%	0.1%
FALLING	0.1%	0.0%	0.1%
FASCICULATION	0.1%	0.0%	0.1%
FECAL ABNORMALITY	0.2%	0.0%	0.2%
FEVER	0.8%	1.0%	0.9%
FLATULENCE	0.0%	0.7%	0.2%
FLU LIKE ILLNESS	0.2%	1.7%	0.5%
FLUID OVERLOAD	0.4%	0.3%	0.4%
FLUSHING	0.8%	1.0%	0.9%
FOLLICULITIS	0.1%	0.0%	0.1%
FRACTURE, ANKLE	0.1%	0.0%	0.1%
FRACTURE, PATELLA, RT	0.1%	0.0%	0.1%
FULLNESS IN EARS	0.1%	0.3%	0.2%
GALLOP RHYTHM	0.0%	0.7%	0.2%
GASTROENTERITIS	0.1%	0.3%	0.2%
GASTROENTERITIS, INFECTIOUS	0.3%	1.0%	0.5%
GGT INCREASED	0.1%	0.3%	0.2%
GLAUCOMA	0.0%	0.3%	0.1%
GLOSSODYNIA	0.1%	0.0%	0.1%
GLYCOSURIA	0.2%	0.0%	0.2%
GOUT	0.5%	0.3%	0.5%
RETINOPATHY, KEITH WAGENER, (II)	0.1%	0.0%	0.1%

Listing of Losartan and Placebo Adverse Event Incidence Rates for Studies 011, 050 and 065 Combined.

	Losartan	Placebo	Total
Number Randomized	985	302	1287
HDL DECREASED	0.1%	0.0%	0.1%
HEADACHE	14.2%	15.9%	14.6%
HEADACHE, VASCULAR	0.0%	0.3%	0.1%
HEARING LOSS	0.1%	0.0%	0.1%
HEART FAILURE	0.2%	0.7%	0.3%
HEMATOCRIT DECREASED	0.2%	0.0%	0.2%
HEMATOCRIT INCREASED	0.0%	0.3%	0.1%
HEMATURIA	0.7%	0.3%	0.6%
HEMIPARESIS	0.1%	0.0%	0.1%
HEMOGLOBIN DECREASED	0.1%	0.0%	0.1%
HEMOGLOBIN INCREASED	0.0%	0.3%	0.1%
HEMOGLOBINURIA	0.3%	0.0%	0.2%
HEMOPHTHALMOS	0.1%	0.0%	0.1%
HEMORRHAGE, RETINAL	0.0%	0.3%	0.1%
HEMORRHAGE, SUBCONJUNCTIVAL	0.1%	0.0%	0.1%
HEPATITIS A AB. POSITIVE	0.1%	0.0%	0.1%
HEPATITIS, VIRAL	0.1%	0.0%	0.1%
HERNIA, INGUINAL	0.1%	0.0%	0.1%
HERPES SIMPLEX	0.2%	0.0%	0.2%
HERPES ZOSTER	0.2%	0.0%	0.2%
HOARSENESS	0.0%	0.7%	0.2%
HYPERCHOLESTEROLEMIA	0.2%	0.0%	0.2%
HYPERESTHESIA	0.0%	0.3%	0.1%
HYPERGLYCEMIA	0.8%	0.3%	0.7%
HYPERKALEMIA	0.1%	0.0%	0.1%
HYPERPIGMENTATION	0.1%	0.0%	0.1%
HYPERTENSION	0.1%	0.0%	0.1%
HYPERTENSION INCREASED	0.1%	0.0%	0.1%
HYPERTRIGLYCERIDES	0.2%	0.3%	0.2%
HYPERURICEMIA	0.5%	0.3%	0.5%
HYPERVENTILATION	0.1%	0.0%	0.1%
HYPESTHESIA	0.2%	0.0%	0.2%
HYPOCALCEMIA	0.1%	0.0%	0.1%
HYPOGLYCEMIA	0.1%	0.0%	0.1%
HYPOKALEMIA	0.2%	0.3%	0.2%
HYPOTENSION, ORTHOSTATIC	0.1%	0.0%	0.1%
IMPETIGO	0.1%	0.0%	0.1%
IMPOTENCE	0.7%	0.3%	0.6%
INFECTION, DENTAL PROCESS	0.2%	0.7%	0.3%
INFECTION, EYE	0.1%	0.0%	0.1%
INFECTION, HERPES	0.1%	0.0%	0.1%
INFECTION, RESPIRATORY	0.1%	0.0%	0.1%
INFECTION, SKIN	0.1%	0.0%	0.1%
INFECTION, ULCER, SKIN	0.1%	0.0%	0.1%
INFECTION, URINARY TRACT	0.7%	1.0%	0.8%
INFECTION, VIRAL	0.1%	0.0%	0.1%
INFLAMMATION, EYELID	0.2%	0.3%	0.2%
INFLUENZA	0.3%	0.3%	0.3%
INSOMNIA	1.2%	0.3%	1.0%
INTRAOCULAR PRES. INCREASE	0.1%	0.0%	0.1%
IRRITABILITY	0.2%	0.3%	0.2%
IRRITABLE BOWEL SYNDROME	0.3%	0.0%	0.2%
IRRITATION, NASAL	0.1%	0.0%	0.1%
ISCHEMIA, MYOCARDIAL	0.1%	0.3%	0.2%
ITCHING, EYE	0.3%	0.3%	0.3%
KERATOSIS, SEBORRHEIC	0.2%	0.0%	0.2%
LACERATION	0.1%	0.3%	0.2%
LARYNGITIS	0.2%	0.3%	0.2%

Listing of Losartan and Placebo Adverse Event Incidence Rates for Studies 011, 050 and 065 Combined.

	Losartan	Placebo	Total
Number Randomized	985	302	1287
LDH INCREASED	0.1%	0.3%	0.2%
LEFT ANTERIOR HEMIBLOCK	0.1%	0.0%	0.1%
LEFT ATRIAL HYPERTROPHY	0.1%	0.3%	0.2%
LEFT BUNDLE BRANCH BLOCK	0.1%	0.3%	0.2%
LEFT VENTRICULAR HYPERTROPHY	0.0%	0.3%	0.1%
LESION, SKIN	0.1%	0.0%	0.1%
LEUKOCYTE COUNT INCREASED	0.1%	0.0%	0.1%
LEUKOCYTES DECREASED	0.4%	1.0%	0.5%
LIBIDO DECREASED	0.6%	0.0%	0.5%
LYMPHADENOPATHY	0.2%	0.7%	0.3%
LYMPHOCYTES DECREASED	0.1%	0.0%	0.1%
LYMPHOCYTES INCREASED	0.0%	0.3%	0.1%
MALaise	0.2%	0.0%	0.2%
MASS, BREAST	0.1%	0.0%	0.1%
MELENA	0.0%	0.3%	0.1%
MEMORY IMPAIRMENT	0.2%	0.3%	0.2%
MENSTRUATION DISORDER	0.2%	0.0%	0.2%
MIGRAINE	0.0%	0.7%	0.2%
MONOCYTES INCREASED	0.0%	0.3%	0.1%
MYALGIA	0.9%	1.0%	0.9%
MYOCARDIAL INFARCTION	0.1%	0.3%	0.2%
MYOPIA	0.1%	0.0%	0.1%
NAIL DISORDER	0.0%	0.3%	0.1%
NAUSEA	1.7%	3.6%	2.2%
NEOPLASM, INTESTINAL, METASTATIC	0.0%	0.3%	0.1%
NEOPLASM, MALIGNANT	0.1%	0.0%	0.1%
NEOPLASM, SKIN, BENIGN	0.2%	0.0%	0.2%
NERVOUSNESS	0.0%	1.3%	0.3%
NEUTROPHILS DECREASED	0.0%	0.7%	0.2%
NEUTROPHILS INCREASED	0.2%	0.0%	0.2%
NOCTURIA	0.0%	0.3%	0.1%
NODULE, CUTANEOUS	0.0%	0.3%	0.1%
NONSPECIFIC ST T CHANGE	0.1%	0.0%	0.1%
OBSTRUCTION, AIRWAY, UPPER	0.1%	0.0%	0.1%
OPACITY, LENS	0.1%	0.0%	0.1%
OPACITY, VITREOUS	0.1%	0.0%	0.1%
ORTHOSTATIC EFFECTS	0.8%	0.0%	0.6%
OSTEOARTHRITIS	0.1%	0.0%	0.1%
OTITIS	0.2%	0.3%	0.2%
OTITIS EXTERNA	0.0%	0.3%	0.1%
OTITIS MEDIA	0.0%	0.3%	0.1%
PAIN	0.2%	0.6%	0.2%
PAIN, ABDOMINAL	1.5%	2.3%	1.7%
PAIN, ANKLE	0.2%	0.0%	0.2%
PAIN, ARM	0.5%	0.3%	0.5%
PAIN, BACK	1.8%	1.3%	1.7%
PAIN, BONE	0.2%	0.0%	0.2%
PAIN, BREAST	0.2%	0.0%	0.2%
PAIN, CHEST	1.3%	1.7%	1.4%
PAIN, DENTAL	0.7%	0.7%	0.7%
PAIN, EAR	0.3%	0.7%	0.4%
PAIN, EYE	0.0%	1.0%	0.2%
PAIN, FINGER	0.2%	0.0%	0.2%
PAIN, FLANK	0.3%	0.0%	0.2%
PAIN, FOOT	0.4%	0.7%	0.5%
PAIN, HAND	0.2%	0.0%	0.2%
PAIN, HIP	0.5%	0.0%	0.4%
PAIN, JAW	0.1%	0.0%	0.1%
PAIN, KNEE	0.6%	0.3%	0.5%

Listing of Losartan and Placebo Adverse Event Incidence Rates for Studies 011, 050 and 065 Combined.

	Losartan	Placebo	Total
Number Randomized	985	302	1287
PAIN, LEG	1.0%	0.0%	0.8%
PAIN, MUSCULOSKELETAL	0.5%	0.0%	0.4%
PAIN, NECK	0.4%	0.7%	0.5%
PAIN, POSTOPERATIVE	0.3%	0.3%	0.3%
PAIN, SHOULDER	0.9%	0.3%	0.8%
PAIN, TOE	0.2%	0.0%	0.2%
PAIN, WRIST	0.2%	0.0%	0.2%
PALPITATION	0.7%	0.3%	0.6%
PARESTHESIA	0.8%	0.3%	0.7%
PTT INCREASE	0.1%	0.3%	0.2%
PERVERSION, TASTE	0.1%	0.3%	0.2%
PHARYNGITIS	1.8%	3.0%	2.1%
PHLEBITIS/THROMBOPHLEBITIS	0.0%	0.3%	0.1%
PHOTOPHOBIA	0.0%	0.3%	0.1%
PHOTOPSIA	0.1%	0.0%	0.1%
PHOTOSENSITIVITY	0.1%	0.0%	0.1%
PLATELET COUNT DECREASED	0.1%	0.0%	0.1%
PLATELET COUNT INCREASED	0.2%	0.0%	0.2%
PNEUMONIA	0.2%	0.0%	0.2%
PNEUMONIA, VIRAL	0.1%	0.0%	0.1%
POLYURIA	0.2%	0.0%	0.2%
PVC	0.2%	0.7%	0.3%
PROLONGED QT INTERVAL	0.2%	0.0%	0.2%
PROTEINURIA	0.8%	1.3%	0.9%
PROTHROMBIN TIME INCREASED	0.1%	0.3%	0.2%
PRURITUS	0.6%	0.3%	0.5%
PRURITUS ANI	0.1%	0.0%	0.1%
PRURITUS VULVAE	0.1%	0.0%	0.1%
PYURIA	0.7%	0.7%	0.7%
RADICULOPATHY, LUMBAR	0.1%	0.0%	0.1%
RASH	0.5%	1.3%	0.7%
RAYNAUD'S PHENOMENON	0.1%	0.3%	0.2%
REDNESS, EYE	0.1%	0.0%	0.1%
RETINOPATHY	0.1%	0.0%	0.1%
RHINITIS	0.5%	0.7%	0.5%
RHINITIS, ALLERGIC	0.2%	0.3%	0.2%
RHINORRHEA	0.1%	1.0%	0.3%
RIGHT BUNDLE BRANCH BLOCK	0.1%	0.0%	0.1%
SALIVATION INCREASE	0.1%	0.0%	0.1%
SCIATICA	0.0%	0.3%	0.1%
SCLEROSIS, NUCLEAR	0.2%	0.0%	0.2%
SCOTOMA	0.1%	0.0%	0.1%
SERUM CREATININE INCREASED	0.1%	0.0%	0.1%
SINUS BRADYCARDIA	0.3%	0.0%	0.2%
SINUS DISORDER	1.6%	1.3%	1.6%
SINUS DISORDER, CHRONIC	0.0%	0.3%	0.1%
SINUSITIS	0.9%	0.3%	0.8%
SLEEP DISORDER	0.1%	0.0%	0.1%
SNEEZING	0.4%	0.0%	0.3%
SOMNOLENCE	0.2%	0.3%	0.2%
SPASM	0.1%	0.0%	0.1%
SPRAIN, ARM	0.1%	0.0%	0.1%
SPRAIN, KNEE	0.1%	0.0%	0.1%
SPRAIN, NECK	0.1%	0.0%	0.1%
STIFFNESS	0.5%	0.0%	0.4%
STRAIN	0.2%	0.3%	0.2%
STRAIN, BACK	0.3%	0.7%	0.4%
SWEATING	0.4%	0.3%	0.4%

Listing of Losartan and Placebo Adverse Event Incidence Rates for Studies 011, 050 and 065 Combined.

	Losartan	Placebo	Total
Number Randomized	985	302	1287
SWELLING, JOINT	0.5%	1.0%	0.6%
SYNCOPE	0.2%	0.0%	0.2%
T WAVE INVERSION	0.0%	0.3%	0.1%
TACHYCARDIA	0.5%	0.3%	0.5%
TASTE LOSS	0.1%	0.0%	0.1%
TEARING	0.2%	0.7%	0.3%
TENDINITIS	0.0%	0.7%	0.2%
THIRST	0.2%	0.3%	0.2%
TIC	0.1%	0.3%	0.2%
TINEA CRURIS	0.1%	0.0%	0.1%
TINNITUS	0.5%	0.0%	0.4%
TM JOINT DYSFUNCTION	0.1%	0.0%	0.1%
TONSILLITIS	0.1%	0.0%	0.1%
TOOTH DISORDER	0.1%	0.0%	0.1%
TOOTH ERUPTION DISTURBANCE	0.1%	0.0%	0.1%
TOTAL BILIRUBIN INCREASED	0.3%	0.0%	0.2%
TRAUMA	0.0%	0.7%	0.2%
TRAUMA, CARTILAGE	0.0%	0.3%	0.1%
TYMPANOSCLEROSIS	0.1%	0.0%	0.1%
ULCER, MOUTH	0.1%	0.0%	0.1%
URI	7.8%	6.3%	7.5%
URINARY FREQUENCY	0.5%	0.7%	0.5%
URINARY URGENCY	0.0%	0.3%	0.1%
URINE SEDIMENT ABNORMALITY	0.1%	0.0%	0.1%
URTICARIA	0.2%	0.7%	0.3%
VAGINITIS	0.1%	0.0%	0.1%
VERTIGO	0.6%	0.0%	0.5%
VISUAL ACUITY DECREASED	0.1%	0.0%	0.1%
VOMITING	0.6%	0.3%	0.5%
WARM SENSATION	0.1%	0.7%	0.2%
WEAKNESS, MUSCLE	0.1%	0.3%	0.2%
WEIGHT LOSS	0.1%	0.0%	0.1%
WHEEZING	0.1%	0.0%	0.1%
TOTAL			

Complete Listing of Losartan Adverse Event Incidence by Dose in Nine Trials.

	10 mg	25 mg	50 mg	100 mg	150 mg	variable	25 mg bid	50/100 mg	50 mg bid	Total
Patients Randomized	80	201	341	134	84	382	106	123	31	1482
Patients with at Least 1 AE	41	112	184	58	47	201	60	69	14	786
Percent with at least 1 AE	51%	56%	61%	43%	56%	53%	57%	56%	45%	53%
Adverse Experience										
ABNORMAL SENSATION	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0	0.0%	0	0.1%
ABRASION, CORNEAL	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
ACCOMMODATION DISORDER	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
ACID REGURGITATION	0.0%	0.0%	0.3%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
ACNE	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
ALK. PHOS. INCREASED	0.0%	0.5%	0.3%	0.0%	0.0%	1.0%	0.9%	0.0%	0.0%	0.5%
ALLERGY	0.0%	0.0%	0.6%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%	0.2%
ALOPECIA	1.3%	0.0%	0.3%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%
ALT INCREASED	3.8%	3.0%	1.5%	3.7%	3.6%	1.0%	0.0%	4.9%	6.5%	2.3%
ALTERATION, RETINAL PIGMENT	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
ANGINA PECTORIS	1.3%	0.0%	0.0%	0.0%	0.0%	1.3%	0.0%	1.6%	0.0%	0.5%
ANOREXIA	0.0%	0.5%	0.9%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.3%
ANOSMIA	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.9%	0.0%	0.0%	0.1%
ANXIETY	1.3%	0.5%	0.9%	0.7%	0.0%	0.3%	0.0%	0.0%	0.0%	0.5%
ANXIETY DISORDER	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
APPETITE CHANGE	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
APPETITE INCREASE	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.9%	0.0%	0.0%	0.1%
ARCUS SENILIS	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
ARRHYTHMIA	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.9%	0.0%	0.0%	0.1%
ARTHRALGIA	0.0%	0.0%	0.3%	0.0%	0.0%	0.8%	0.0%	0.0%	0.0%	0.3%
ARTHRITIS	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%	0.9%	0.0%	0.0%	0.2%
AST INCREASED	2.5%	2.0%	1.2%	0.7%	1.2%	0.5%	0.0%	2.4%	6.5%	1.3%
ASTHENIA/FATIGUE	3.8%	2.5%	3.5%	3.0%	4.8%	6.0%	5.7%	1.6%	3.2%	4.0%
ASTHMA	0.0%	0.5%	0.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%
ATAXIA	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%	0.0%	0.0%	0.0%	0.1%
ATRIAL FIBRILLATION	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
AV BLOCK, FIRST DEGREE	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.6%	0.0%	0.1%
AV BLOCK, SECOND DEGREE	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
AXIS DISTURBANCE	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.9%	0.8%	0.0%	0.2%
BACTERIURIA	0.0%	0.5%	0.0%	1.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%
BENIGN PROSTATIC HYPERTROPHY	0.0%	0.0%	0.0%	0.0%	3.0%	0.0%	0.9%	0.0%	0.0%	0.1%
BICARBONATE DECREASED	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	3.2%	0.1%
BLURRED VISION	0.0%	0.5%	0.3%	0.0%	0.0%	0.3%	0.0%	0.8%	0.0%	0.3%
BONE FIXATION DEVICE	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
BOWEL PATTERN CHANGE	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
BRADYCARDIA	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
BRONCHITIS	0.0%	1.5%	0.0%	0.0%	1.2%	0.8%	1.9%	1.6%	3.2%	0.8%
BROWACHE	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
BUN INCREASED	0.0%	0.0%	0.0%	0.0%	0.0%	1.0%	0.0%	0.0%	0.0%	0.3%
BURN	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
BURNING/STINGING, EYE	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.4%	0.0%	0.2%
CARBON DIOXIDE INCREASED	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%	0.0%	0.0%	0.0%	0.1%
CARDIOMEGALY	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
CARPAL TUNNEL SYNDROME	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.9%	0.0%	0.0%	0.1%
CELLULITIS	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
CHILLS	0.0%	0.5%	0.6%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%	0.3%
CHOLECYSTITIS	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
CHOLELITHIASIS	1.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
COLD EXTREMITIES	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
COLD SENSATION	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
CONFUSION	0.0%	0.0%	0.0%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%	0.1%
CONGESTION, NASAL	0.0%	1.5%	2.6%	2.2%	3.6%	0.3%	2.8%	1.6%	6.5%	1.8%

Complete Listing of Losartan Adverse Event Incidence by Dose in Nine Trials.

	10 mg	25 mg	50 mg	100 mg	150 mg	variable	25 mg bid	50/100 mg	50 mg bid	Total
CONGESTION, PULMONARY	0.0%	1.0%	0.0%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%
CONGESTION, RESPIRATORY	1.3%	1.0%	0.6%	1.5%	0.0%	0.3%	0.0%	0.8%	0.0%	0.6%
CONJUNCTIVITIS	0.0%	0.0%	0.3%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
CONSTIPATION	1.3%	1.0%	0.3%	0.0%	1.2%	0.5%	0.0%	0.0%	3.2%	0.5%
CONTUSION	1.3%	0.0%	0.0%	0.0%	1.2%	0.3%	0.0%	0.0%	0.0%	0.2%
COSTOCHONDRITIS	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.9%	0.0%	0.0%	0.1%
COUGH	6.3%	4.0%	2.5%	3.0%	3.6%	3.1%	2.8%	4.9%	3.2%	3.4%
CRAMP, MUSCLE	0.0%	1.5%	0.9%	0.0%	0.0%	0.5%	0.9%	2.4%	0.0%	0.8%
CVA	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.9%	0.0%	0.0%	0.1%
DEFECT, RETINAL	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
DEFORMITY, LOWER EXTREMITY	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
DENTAL CARIES	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
DEPRESSION	0.0%	0.0%	0.9%	0.0%	1.2%	0.3%	0.0%	0.8%	0.0%	0.4%
DERMATITIS	0.0%	0.0%	0.3%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
DERMATITIS, CONTACT	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
DERMATOMYCOSIS	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.9%	0.0%	0.0%	0.1%
DIARRHEA	3.8%	2.0%	2.9%	1.5%	2.4%	1.3%	1.9%	1.6%	3.2%	2.1%
DIPLOPIA	0.0%	0.0%	0.3%	0.0%	6.0%	0.0%	0.0%	0.0%	0.0%	0.1%
DISCOMFORT, PHARYNGEAL	0.0%	1.5%	0.3%	0.7%	0.0%	0.3%	0.9%	0.0%	0.0%	0.5%
DISCOMFORT, VISUAL	0.0%	0.5%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
DISORIENTATION	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
DISTENTION, ABDOMINAL	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
DIZZINESS	2.5%	4.5%	4.1%	0.7%	2.4%	6.5%	3.8%	3.3%	3.2%	4.2%
DREAM ABNORMALITY	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.0%	3.2%	0.3%
DRY EYES	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
DRY MOUTH	0.0%	0.0%	0.6%	0.0%	0.0%	0.3%	0.9%	0.0%	0.0%	0.3%
DYSCHIZIA	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
DYSPEPSIA	1.3%	1.0%	0.9%	0.7%	3.6%	1.6%	1.9%	0.8%	0.0%	1.3%
DYSPHASIA	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
DYSPNEA	0.0%	0.0%	0.9%	0.0%	0.0%	0.3%	0.0%	2.4%	0.0%	0.5%
DYSPNEA, EXERTIONAL	1.3%	0.0%	0.0%	0.0%	1.2%	0.3%	0.0%	0.0%	0.0%	0.2%
DYSURIA	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
ECZEMA	0.0%	0.0%	0.0%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
EDEMA, EYELID	0.0%	0.0%	0.0%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%	0.1%
EDEMA, FACIAL	0.0%	0.0%	0.0%	0.0%	1.2%	0.3%	0.0%	0.0%	0.0%	0.1%
EDEMA/SWELLING	1.3%	1.5%	2.9%	0.7%	0.0%	2.6%	0.0%	2.4%	0.0%	1.9%
EMBOLISM/INFARCTION, PULMONARY	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
EMOTIONAL CHANGES	0.0%	0.0%	0.0%	0.7%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
ENTRAPMENT, NERVE	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
EOSINOPHILS INCREASED	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.0%	0.0%	0.2%
EPISTAXIS	1.3%	0.5%	1.2%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.5%
ERYTHEMA	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
ESOPHAGITIS	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
EUSTACHIAN TUBE DISORDER	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
EXCORIATION	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
EXTRAOCULAR MUSCLE IMBALANCE	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
EYE MOVEMENT DISORDER	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
FALLING	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.9%	0.0%	0.0%	0.1%
FASCICULATION	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
FASTING GLUCOSE INCREASED	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%	0.0%	0.0%	0.0%	0.1%
FECAL ABNORMALITY	0.0%	0.5%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
FEVER	0.0%	0.5%	0.6%	0.7%	2.4%	0.0%	0.9%	1.6%	0.0%	0.6%
FLATULENCE	0.0%	0.0%	0.0%	0.0%	0.0%	1.0%	0.0%	0.0%	0.0%	0.3%
FLU LIKE ILLNESS	0.0%	0.0%	0.6%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.2%
FLUID OVERLOAD	0.0%	0.5%	0.9%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%
FLUSHING	0.0%	0.0%	1.2%	0.7%	3.6%	0.3%	0.0%	0.8%	0.0%	0.7%
FOLLICULITIS	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%

Complete Listing of Losartan Adverse Event Incidence by Dose in Nine Trials.

	10 mg	25 mg	50 mg	100 mg	150 mg	variable	25 mg bid	50/100 mg	50 mg bid	Total
INFECTION, RESPIRATORY	0.0%	0.0%	0.3%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
INFECTION, SKIN	1.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
INFECTION, ULCER, SKIN	0.0%	0.0%	0.0%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%	0.1%
INFECTION, URINARY TRACT	0.0%	0.5%	0.6%	2.2%	0.0%	0.8%	0.9%	0.0%	0.0%	0.7%
INFECTION, VIRAL	0.0%	0.0%	0.3%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
INFLAMMATION, EYELID	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
INFLUENZA	0.0%	0.0%	0.0%	0.0%	1.2%	2.4%	0.9%	0.8%	3.2%	0.9%
INFUSED VEIN COMPLICATION	0.0%	0.0%	0.0%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
INSOMNIA	1.3%	1.5%	1.8%	0.7%	0.0%	1.3%	0.9%	0.0%	0.0%	1.1%
INTRAOCULAR PRES. INCREASE	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
IRRITABILITY	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
IRRITABLE BOWEL SYNDROME	1.3%	0.5%	0.0%	0.0%	0.0%	0.0%	0.9%	0.0%	0.0%	0.2%
IRRITATION, NASAL	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
ISCHEMIA, MYOCARDIAL	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
ITCHING, EYE	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	1.6%	0.0%	0.2%
KERATOSIS, SEBORRHEIC	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.6%	0.0%	0.1%
LACERATION	1.3%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
LARYNGITIS	0.0%	0.0%	0.3%	0.0%	1.2%	0.0%	0.0%	0.8%	0.0%	0.2%
LDH INCREASED	0.0%	0.0%	0.0%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%	0.1%
LEFT ANTERIOR HEMIBLOCK	1.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
LEFT ATRIAL HYPERTROPHY	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
LEFT BUNDLE BRANCH BLOCK	1.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
LEFT VENTRICULAR HYPERTROPHY	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
LESION, SKIN	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
LEUKOCYTE COUNT INCREASED	0.0%	0.0%	0.3%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
LEUKOCYTES DECREASED	0.0%	1.0%	0.0%	0.7%	1.2%	0.0%	0.0%	0.0%	0.0%	0.3%
LIBIDO DECREASED	1.3%	0.5%	0.6%	0.0%	0.0%	0.0%	1.9%	0.0%	0.0%	0.4%
LIVER PALPABLE	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
LYMPHADENOPATHY	0.0%	0.0%	0.0%	1.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
LYMPHOCYTES DECREASED	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
LYMPHOCYTES INCREASED	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
MALaise	0.0%	0.5%	0.0%	0.0%	1.2%	0.3%	0.0%	0.0%	0.0%	0.2%
MASS, BREAST	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
MEMORY IMPAIRMENT	0.0%	0.0%	0.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
MENSTRUATION DISORDER	0.0%	1.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%
MURMUR, HEART	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
MYALGIA	1.3%	0.5%	0.6%	0.7%	1.2%	0.5%	1.9%	0.8%	3.2%	0.8%
MYOCARDIAL INFARCTION	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
MYOPIA	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
NAUSEA	1.3%	2.0%	2.6%	0.7%	0.0%	2.9%	0.0%	2.4%	3.2%	2.0%
NEOPLASM, MALIGNANT	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.9%	0.0%	0.0%	0.1%
NEOPLASM, SKIN, BENIGN	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
NEUTROPHILS INCREASED	0.0%	0.0%	0.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
NONSPECIFIC ST T CHANGE	1.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
OBSTRUCTION, AIRWAY, UPPER	0.0%	0.0%	0.0%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
OCCCLUSION, ARTERIAL	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
OPACITY, LENS	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
OPACITY, VITREOUS	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
ORTHOSTATIC EFFECTS	0.0%	0.0%	0.6%	2.2%	3.6%	1.0%	0.0%	0.0%	0.0%	0.8%
OSTEOARTHRITIS	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
OSTEOARTHRITIS, ELBOW	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
OTITIS	0.0%	0.5%	0.0%	0.0%	0.0%	0.3%	0.9%	0.0%	0.0%	0.2%
OTITIS MEDIA	0.0%	0.0%	0.0%	0.7%	0.0%	0.3%	0.0%	0.0%	3.2%	0.2%
PAIN	0.0%	0.0%	0.6%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.2%
PAIN, ABDOMINAL	3.8%	1.0%	2.1%	1.5%	1.2%	2.4%	0.0%	0.8%	0.0%	1.7%
PAIN, ANKLE	0.0%	0.5%	0.3%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.2%
PAIN, ARM	0.0%	0.5%	0.3%	0.0%	0.0%	0.8%	0.9%	1.6%	0.0%	0.5%
PAIN, BACK	3.8%	2.0%	2.1%	1.5%	2.4%	2.1%	0.9%	0.8%	0.0%	1.9%

Complete Listing of Losartan Adverse Event Incidence by Dose in Nine Trials.

	10 mg	25 mg	50 mg	100 mg	150 mg	variable	25 mg bid	50/100 mg	50 mg bid	Total
PAIN, BONE	0.0%	0.0%	0.0%	0.7%	0.0%	0.3%	0.0%	0.8%	0.0%	0.2%
PAIN, BREAST	1.3%	0.5%	0.0%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%
PAIN, CHEST	1.3%	2.0%	1.2%	0.7%	1.2%	1.6%	1.9%	0.0%	0.0%	1.3%
PAIN, DENTAL	0.0%	0.0%	0.9%	1.5%	0.0%	0.3%	0.9%	0.8%	0.0%	0.5%
PAIN, EAR	0.0%	0.5%	0.3%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%	0.2%
PAIN, FINGER	0.0%	0.0%	0.0%	0.7%	0.0%	0.3%	0.9%	0.0%	0.0%	0.2%
PAIN, FLANK	0.0%	0.0%	0.3%	1.5%	1.2%	0.0%	0.0%	0.0%	0.0%	0.3%
PAIN, FOOT	0.0%	0.0%	0.6%	0.7%	0.0%	0.3%	0.0%	0.8%	0.0%	0.3%
PAIN, HAND	0.0%	0.0%	0.0%	0.0%	1.2%	0.0%	0.9%	0.0%	0.0%	0.1%
PAIN, HIP	2.5%	0.0%	0.6%	0.0%	0.0%	0.5%	0.0%	0.8%	0.0%	0.5%
PAIN, JAW	0.0%	0.0%	0.0%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%	0.1%
PAIN, KNEE	0.0%	2.5%	0.6%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%
PAIN, LEG	2.5%	1.0%	1.5%	0.7%	0.0%	0.5%	0.0%	1.6%	0.0%	0.9%
PAIN, MUSCULOSKELETAL	0.0%	0.5%	0.6%	1.5%	0.0%	0.3%	0.9%	0.8%	0.0%	0.5%
PAIN, NECK	0.0%	0.5%	0.6%	0.7%	0.0%	0.5%	0.0%	0.0%	0.0%	0.4%
PAIN, PLEURITIC	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
PAIN, POSTOPERATIVE	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.9%	0.8%	0.0%	0.2%
PAIN, SHOULDER	1.3%	1.0%	1.2%	0.0%	2.4%	0.3%	0.0%	0.0%	0.0%	0.7%
PAIN, TOE	0.0%	0.5%	0.3%	0.0%	0.0%	0.3%	0.0%	0.8%	0.0%	0.3%
PAIN, WRIST	0.0%	0.5%	0.3%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.2%
PALLOR	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
PALPITATION	0.0%	1.0%	0.9%	0.0%	0.0%	0.3%	1.9%	0.8%	3.2%	0.7%
PANIC DISORDER	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
PARANOID DISORDER	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
PARESTHESIA	0.0%	1.5%	0.9%	0.0%	1.2%	0.3%	0.0%	0.8%	0.0%	0.6%
PERCUSSION ABNORMAL, LUNG	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
PERVERSION, TASTE	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.9%	0.0%	0.0%	0.1%
PHARYNGITIS	1.3%	2.0%	4.1%	0.7%	0.0%	1.6%	0.0%	0.0%	3.2%	1.8%
PHOTOPSIA	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
PHOTOSENSITIVITY	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
PLATELET COUNT DECREASED	0.0%	0.5%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
PLATELET COUNT INCREASED	1.3%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
PNEUMONIA	0.0%	0.5%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
PNEUMONIA, VIRAL	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
POLYURIA	0.0%	0.0%	0.3%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%	0.1%
PROLONGED QT INTERVAL	0.0%	0.0%	0.3%	0.0%	0.0%	0.3%	0.0%	0.8%	0.0%	0.2%
PROTEINURIA	1.3%	0.5%	1.2%	0.7%	0.0%	0.8%	0.0%	0.8%	0.0%	0.7%
PROTHROMBIN TIME INCREASED	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
PRURITUS	1.3%	1.0%	0.3%	0.0%	0.0%	0.8%	0.9%	0.8%	0.0%	0.6%
PRURITUS ANI	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
PRURITUS VULVAE	0.0%	0.0%	0.0%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
PSORIASIS	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
PTT INCREASED	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
PVC	1.3%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
PYURIA	1.3%	0.5%	0.3%	0.7%	2.4%	0.0%	0.0%	0.8%	0.0%	0.5%
RADICULOPATHY, LUMBAR	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
RASH	0.0%	0.5%	0.6%	0.0%	0.0%	0.8%	0.9%	0.8%	0.0%	0.5%
RAYNAUD'S PHENOMENON	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
REDNESS, EYE	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
REFLUX ESOPHAGITIS	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
RETINOPATHY	1.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
RETINOPATHY, HYPERTENSIVE	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
RETINOPATHY, KEITH WAGENER, (II)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
RHINITIS	1.3%	0.5%	0.6%	0.0%	0.0%	0.8%	0.9%	0.0%	0.0%	0.5%
RHINITIS, ALLERGIC	0.0%	0.0%	0.3%	0.0%	0.0%	0.8%	0.0%	0.8%	0.0%	0.3%
RHINORRHEA	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%	0.9%	0.0%	0.0%	0.2%
RIGHT BUNDLE BRANCH BLOCK	0.0%	0.0%	0.0%	0.7%	0.0%	0.5%	0.0%	0.0%	0.0%	0.2%

Complete Listing of Losartan Adverse Event Incidence by Dose in Nine Trials.

	10 mg	25 mg	50 mg	100 mg	150 mg	variable	25 mg bid	50/100 mg	50 mg bid	Total
SALIVATION INCREASE	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
SALPINGO OOPHORITIS	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
SCLEROSIS, NUCLEAR	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
SCOTOMA	0.0%	0.0%	0.0%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
SERUM CREATININE INCREASED	0.0%	0.0%	0.3%	0.0%	0.0%	1.3%	0.0%	0.0%	0.0%	0.4%
SINUS ARRHYTHMIA	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	3.2%	0.1%
SINUS BRADYCARDIA	0.0%	0.0%	0.3%	0.7%	0.0%	0.3%	0.0%	0.8%	0.0%	0.3%
SINUS DISORDER	2.5%	1.0%	1.5%	1.5%	2.4%	0.3%	0.9%	2.4%	0.0%	1.2%
SINUS TACHYCARDIA	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
SINUSITIS	0.0%	1.0%	1.5%	0.7%	0.0%	0.5%	0.9%	0.8%	0.0%	0.8%
SLEEP DISORDER	0.0%	0.5%	0.0%	0.0%	0.0%	1.0%	0.0%	0.0%	0.0%	0.3%
SNEEZING	1.3%	0.5%	0.3%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%	0.3%
SOMNOLENCE	0.0%	0.0%	0.0%	0.7%	0.0%	1.8%	0.0%	0.8%	0.0%	0.6%
SPASM	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.9%	0.0%	0.0%	0.1%
SPRAIN, ARM	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
SPRAIN, KNEE	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
SPRAIN, NECK	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
STIFFNESS	0.0%	0.5%	0.3%	0.0%	0.0%	0.8%	1.9%	0.8%	0.0%	0.5%
STOMATITIS, APHTHOUS	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
STRAIN	1.3%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
STRAIN, BACK	0.0%	0.0%	0.3%	0.0%	0.0%	0.3%	1.9%	0.0%	0.0%	0.3%
SWEATING	0.0%	0.0%	0.9%	0.0%	0.0%	0.5%	0.9%	0.0%	0.0%	0.4%
SWELLING, JOINT	0.0%	1.5%	0.3%	0.0%	0.0%	0.3%	0.0%	0.8%	0.0%	0.4%
SYNCOPE	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	1.6%	0.0%	0.2%
T WAVE INVERSION	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%	0.0%	0.0%	0.0%	0.1%
TACHYCARDIA	0.0%	0.0%	0.9%	0.0%	1.2%	0.5%	0.0%	0.8%	0.0%	0.5%
TASTE LOSS	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.9%	0.0%	0.0%	0.1%
TEARING	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
TENDINITIS	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%	0.0%	0.0%	0.0%	0.1%
THIRST	0.0%	0.0%	0.0%	0.0%	1.2%	0.5%	0.9%	0.0%	0.0%	0.3%
TIC	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
TINEA CRURIS	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
TINNITUS	0.0%	0.0%	1.2%	0.7%	0.0%	0.5%	0.0%	0.8%	0.0%	0.5%
TM JOINT DYSFUNCTION	1.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
TONSILLITIS	0.0%	0.0%	0.3%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
TOOTH DISORDER	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.9%	0.0%	0.0%	0.1%
TOOTH ERUPTION DISTURBANCE	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
TOTAL BILIRUBIN INCREASED	1.3%	0.0%	0.0%	0.0%	2.4%	0.0%	0.0%	0.0%	0.0%	0.2%
TRAUMA	0.0%	0.5%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
TYMPANOSCLEROSIS	0.0%	0.0%	0.0%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%	0.1%
ULCER, DUODENAL	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
ULCER, MOUTH	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
ULCER, PEPTIC	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
URI	1.3%	9.5%	7.0%	6.0%	8.3%	7.1%	10.4%	8.1%	9.7%	7.4%
URINARY FREQUENCY	1.3%	0.0%	0.3%	0.0%	1.2%	0.0%	1.9%	0.0%	0.0%	0.3%
URINARY INCONTINENCE	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
URINE SEDIMENT ABNORMALITY	0.0%	0.0%	0.0%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
URTICARIA	0.0%	0.0%	0.3%	0.0%	0.0%	0.3%	0.9%	0.0%	0.0%	0.2%
VAGINITIS	1.3%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
VERTIGO	1.3%	0.5%	0.0%	2.2%	2.4%	1.3%	0.0%	0.0%	0.0%	0.8%
VISUAL ACUITY DECREASED	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
VOMITING	0.0%	0.5%	0.6%	0.7%	0.0%	0.8%	0.0%	1.6%	0.0%	0.6%
WARM SENSATION	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.9%	0.0%	0.0%	0.1%
WEAKNESS, MUSCLE	0.0%	0.0%	0.3%	0.0%	0.0%	0.5%	0.0%	0.0%	0.0%	0.2%
WEIGHT LOSS	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
WHEEZING	0.0%	0.0%	0.0%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%	0.1%
TOTAL (Number of Events)	86	232	409	116	100	450	124	164	29	1710

Serious Nonfatal Adverse Experiences in Hypertensive Patients From All Sources

Protocol # / Study #	Patient #	Age/Sex	Treatment	Dose (mg)	Relative Day of Onset	Adverse Experience	Discontinued	Outcome
011-002	0033	56/M	Los	150	1	Pain, Chest	Yes	Recovered
011-004	0070	53/M	Los	50	289	Pain, Bone	No	Recovered
011-019	0381	52/M	Los	50	542*	Myocardial Infarction	No	Present
011-022	0442	64/F	Los	100	293	Depression	No	Recovered
			Los	50	399	Depression	No	Recovered
			Los	50	452	Depression	No	Recovered
			Los	50	467	Depression	No	Recovered
011-022	0450	56/M	Los	50	525*	Hemorrhage, Gastrointestine	No	Recovered
011-032	0882	53/F	Los	50	453	Aneurysm	Yes	Present
011-038	0783	61/M	Los/HCTZ	100/12.5	218	Diarrhea	Yes	Recovered
021-001	0006	69/F	Off-drug	--	62	Allergy	No	Recovered
011-002	0027	57/M	Los/HCTZ	150/25	403	Neoplasm, Skin, Malignant	No	Present
011-002	0027	58/M	Los/HCTZ	150/25	458*	Bacteremia	No	Present
011-003	0048	36/M	Los/HCTZ	100/12.5	185	Pneumonia	No	Recovered
021-004	0072	63/F	Los	50	363	Pneumonia	No	Recovered
			Los	50	363	Sinusitis	No	Recovered
011-004	0071	49/M	Los	50	237	Neoplasm, Skin, Malignant	No	Recovered
011-004	0071	50/M	Los/HCTZ	150/12.5	362	Bursitis	No	Recovered
011-005	0095	51/M	Los	100	108	Angina Pectoris	Yes	Recovered
			Los	100	108	Supraventricular Tachycard.	Yes	Recovered
011-019	0399	64/M	Los	10	15	Edema/Swelling	Yes	Present
					32	Angina Pectoris	Yes	Present
					32	Dyspnea, Exertional	Yes	Present
011-022	0444	73/F	Los	150	357	CVA	No	Recovered
			Los	150	357	Paresis	No	Present
011-024	0495	48/F	Los/HCTZ	100/12.5	409*	Neoplasm, Uterine, Benign	No	Recovered
011-025	0508	66/M	Los/HCTZ	150/12.5	498	Melanoma	No	Present
011-025	0508	67/M	Los/HCTZ	150/12.5	594*	Neoplasm, Intestinal, Malig.	No	Present
011-025	0510	40/M	Los	50	534	Hearing Loss	Yes	Present
011-025	0517	57/M	Los	100	333	Arthropathy, Traumatic	No	Recovered
011-026	0527	53/M	Off-drug	--	322	Effusion, Pericardial	No	Recovered
011-026	0530	52/F	Los/HCTZ	100/25	247	Cholelithiasis	No	Recovered
011-027	0548	52/M	Los	150	28	Hepatitis, Viral	Yes	Recovered
			Los	150	28	Serum Bilirubin Increased	Yes	N/A
			Los	150	28	AST Increased	Yes	N/A
			Los	150	28	ALT Increased	Yes	N/A
			Los	150	30	Asthenia/Fatigue	Yes	Recovered
			Los	150	30	Malaise	Yes	Recovered
			Los	150	30	Fever	Yes	Recovered
			Los	150	34	Serum Bilirubin Increased	Yes	N/A
			Los	150	34	AST Increased	Yes	N/A
			Los	150	34	ALT Increased	Yes	N/A
			Los	150	34	GGT Increased	Yes	N/A
			Los	150	34	LDH Increased	Yes	N/A
			Los	150	34	Hep. A Antibody Positive	Yes	N/A
			Los	150	35	Serum Bilirubin Increased	Yes	N/A
			Los	150	35	AST Increased	Yes	N/A
			Los	150	35	ALT Increased	Yes	N/A
			Los	150	35	GGT Increased	Yes	N/A
			Off-drug	--	39	Serum Bilirubin Increased	Yes	N/A
			Off-drug	--	39	AST Increased	Yes	N/A
			Off-drug	--	39	ALT Increased	Yes	N/A
Off-drug	--	42	Serum Bilirubin Increased	Yes	N/A			
Coff-drug	--	42	AST Increased	Yes	N/A			
Off-drug	--	42	ALT Increased	Yes	N/A			
011-028	0577	/F	Los	50	396*	Neoplasm, Breast, Malig.	No	Recovered
011-028	0578	60/F	Los	50	648*	Atrial Fibrillation	No	Present
011-030	0615	54/M	Los/HCTZ/Fel	100/25/5	644*	Pain, Chest	No	Recovered
011-032	0652	33/M	Los	100	101	Tear, Ligament	No	Recovered
011-032	0655	29/M	Los	50	101	Pain, Chest	No	Recovered
			Los	50	102	T-Wave Abnormality	No	--

Serious Nonfatal Adverse Experiences in Hypertensive Patients From All Sources

Protocol #./ Study #	Patient #	Age/Sex	Treatment	Dose (mg)	Relative Day of Onset	Adverse Experience	Discontinued	Outcome
011-032	0656	51/M	Los/HCTZ	100/25	369	Atrial Fibrillation	No	Recovered
011-032	0666	58/F	Los	100	66	Neoplasm, Skin, Malignant	Yes	Present
011-032	0668	49/M	Los/HCTZ	150/12.5	338	Detachment, Retinal	No	Recovered
011-032	0668	51/M	Los/HCTZ	50/12.5	576*	Detachment, Retinal	No	Recovered
011-034	0705	47/M	Los/HCTZ	150/25	403*	Intervertebral Disc Disorder	No	Recovered
011-039	0818	53/M	Los	50	399	Atrial Fibrillation	Yes	-
			Los	50	419	Dyspnea	Yes	Present
011-040	0832	65/M	Off-drug	--	133	Neoplasm, Skin, Malignant	No	Recovered
011-040	0832	59/F	Los/HCTZ	100/12.5	274*	Pain, Leg	No	Present
011-040	0832	61/F	Los/HCTZ	100/12.5	381*	Hematuria	Yes	Present
			Los/HCTZ	100/12.5	464*	Neoplasm, Bladder, Malig.	Yes	Present
011-040	0833	70/M	Los/HCTZ/Fel	150/25/5	493*	Neoplasm, Prostate, Malignant	No	Present
044-001	3021	60/M	Los/HCTZ	50/6.25	154	Syncope	No	Recovered
044-001	3026	63/M	Los/HCTZ/Fel	50/12.5/12.5	200*	Neoplasm, Prostate, Benign	No	Present
			Los/HCTZ/Fel	50/12.5/12.5	215*	Premature Ventric. Contract.	No	Recovered
044-001	3240	41/F	Los/HCTZ/Fel	50/12.5/10	91*	Myocardial Infarction	Yes	Recovered
044-006	3083	61/F	Los	50	34*	Syncope	No	Recovered
044-006	3095	57/F	Los	50	107*	Myocardial Infarction	Yes	Recovered
044-007	3125	59/F	Los	100	66	Salpingo-Oophoritis	Yes	Present
044-008	3142	37/M	Off-drug	--	97	Gout	Yes	Present
045-006	4189	57/M	Los	100	78	Embolism/Infarction, Pulm.	No	Recovered
			Los	100	78	Pain, Pleuritic	No	Recovered
045-009	4129	70/F	Los	50	2	Pain, Abdominal	Yes	Present
045-012	4203	59/M	Los	50	183*	Myocardial Infarction	Yes	Recovered
048-010	0363	41/F	Los	50	24*	Hypoglycemia	Yes	Recovered
048-011	6064	57/M	Los/HCTZ	50/6.25	67	Hemophthalmos	Yes	Present
			Los/HCTZ	50/6.25	67	Edema, Macular	Yes	Present
048-012	6343	49/F	Los	50	70	Syncope	No	Recovered
			Los	50	70	Paresthesia	No	Recovered
048-013	0535	53/M	Los/HCTZ	50/12.5	148*	Lymphoma	Yes	Present
048-014	6281	71/F	Los/HCTZ	50/6.25	7*	Atrial Fibrillation	No	Recovered
			Los/HCTZ	50/6.25	7*	Congestion, Pulmonary	No	Recovered
			Los/HCTZ	50/6.25	7*	Pain, Chest	No	Recovered
			Los/HCTZ	50/6.25	7*	Tachycardia	No	Recovered
048-014	0782	61/F	Los	50	151*	Cholecystitis	No	Recovered
048-015	6231	49/M	Los/HCTZ	50/12.5	89	Atrial Fibrillation	No	Recovered
			Los/HCTZ	50/12.5	101	Heart Disorder, Ischemic	No	Present
048-016	6291	63/M	Los/HCTZ	50/6.25	82	Pneumonia	No	Recovered
048-016	6304	51/M	Los/HCTZ	50/6.25	112	Encephalopathy, Hyperten.	Yes	Recovered (Death***)
048-017	6431	48/M	Los/HCTZ	50/12.5	43	Dizziness	Yes	Recovered
			Los/HCTZ	50/12.5	43	Nausea	Yes	Recovered
			Los/HCTZ	50/12.5	43	Vomiting	Yes	Recovered
			Los/HCTZ	50/12.5	43	Sweating	Yes	Recovered
048-023	6115	54/M	Off-drug	--	12	Colic, Renal	No	Recovered
048-024	6417	54/F	Los	50	7	Headache	No	Recovered
048-024	6439	51/M	Los/HCTZ	50/25	209*	Hematoma	Yes	Recovered
			Los/HCTZ	50/25	210*	Hypokalemia	Yes	Recovered
			Los/HCTZ	50/25	210*	Creatine Phosphokin. Inc.	Yes	Recovered
			Los/HCTZ	50/25	210*	Liver Function Abnorm.	Yes	Unknown
			Los/HCTZ	50/25	210*	Hyperbilirubinemia	Yes	Unknown
			Los/HCTZ	50/25	210*	Serum Creatinine Increase	Yes	Unknown
049-004	7102	55/M	Off-drug	--	10	Hypotension	Yes	Recovered
049-007	7137	50/F	Los/HCTZ	100/25	74	Gallbladder Disorder	No	Recovered
049-008	7156	48/M	Los/HCTZ	25/25	60	Urolithiasis	No	Recovered
049-010	7172	58/M	Off-drug	--	209	Hemiplegia	No	Present
049-013	7214	48/F	Los/HCTZ/Fel	50/6.25/5	261*	Myocardial Infarction	Yes	Present
049-014	7236	48/M	Los	50	59	Urolithiasis	No	Recovered

Serious Nonfatal Adverse Experiences in Hypertensive Patients From All Sources

Protocol #./ Study #.	Patient #	Age/Sex	Treatment	Dose (mg)	Relative Day of Onset	Adverse Experience	Discontinued	Outcome
049-015	7251	50/M	Los/HCTZ	50/25	58	Fracture, Ankle	Yes	Present
049-016	7447	49/M	Los/HCTZ	50/12.5	222*	Neoplasm, Metastatic	Yes	Present
			Los/HCTZ	50/12.5	222*	Neoplasm, Lung, Malignant	Yes	Present
049-017	7279	52/M	Los	50	267	Neoplasm, Tongue, Malig.	Yes	Present
049-017	7280	62/M	Los/HCTZ	25/25	48	Lung Neoplasm, Malignant	Yes	Present
049-017	7288	34/F	Los/HCTZ	50/25	38	Neoplasm, Uterine, Benign	No	Recovered
			Los/HCTZ	50/25	40	Hemorrhage, Vaginal	No	Recovered
049-023	7411	61/M	Off-drug	-	293	Neoplasm, Kidney, Malig.	Yes	Recovered
049-024	7418	64/M	Los/HCTZ	100/25	42	Neoplasm, Intestinal, Malig.	Yes	Still Present
049-024	7425	51/M	Los	50	257*	Urolithiasis	No	Recovered
049-024	7427	41/M	Los/HCTZ	25/25	21	Anxiety	Yes	Present
			Los/HCTZ	25/25	21	Depression	Yes	Present
050-002	2020	75/M	Los	50	36	Angina Pectoris	Yes	Present
050-002	2022	66/M	Los	50	336	Neoplasm, Prostate, Malig.	No	Present
050-003	2042	62/M	Los	50	217	Obstruction, Carotid Artery	Yes	Present
050-005	2084	54/M	Los	50	36	Tachycardia	No	Recovered
050-007	2109	39/M	Los/HCTZ	50/6.25	112*	Intervertebral Disc Disorder	No	Recovered
050-007	2121	60/M	Los/HCTZ/Fel	50/12.5/5	134*	Pain, Chest	Yes	Present
050-009	2161	44/F	Los	50	17	Pain, Abdominal	No	Recovered
			Los	50	17	Menstruation Disorder	No	Recovered
050-010	2170	45/F	Los	50	1	Dysphasia	Yes	Recovered
			Los	50	1	Hemiparesis	Yes	Recovered
050-013	2226	32/M	Off-drug**	-	323	Suicide Attempt	Yes	Recovered
050-014	2246	54/M	Los	50	127	Urolithiasis	No	Recovered
050-015	2266	50/F	Los	50	32	Angina Pectoris	Yes	Recovered
050-017	2289	60/M	Los	50	35	Hernia, Inguinal	No	Recovered
050-018	2316	47/F	Los	100	64	Dyspnea	Yes	Recovered
050-021	2373	59/M	Los/HCTZ/Fel	50/12.5/5	197	Myocardial Infarction	Yes	Recovered
050-023	2397	75/M	Los	50	5	Myocardial Infarction	Yes	Recovered
			Los	50	5	Heart Failure	Yes	Present
054-004	8095	48/M	Los/HCTZ	50/12.5	81*	Intervertebral Disc Disorder	No	Recovered
054-005	8120	66/M	Los/HCTZ	50/12.5	5*	Myocardial Infarction	No	Present
054-006	8153	42/F	Los/HCTZ	50/6.25	5*	Bronchitis	Yes	Recovered
054-011	8254	72/M	Los/HCTZ	50/6.25	204*	Neoplasm, Prostate, Malig.	No	Present
054-015	8330	39/F	Los/HCTZ	50/6.25	271*	Neoplasm, Uterine, Malig.	No	Recovered
054-018	8388	55/F	Los/HCTZ	50/6.25	101*	Confusion	No	Present
			Los/HCTZ	50/6.25	101*	Fracture, Rib	No	Present
054-019	8403	54/M	Los/HCTZ/Fel	50/12.5/5	255*	Myocardial Infarction	No	Present
054-019	8871	71/F	Los/HCTZ	50/6.25	273*	Neoplasm, Skin, Malignant	No	Recovered
054-019	8898	78/M	Los/HCTZ	50/6.25	83*	Cholecystitis	No	Recovered
054-020	8433	70/M	Los/HCTZ	50/50	19*	Neoplasm, Prostate, Malig.	Yes	Present
054-022	8473	57/F	Los/HCTZ	50/12.5	139*	Fracture, Tibia, Lt.	No	Recovered
054-025	8521	67/M	Los/HCTZ	50/6.25	62*	Trauma, Muscle	No	Recovered
054-026	8560	44/F	Los/HCTZ/Fel	50/12.5/5	279*	Ulcer, Peptic	No	Recovered
			Los/HCTZ/Fel	50/12.5/5	279*	Adhesion, Peritoneal	No	Recovered
			Los/HCTZ/Fel	50/12.5/5	279*	Obstruction, Intestinal	No	Recovered
054-027	8562	70/M	Los/HCTZ	50/12.5	86*	Myocardial Infarction	Yes	Recovered
054-029	8602	70/M	Los/HCTZ	50/6.25	N/A	Hernia, Inguinal	No	Recovered
054-035	8729	67/M	Los/HCTZ/Fel	50/12.5/5	50*	Benign Prostatic Hypertroph.	No	Recovered
054-035	8733	59/M	Los/HCTZ	50/6.25	115*	Pain, Back	No	Present
054-035	8733	59/M	Los/HCTZ	50/6.25	179*	Obstruction, Intestinal	No	Recovered
054-038	8788	54/F	Los/HCTZ	50/12.5	56*	Bronchitis	No	Present
054-038	8788	54/F	Los/HCTZ	50/12.5	159*	Pain, Chest	No	Present
054-038	8792	54/F	Los/HCTZ	50/6.25	227*	Cholecystitis, Chronic	No	Recovered
054-038	8793	42/F	Off-drug	-	6	Pain, Chest	Yes	Recovered
054-039	8804	68/M	Los/HCTZ	50/6.25	85	Strain	No	Recovered

Serious Nonfatal Adverse Experiences in Hypertensive Patients From All Sources

Protocol #/ Study #	Patient #	Age/Sex	Treatment	Dose (mg)	Relative Day of Onset	Adverse Experience	Discon- tinued	Outcome
055-010	5171	69/F	Los	50	39*	CVA	Yes	Recovered
055-010	5188	68/F	Los	100	82	Headache	No	Recovered
			Los	100	82	Influenza	No	Recovered
			Los	100	85	Hypokalemia	No	N/A
055-012	5307	67/M	Los	100	N/A	Malaise	Unknown	Unknown
055-012	5308	65/F	Los	50	66*	Pain, Chest	No	Recovered
055-015	5318	88/M	Los	100	125*	Falling	No	Recovered
056-001	3506	67/M	Los	100	254*	Neoplasm, Prostate, Malignant	Yes	Present
056-001	3559	74/M	Los	50	28*	Cholelithiasis	No	Recovered
			Los	50	28*	Jaundice	No	Recovered
056-015	3683	63/M	Los/Fel	100/10	206	Myocardial Infarction	No	Recovered
059-001	5501	38/M	Los	100	29	Seizure Disorder	Yes	Recovered
059-003	5525	44/M	Los/HCTZ	100/25	70	Pneumonia	Yes	Present
			Los/HCTZ	100/25	75	Hypotension	No	Present
			Los/HCTZ	100/25	76	Sinus Tachycardia	No	--
			Off-drug	--	76	Hemoptysis	No	Recovered
			Off-drug	--	76	Septicemia	No	Present
059-003	5527	50/M	Los/HCTZ/Fel	100/25/10	146	Hyperglycemia	No	Recovered
059-006	5551	41/M	Los/HCTZ/Fel	100/25/10	303	Occlusion, Vascular, Retinal	No	Recovered
059-021	5725	56/F	Los/HCTZ ¹	100/12.5	48	PVC	Yes	--
			Los/Aten	100/25	48	Syncope	Yes	Recovered
			Los/Aten	100/25	48	Premature Beat	No	Recovered
			Los/Aten	100/25	48	Palpitation	No	Recovered
			Los/Aten	100/25	48	Pulse Abnormality	No	Recovered
			Los/Aten	100/25	49	Palpitation	No	Recovered
065-002	1109	41/F	Los	50	193*	Pain, Chest	No	Present
065-002	1110	45/M	Off-drug	--	34	Pain, Abdominal	No	Recovered
			Off-drug	--	34	Pain, Chest	No	Recovered
065-003	1607	40/M	Los	50	16	Pain, Chest	Yes	Recovered
			Los	50	16	Pain, Arm	Yes	Recovered
065-007	1673	61/M	Los/Aten	100/100	115*	Obstruction, Carotid Artery	Yes	Recovered
065-009	1173	74/F	Off-drug	--	82*	Phlebitis/Thrombophlebitis	No	Recovered
065-011	1582	65/M	Unknown	--	40	Hematuria	No	Present
065-017	1336	60/M	Los	50	83*	Hypertension	Yes	Present
065-017	1338	66/M	Los	50	21*	Angina Pectoris	Yes	Recovered
065-021	1314	42/M	Los	25	68	Fracture, Patella, Right	No	Present
			Off-drug	--	69	Bone Fixation Device	No	Recovered
065-021	1317	56/M	Los/Fel	100/5	165*	Myocardial Infarction	Unknown	Present
065-029	1194	64/M	Los	50	15	Neoplasm, Malignant	No	Recovered
065-031	1144	53/M	Los/Aten	100/Unknown	54*	Ileus	Yes	Recovered
A- 201/RG954	1-9	49/F	Los	50	25	Liver Function Abnormality	Yes	Recovered
			Los	50	25	Somnolence	Yes	Recovered
			Los	50	25	Malaise	Yes	Recovered
076-005	0062	44/M	Los	50	1	Hypotension, Orthostatic	Yes	Recovered
			Los	50	1	Gastroenteritis	Yes	Recovered
049-013	7145	48/M	Los	50	286*	Neoplasm Skin, Malignant	No	Recovered
011-034	0710	50/F	Los	100	2*	Cervical Herniated Disk	No	Recovered
041-00	N/A	66/F	Los	50	42	Carcinoma	Yes	Recovered
082-00	N/A	68/F	Los	100	136	Neoplasm, Stomach, Malig.	Yes	Recovered

* Study day calculated from start of losartan therapy in open-label extension.

** Unknown amount of Losartan and HCTZ

*** Patient died, but not considered related to hypertensive encephalopathy.

¹ Dosage information for the serious adverse experience observed by CG (PVC) includes therapy from the prior day, i.e., Los 100 mg/HCTZ 12.5 mg, while dosage information for the clinical adverse experience includes atenolol 25 mg which was administered to treat the adverse experience.

Discontinuations Due to Clinical Adverse Experience in Losartan-Treated Hypertensive Patients (Double-Blind)
 [Includes Patients from Studies Reviewed by Dr. Knudsen; Studies 48, 49 and 50]

Protocol No./ Study No.	Patient #	Age/Sex	Treatment	Daily Dose (mg)	Relative Day of Onset	Relative Day Discontinued	Adverse Experience	Outcome
011/019	0399	64/M	Losartan	10	15	36	Edema/Swelling*	Present
					32	36	Angina Pectoris	Present
					32	36	Dyspnea, Exertional	Present
011/024	0489	69/F	Off-drug	--	25	25	Tremor	Recovered
					25	25	Rash	Recovered
					25	25	IG ⁺ Increased	Recovered
011/031	0648	44/M	Losartan	25	1	88	Weight Loss	Recovered
011/033	0684	52/F	Losartan	25	34	41	Headache	Recovered
011/005	0085	64/F	Losartan	50	30	34	Asthma	Recovered
048/004	6111	52/M	Losartan	50	59	70	Tachycardia	Present
050/014	2248	53/M	Losartan	50	1	217	Myalgia	Present
			Losartan	50	1	217	Swelling, Joint	Recovered
			Losartan	50	1	217	Edema/Swelling	Recovered
054/004	8081	55/M	Losartan	50	73	76	Asthenia/Fatigue	Recovered
054/012	8265	56/F	Losartan	50	1	2	Dyspepsia	Recovered
054/013	8282	63/M	Losartan	50	2	9	Dizziness	Recovered
054/041	8848	64/M	Losartan	50	49	63	Hypotension	Recovered
065/034	1301	38/F	Losartan	50	3	4	Tachycardia	Recovered
011/014	0294	65/M	Losartan	100	34	36	Hematuria	Recovered
021/005	0088	58/M	Los/HCTZ	100/12.5	32	39	Vertigo	Recovered
021/008	0160	58/M	Losartan	100	13	20	Tinnitus	Recovered
			Losartan	100	13		Headache	Recovered
043/004	0056	62/M	Losartan	100	1	1	Hypotension	Recovered
005/003	0039	68/F	Losartan	150	2	2	Orthostatic Effect	Recovered
011/002	0033	56/M	Losartan	150	1	17	Pain, Chest*	Recovered
011/024	0488	73/F	Losartan	150	18	20	Edema, Eyelid	Recovered
			Losartan	150	18	20	Edema, Facial	Recovered
011/027	0548	52/M	Losartan	150	28	34	Hepatitis, Viral ⁺	Recovered
			Losartan	150	30	34	Asthenia/Fatigue	Recovered
			Losartan	150	30	34	Malaise	Recovered
			Losartan	150	30	34	Fever	Recovered
011/030	0617	43/M	Losartan	150	28	28	Tachycardia	Recovered
044/001	3025	63/M	Losartan	50	2	21	Cough	Recovered
			Losartan	50	2	21	Rhinitis, Allergic	Recovered
044/002	3036	56/M	Losartan	50	19	19	Orthostatic Effects	Recovered
044/002	3043	60/M	Losartan	50	23	24	Dizziness	Recovered
044/002	3044	55/M	Losartan	50	42	62	Headache	Recovered
044/003	3048	48/M	Losartan	50	4	55	Dizziness	Recovered
044/003	3049	59/F	Losartan	50	3	18	Psoriasis	Present
044/005	3078	67/F	Losartan	50	59	70	Dizziness	Recovered
			Losartan	50	59	70	Nausea	Recovered
			Losartan	50	62	70	Pain, Chest	Recovered
			Losartan	50	62	70	Hypertension, Increased	Present
044/007	3125	59/F	Losartan	100	66	69	Salpingo-Oophoritis*	Present
044/008	3142	37/M	Off-drug	--	85	84	Arthritis	Recovered
					91	84	Gout	Present
					97	84	Gout*	Present
044/013	3191	79/M	Losartan	100	51	53	Vomiting	Recovered
045/007	4061	33/F	Losartan	50	64	78	Dizziness	Recovered
045/009	4129	70/F	Losartan	50	2	40	Pain, Abdominal*	Present
055/003	5053	78/M	Losartan	50	9	10	Ataxia	Recovered
055/005	5271	66/F	Losartan	50	1	3	Vomiting	Recovered
			Losartan	50	1		Malaise	Recovered
055/006	5273	78/M	Losartan	50	40	42	Angina Pectoris	Recovered
			Off-drug	--	43		Hypotension	Recovered
065/003	1607	40/M	Losartan	50	16	16	Pain, Chest*	Recovered
			Losartan	50	16		Pain, Arm	Recovered
065/004	1415	61/F	Losartan	50	1	16	Dizziness	Recovered

* Serious

Discontinuations Due to Clinical Adverse Experiences in Losartan-Treated Hypertensive Patients (Double-Blind)
 [Includes Patients from Studies Reviewed by Dr. Knudsen; Studies 48, 49 and 54] (con't)

Protocol No./ Study No.	Patient #	Age/Sex	Treatment	Daily Dose (mg)	Relative Day of Onset	Relative Day Discontinued	Adverse Experience	Outcome
065/011	1596	78/M	Losartan Losartan	50 50	41 41	41	CVA* Hypertension	Present
048/010	6320	36/F	Los/HCTZ	50/6.25	64	70	Discomfort, Pharyngeal	Recovered
048/011	6064	57/M	Los/HCTZ Los/HCTZ	50/6.25 50/6.25	67 67	74 74	Hemophthalmos* Edema, Macular	Present Present
048/016	6304	51/M	Los/HCTZ	50/6.25	112	112	Encephalopathy, *Hypertensive	Recovered
054/003	8065	44/F	Los/HCTZ Los/HCTZ	50/6.25 50/6.25	7 7	20 20	Headache Libido Decreased	Recovered Recovered
054/015	8883	32/F	Los/HCTZ	50/6.25	11	12	Dizziness	Recovered
054/017	8779	49/M	Los/HCTZ	50/6.25	1	19	Alopecia	Recovered
054/038	8793	42/F	Off-drug	-	6	4	Pain, Chest*	Recovered
048/004	6105	46/M	Los/HCTZ	50/12.5	29	35	Headache	Present
048/017	6431	48/M	Los/HCTZ Los/HCTZ Los/HCTZ Los/HCTZ	50/12.5 50/12.5 50/12.5 50/12.5	43 43 43 43	45 45 45 45	Dizziness* Nausea Vomiting Sweating	Recovered Recovered Recovered Recovered
054/020	8428	63/M	Los/HCTZ	50/12.5	46	46	Panic Disorder	Recovered
054/027	8567	57/F	Los/HCTZ Los/HCTZ	50/12.5 50/12.5	91 91	91 91	Pain, Abdominal Nausea	Recovered Recovered
054/028	8591	65/M	Los/HCTZ Los/HCTZ Los/HCTZ	50/12.5 50/12.5 50/12.5	1 1 1	2 2 2	Anxiety Palpitation Tachycardia	Recovered Recovered Recovered
054/037	8773	61/M	Los/HCTZ	50/12.5	27	33	Headache	Present
054/038	8786	46/F	Los/HCTZ	50/12.5	32	46	Rash	Present
050/002	2020	75/M	Losartan	50	36	36	Angina Pectoris*	Present
050/009	2160	42/F	Losartan Losartan	50 50	11 11	11 11	Headache Folliculitis	Present Present
050/010	2170	45/F	Losartan Losartan	50 50	1 1	1 1	Dysphasia* Hemiparesis	Recovered Recovered
050/015	2266	50/F	Losartan	50	32	32	Anginal Pectoris*	Recovered
050/016	2271	63/M	Losartan Losartan Losartan	50 50 50	22 22 22	47 47 47	Dizziness Headache Nausea	Present Present Present
050/022	2386	65/M	Losartan Losartan Losartan Losartan	50 50 50 50	9 9 9 9	21 21 21 21	Cough Fever Congestion, Nasal Pain, Musculoskeletal	Recovered Recovered Recovered Present
050/023	2397	75/M	Losartan Losartan	50 50	5 5	9 9	Myocardial Infarction* Heart Failure	Recovered Present
049/017	7280	62/M	Los/HCTZ	25/25	48	54	Neoplasm, Lung, *Malignant	Present
049/024	7427	41/M	Los/HCTZ Los/HCTZ	25/25 25/25	21 21	32 32	Anxiety* Depression	Present Present
048/011	6063	50/F	Los/HCTZ	50/25	40	42	Rash	Recovered
048/023	6128	74/M	Los/HCTZ	50/25	50	70	Asthenia/Fatigue	Present
049/004	7102	55/M	Los/HCTZ Los/HCTZ Los/HCTZ Off-drug	50/25 50/25 50/25 -	8 8 8 -	9 9 9 -	Dizziness Nausea Sweating Hypotension*	Recovered Recovered Recovered Recovered
049/007	7130	44/F	Los/HCTZ	50/25	21	63	Dermatitis, Atopic	Present
049/015	7251	50/M	Los/HCTZ	50/25	58	58	Fracture, Ankle*	Present
049/021	7378	61/F	Los/HCTZ	100/25	64	80	Dizziness	Recovered

* Serious

Discontinuations Due to Clinical Adverse Experiences in Losartan-Treated Hypertensive Patients (Double-Blind)
 [Includes Patients from Studies Reviewed by Dr. Knudson; Studies 48, 49 and 54] (con't.)

Protocol No./ Study No.	Patient #	Age/Sex	Treatment	Daily Dose (mg)	Relative Day of Onset	Relative Day Discontinued	Adverse Experience	Outcome
049/024	7418	64/M	Los/HCTZ	100/25	42	57	Neoplasm, Intestinal, Malignant*	Present
021/001	0011	52/F	Losartan	100	1	3	Diarrhea	Recovered
			Losartan	100	1		Nausea	Recovered
048/001	0193	53/M	Losartan	50	23	28	Hemorrhoids	Present

* Serious

Discontinuations Due to Clinical Adverse Experiences in Losartan-Treated Hypertensive Patients (Open-Label)

Protocol #/ Study #	Patient #	Age/Sex	Treatment	Daily Dose (mg)	Relative Day of Onset	Relative Day Discontinued	Adverse Experience	Outcome
011/004	0068	62/F	Losartan	100	114	117	Arthralgia	Recovered
011/009	0172	60/M	Losartan	50	581	589	Rash	Present
011/016	0322	51/M	Losartan	50	97	265	Libido Decreased	Present
011/020	0402	48/M	Los/HCTZ	100/12.5	176	178	Myalgia	Recovered
011/032	0666	58/F	Losartan	100	66	72	Neoplasm, Skin, Malig.**	Present
011/039	0818	53/M	Losartan	50	419	419	Dyspnea**	Present
			Losartan	50	419	419	Atrial Fibrillation	Present
011/009	0170	53/F	Los/HCTZ	100/12.5	160	164	Rash	Recovered
011/024	0493	71/M	Los/HCTZ	100/12.5	175	181	Edema/Swelling	Recovered
			Los/HCTZ	100/12.5	175		Erythema	Recovered
			Los/HCTZ	100/12.5	175		Pain, Toe	Recovered
011/032	0882	53/F	Losartan	50	453	454	Aneurysm**	Present
011/037	0764	44/M	Losartan	150	206	266	Impotence	Present
011/005	0097	67/M	Losartan	100	269	269	Atrial Fibrillation	Recovered
011/009	0174	70/M	Losartan	100	89	89	Coma**	Recovered
			Losartan	100	89		CVA	Recovered (Death)
011/013	0260	71/F	Losartan	50	108	150	Arrhythmia	Present
			Losartan	50	108		Dyspnea	Present
011/031	0644	51/M	Los/HCTZ	100/12.5	323	383	Dyspnea, Exertional	Present
			Los/HCTZ	100/12.5	323		Pain, Chest	Present
011/036	0783	61/M	Los/HCTZ	100/12.5	218	286	Diarrhea**	Recovered
050/003	2042	62/M	Losartan	50	217	222	Obstruc., Carotid Artery**	Present
050/014	2241	46/M	Los/HCTZ	50/6.25	119	126	Agitation	Recovered
			Los/HCTZ	50/6.25	119		Malaise	Recovered
050/014	2246	54/M	Los/HCTZ/ Fel	50/12.5/5	166	228	Edema/Swelling	Present
050/023	2414	46/M	Los/HCTZ	50/6.25	244	244	Aneurysm, Cerebral**	Death
011/014	0276	53/F	Los/HCTZ	100/12.5	291	296	Dizziness	Present
			Los/HCTZ	100/12.5	291		Nausea	Present
011/020	0406	48/F	Losartan	150	113	114	Rash	Present
011/020	0407	50/M	Los/HCTZ	150/25	155	162	Impotence	Recovered
011/005	0095	51/M	Losartan	100	108	108	Angina Pectoris**	Recovered
			Losartan	100	108		Supravent. Tachycardia	Recovered
011/036	0740	39/F	Losartan	50	70	79	Pain, Chest	Recovered
			Losartan	50	70		Dyspnea	Recovered
011/037	0766	53/M	Losartan	100	206	218	Prostate Disorder	Present
059/001	5501	38/M	Losartan	100	29	29	Seizure Disorder**	Recovered
059/003	5525	44/M	Los/HCTZ	100/25	70	75	Pneumonia**	Present
059/019	5708	34/F	Los/HCTZ	100/25	32	42	Paresthesia	Recovered
			Los/HCTZ	100/25	32		Weakness, Muscle	Recovered
059/020	5675	39/F	Losartan	100	8	8	Anxiety	Recovered
			Losartan	100	8		Vertigo	Recovered
059/021	5725	56/F	Los/Aten	100/25	48	50	Syncope**	Recovered
			Los/Aten	100/25	48		Premature Beat**	Recovered
059/021	5729	55/F	Losartan	100	10	12	Depression	Recovered
054/039	8815	55/F	Los/HCTZ/ Fel	50/12.5/5	162	205	Depression	Present
050/011	2187	52/M	Los/HCTZ/ Fel	50/12.5/10	238	245	Edema/Swelling	Recovered
050/012	2212	70/M	Los/HCTZ	50/6.25	184	193	Asthma	Present
050/013	2217	52/F	Los/HCTZ	50/12.5	317	317	Dyspnea	Recovered
			Los/HCTZ	50/12.5	317		Pain, Chest	Recovered
			Los/HCTZ	50/12.5	317		Atrial Tachycardia	Recovered
050/013	2226	32/M	Off-drug*	--	323	322	Suicide Attempt**	Recovered
050/015	2255	48/M	Los/HCTZ/ Fel	50/12.5/10	216	273	Edema/Swelling	Recovered

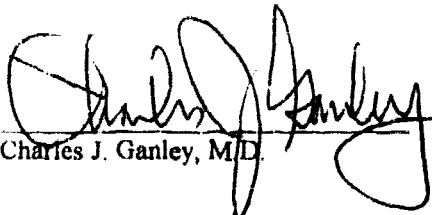
* Unknown amount of losartan, HCTZ and other medications taken in attempted suicide. ** Serious Adverse Event

Discontinuations Due to Clinical Adverse Experiences in Losartan-Treated Hypertensive Patients (Open-Label) (con't.)

Protocol #/ Study #	Patient #	Age/Sex	Treatment	Daily Dose (mg)	Relative Day of Onset	Relative Day Discontinued	Adverse Experience	Outcome
050/016	2283	44/M	Losartan Losartan	50 50	206 206	264	Asthenia/Fatigue Hypotension, Orthostatic	Present Present
050/019	2336	61/M	Los/HCTZ/ Fel	50/12.5/10	172	202	Edema/Swelling	Present
049/016	7264	68/F	Losartan Losartan Los/Fel	50 50 50/5	85 203 259	267	Pain, Abdominal Rash Asthenia/Fatigue	Recovered Recovered Recovered
049/023	7414	56/M	Losartan	50	98	114	Myalgia	Present
049/012	7199	41/M	Los/HCTZ/ Fel	50/25/10	307	307	Gastroenteritis	Recovered
049/023	7453	52/M	Los/HCTZ/ Fel	50/25/5	168	181	Tachycardia	Recovered
049/017	7279	52/M	Losartan	50	267	338	Neoplasm, Tongue, Malig.**	Present
049/023	7411	61/M	Off-drug	-	293	286	Neoplasm, Kidney, Malig.**	Recovered
011/017	0339	53/F	Losartan	150	111	132	Asthenia/Fatigue	Recovered
011/018	0365	60/M	Losartan	100	86	90	Depression	Recovered
011/025	0519	63/M	Losartan	50	561	563	Rash	Present
011/031	0646	34/M	Los/HCTZ Los/HCTZ	150/12.5 150/12.5	128 128	133	Nocturia Urinary Frequency	Recovered Recovered
049/001	7016	52/M	Los/HCTZ/ Fel	50/25/10	292	326	Impotence	Present
049/014	7236	48/M	Los/HCTZ/ Fel	50/12.5/10	133	139	Edema/Swelling	Present
049/027	7361	45/M	Los/HCTZ/ Fel	50/12.5/5	147	159	Headache	Recovered
011/025	0510	40/M	Losartan	50	534	553	Hearing Loss**	Present
011/028	0579	70/M	Los/HCTZ	150/12.5	350	364	Pain, Chest	Present
050/019	2325	42/M	Losartan	50	99	153	Impotence	Recovered
050/021	2365	61/M	Losartan Losartan	50 50	59 59	59	Edema, Facial Rash	Present Present
050/021	2371	50/F	Los/HCTZ/ Fel Los/HCTZ/ Fel Los/HCTZ/ Fel	50/12.5/10 50/12.5/10 50/12.5/10	304 304 304	332	Tachycardia Weakness, Muscle Flushing	Present Present Present
050/021	2373	59/M	Los/HCTZ/ Fel	50/12.5/5	197	197	Myocardial Infarction**	Recovered

** Serious Adverse Event

NOTE: Counts total 57 discontinued but listing includes 58 discontinued; cannot identify error.



Charles J. Ganley, M.D.

cc: orig.
HFD-110 file
HFD-110/c.ganley/r.lipicky/cso/k.knudson/a.proakis
HFD-426/e.fadiran
HFD-110/w.nuri

CHEMIST'S REVIEW

MAR 2 1995

DIVISION OF CARDIO-RENAL DRUG PRODUCT
Review of Chemistry, Manufacturing, and Control

NDA #: **20-386** CHEM. REVIEW #: 3 REVIEW DATE: 17-FEB-95

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
BC	21-OCT-94	25-OCT-94	27-OCT-94
BC	11-JAN-95	12-JAN-95	17-JAN-95
BL	27-JAN-95	30-JAN-95	30-JAN-95
BC	25-JAN-95	30-JAN-95	31-JAN-95
BC	08-FEB-95	09-FEB-95	13-FEB-95

NAME & ADDRESS OF SPONSOR

Merck Research Laboratories
Merck & Co. Inc.
West Point, PA 19486

Telephone: 610-397-2310

DRUG PRODUCT NAME

Proprietary: COZAAR
Nonproprietary/USAN: Losartan Potassium Tablets
Code Name/#: MK-954; DuP-753; 1-158,086; L-158,086-005H; E-3340
Chem.Type/Ther.Class: 18

ANDA Suitability Petition/DESI/Patent Status:

U.S. Patent 5,138,069 expiration date - 8/11/2009;
USP 5,153,197 expiration date 10/06/2009 - both licensed from DuPont

PHARMACOL. CATEGORY/INDICATION:

An angiotensin II receptor agonist; said to reduce systolic and diastolic blood pressure in patients with mild to moderate essential hypertension.

DOSAGE FORM: Film coated tablets

STRENGTH: 20, 50, 100 mg

ROUTE OF ADMINISTRATION: ORAL

DISPENSED: Rx

CHEMICAL NAME:

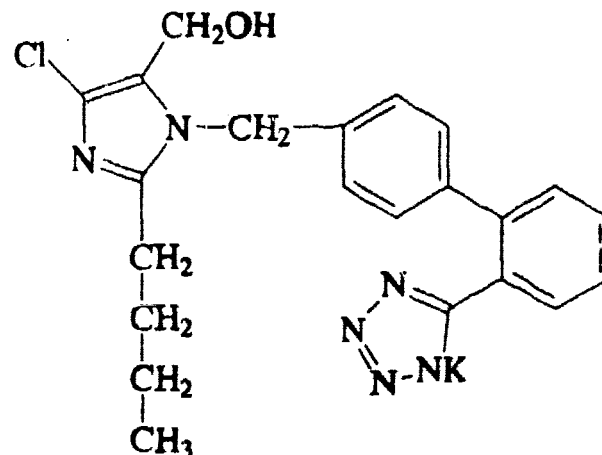
2-butyl-4-chloro-1[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]-methyl]-1H-imidazole-5-methanol, monopotassium salt.

CAS #: 124750-99-8

MOLECULAR FORMULA: C₂₂H₂₂ClKN₆O

MOLECULAR WEIGHT: 461.01

STRUCTURAL FORMULA:



SUPPORTING DOCUMENTS:

Covered in review # 1.

RELATED DOCUMENTS:

Covered in review # 1.

CONSULTS:

FUR was sent on February 2, 1995. Reply to Agency's EA was received on January 30, 95 and has been sent to HFD-102 for consultation.

Division of Biopharmaceutics has completed their review and recommended a change in dissolution specifications.

Confidential Revised Environmental Assessment and Non-Confidential Revised Environmental Assessment were received on February 9, 1995. These assessments have been sent to HFD-102 for consultation.

REMARKS/COMMENTS:

The applicant has withdrawn 100 mg losartan potassium tablets from the subject NDA, due to lack of marketing interest.

During scale up to a full-scale production during validation and initial imprinting of the final markings on the tablets, a slight picking was observed. As a result of this, minor manufacturing changes in blend time during lubrication were made and concavity of the tablets was slightly altered.

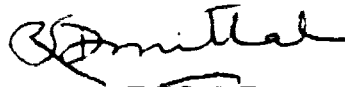
CONCLUSIONS & RECOMMENDATIONS:

Recommend that, so far, this Application is approvable, pending FUR, EA reviews.

cc:

Orig. NDA
HFD-110/Division File
HFD-110/Ram Mittal/date
HFD-110/CSO

R/D Init by: RWolters/
RWolters 2/22/95



Ramsharan D. Mittal Ph.D., Review Chemist
filename: C:\NDA\20386\20386.R01

PHARMACOLOGIST'S

REVIEW

**M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: 2/27/95

FROM: Anthony G. Proakis, Ph.D. *APP*

SUBJECT: COZAAR (Losartan) Labeling

TO: Dr. Ray Lipicky

I have read the attached comments by ODE I on the Pharmacology/Toxicology portion of the labeling for Losartan.

Appropriate changes were made (Dr. Temple's mark-up) to address comments 1 and 2 (Note: the multiples of the human dose under Overdose/Lethality sections were corrected to 44 and 170 times rather than 75 and 300 times shown in the mark-up).

The 3rd comment regarding the inclusion of the statement on pancreatic acinar adenomas was discussed in the Exec-CAC (See last paragraph of attached Exec-CAC minutes). This statement should remain in labeling.

N. B.

DEC - 7 1994

NDA #20,386

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

G. Jagadeesh, Ph.D.

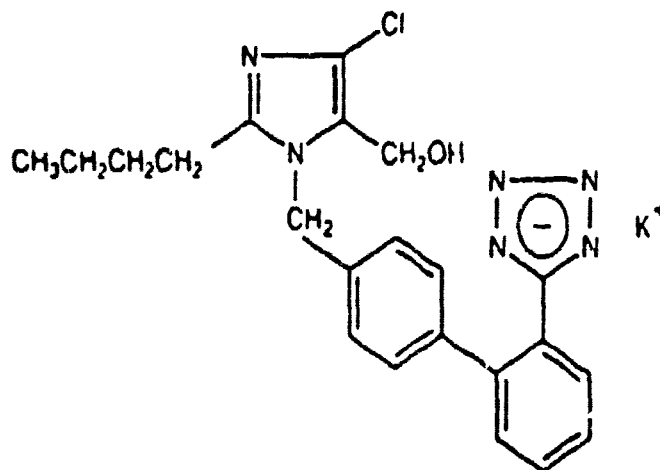
A. Proakis, Ph.D.

12.6.1994

SPONSOR Merck Research Laboratories, Merck & Co., Inc.,
West Point, PA 19486

PRODUCT COZAAR® (Losartan potassium) Tablets

CHEMISTRY Losartan (also referred to as MK-954, L-158,086, DuP 753, E-3340) is the potassium salt of 2-n-butyl-4-chloro-5-hydroxymethyl-1-[[[(2'-1H-tetrazol-5-yl) biphenyl-4-yl] methyl]imidazole. The substance is a white to off-white crystalline solid with no chiral centers and a molecular weight of 461.01. Losartan potassium is hygroscopic and freely soluble in water. Solid losartan potassium drug substance, stored under ambient conditions of temperature and humidity, is claimed to be stable for at least three years.



PHARMACOLOGICAL CLASS Angiotensin II receptor antagonist

PROPOSED INDICATION Treatment of hypertension

FORMULATION AND ROUTE OF ADMINISTRATION Losartan is intended for oral use and is supplied as green teardrop-shaped or white scored oval tablets containing 25, 50 or 100 mg losartan potassium (excipients: microcrystalline cellulose, lactose hydrous, pregelatinized starch, magnesium stearate, hydroxypropyl cellulose or methylcellulose, titanium dioxide and approved coloring agents).

PROPOSED DOSAGE REGIMEN 50 mg once daily in most patients. The maximum recommended dose is 100 mg once daily.

IND UNDER WHICH CLINICAL TRIALS WERE CONDUCTED

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INTRODUCTION

Hypertension is a major public health problem affecting at least 10% of the adult population. A number of approaches to the development of the drug therapy of essential hypertension have been tried over five decades. Diuretics and β -adrenergic blockers have maintained a dominant position in this category of drugs. One of the approaches to the treatment of hypertension, which may be considered as a major scientific advancement, involves drugs affecting the renin angiotensin aldosterone system (RAAS).

Control of blood pressure by the RAAS is exerted through multiple actions of angiotensin II, a small peptide which, as the end product of the RAAS, is a potent vasoconstrictor hormone implicated in the genesis and maintenance of hypertension. The importance of the RAAS is reflected in the observation that angiotensin II levels are elevated in renovascular and malignant hypertension. Actions of angiotensin II involved in the control of arterial pressure and volume homeostasis include vasoconstriction, aldosterone formation, renal sodium absorption, and norepinephrine release. Furthermore, elevated plasma renin activity is associated with increased morbidity and mortality in patients with essential hypertension. Aldosterone, an important component of this system, is known to cause increased sodium retention and increased volume. Therefore, it is hypothesized that angiotensin II, because of its dual role in influencing both vasoconstriction and volume mechanisms, is a critical hormone in the development and maintenance of hypertension.

The drugs directed against the RAAS fall into three categories. First, the angiotensin converting enzyme (ACE) inhibitors, beginning with captopril. They act by blocking the conversion of angiotensin I to angiotensin II. A second approach is to inhibit selectively the enzyme renin which acts on angiotensinogen (renin substrate), to release the decapeptide angiotensin I. Renin inhibitors are as effective as ACE inhibitors experimentally, but progress has been limited by the lack of orally active compounds. Third, and newest approach to the treatment of hypertension, is the use of angiotensin II receptor antagonists. This approach dates back to saralasin, a peptidergic angiotensin II receptor antagonist. Because of its peptide structure, that compound had a short duration of action and its use was limited to parenteral administration only. In addition, saralasin had substantial partial agonist activity resulting in the elevation of blood pressure in some patients.

The introduction of nonpeptide angiotensin II receptor antagonists has opened new vistas in understanding the additional physiological effects of angiotensin II. The specific receptors with which angiotensin II binds are differentiated into subtypes AT_1 and AT_2 based on their sensitivity to non-peptide angiotensin II receptor antagonists. Losartan, the current drug candidate for approval, is about 10,000 times more selective for the AT_1 site than for the AT_2 site. Losartan potassium represents the first nonpeptide angiotensin II receptor antagonist which is orally bioavailable, lacks partial agonist activity and is highly specific for antagonizing receptors of angiotensin II linked to the cardiovascular system. The sponsor's NDA contains extensive preclinical data supporting this classification.

1. PHARMACODYNAMICS

1.1. Effects Related to Proposed Therapeutic Indication

1.1.1. Angiotensin II Receptor Antagonism

A. *In vivo* Inhibition of Exogenous Angiotensin II Pressor Response

a) *Pithed Rat*:

The ability of losartan to selectively antagonize angiotensin II-induced pressor response following i.v. or oral administration was evaluated in rats which were anesthetized, pithed, and maintained on artificial respiration. In this study a cumulative dose-pressor response curve for i.v. angiotensin II was constructed. Before injection of angiotensin II, each animal was pretreated with saline or losartan (3 or 10 mg/kg, i.v.). A similar protocol was followed with norepinephrine and vasopressin to determine specificity.

Losartan at 3 and 10 mg/kg i.v. shifted the log dose-pressor response curve for angiotensin II dose-dependently to the right without altering the maximal response to angiotensin II (Fig. 1) or angiotensin III, suggesting competitive angiotensin II antagonism. A dose of 10 mg/kg significantly lowered diastolic b.p. (26 mm Hg *versus* control of 41 mm Hg) but did not alter heart rate. Neither of these doses altered the dose-heart rate response curve for isoproterenol, suggesting that losartan does not have affinity for the β -1 adrenergic receptor. Losartan did not alter the dose response curves for norepinephrine or vasopressin, further evidence of its selectivity. Losartan given orally to pithed rats at a dose of 10 mg/kg shifted the dose-pressor response curve for angiotensin II about 20- and 5-fold to the right at 2 hr and 24 hr postdose, respectively (Fig. 2). Diastolic b.p. was significantly decreased to 31 mm Hg at 2 hr

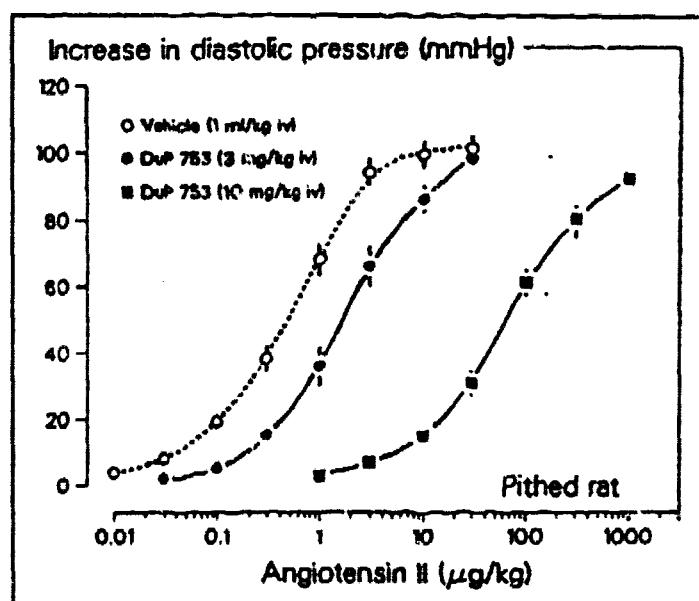


Figure 1: Effects of losartan (3 and 10 mg/kg i.v.) on the pressor response for angiotensin II in the pithed rat

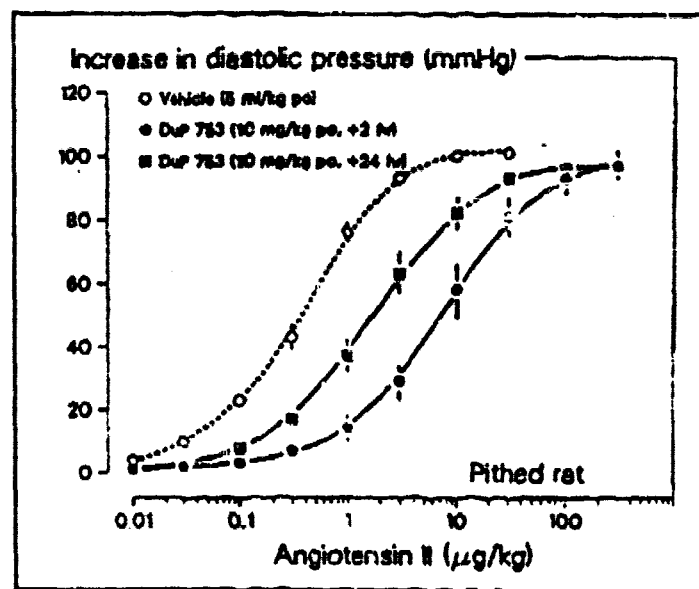


Fig. 2: Effect of losartan at 10 mg/kg p.o. at 2 and 24 hr postdose on the log dose-pressor response curve for angiotensin II in the pithed rat

and to 32 mm Hg at 24 hr postdose *versus* vehicle control response of 40 mm Hg, suggesting a long duration of angiotensin II antagonism.

In a separate study, the potency and selectivity of E-3174 (L-158641, EXP3174), a major metabolite found in rat plasma after the oral administration of losartan, was evaluated utilizing the protocol discussed above. E-3174 at 0.03, 0.1 and 0.3 mg/kg i.v. shifted the log dose-pressor response curve dose-dependently to the right and reduced the maximal pressor response to angiotensin II (Fig. 3), suggesting noncompetitive antagonism. The mean diastolic b.p. for the vehicle control and the 0.03, 0.1 and 0.3 mg E-3174-treated groups were 41, 40, 30 ($P \leq 0.05$) and 25 mm Hg ($P \leq 0.05$), respectively. E-3174 did not alter heart rate, suggesting that it is devoid of a myocardial depressant activity. However, at 0.1 and 0.3 mg/kg i.v. E-3174 *per se* lowered b.p. The inhibitory effect of E-3174 on the response to angiotensin II is selective, since E-3174 did not alter the pressor dose response curve for norepinephrine or vasopressin at an effective angiotensin II inhibitory dose (0.3 mg/kg i.v.).

b) *Normotensive Conscious Rats*

The tolerance to the inhibitory effects of losartan on the blood pressure response to angiotensin II was evaluated in normotensive conscious rats. These rats were treated daily with losartan at 10, 30 and 100 mg/kg p.o. for 11 days. The blood pressure response to angiotensin II at 0.1 $\mu\text{g}/\text{kg}$ i.v. was measured 2 hr after the first dose of losartan in one group and on the 11th day of dosing before and two hours after losartan or vehicle in the second group. In both groups of rats losartan caused a dose-dependent inhibitory effect on the pressor response to angiotensin II (Fig. 4), both acutely and after 11 days of treatment. Thus, no tolerance developed to the angiotensin II antagonistic effects of losartan.

In a second study, chronically catheterized conscious rats were challenged with intravenous

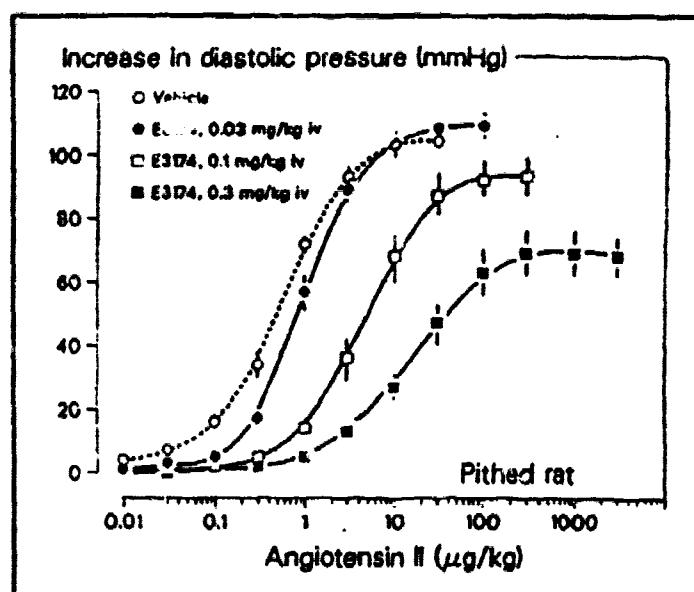


Fig. 3: Effects of E-3174 at 0.03, 0.1, and 0.3 mg/kg i.v. and the vehicle on the log dose-pressor response curve for angiotensin II in the pithed rat

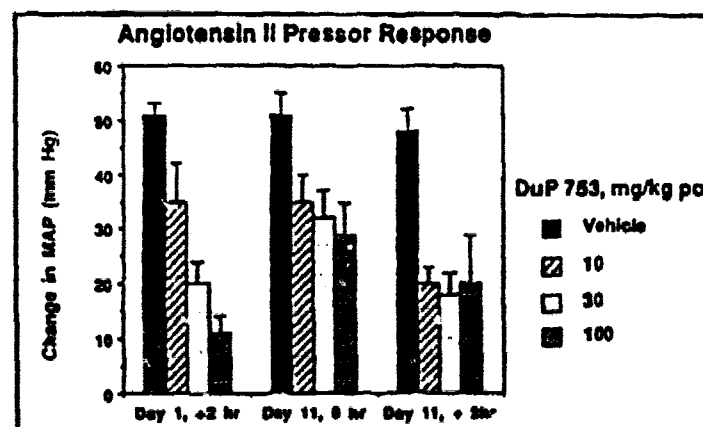


Fig. 4: Effects of losartan at 10, 30, and 100 mg/kg/day p.o. for 11 days on the pressor response to angiotensin II at 0.1 $\mu\text{g}/\text{kg}$ i.v. in normotensive rats

bolus doses of angiotensin II (0.1 µg/kg) and methoxamine (50 µg/kg). Following calibration, rats were dosed orally or intravenously with losartan (0.3, 1 and 3 mg/kg) and percent pressor responses to angiotensin II challenges during the subsequent 6 hours and at 24 hours were used as a measure of efficacy. Following an oral dose of 1 mg/kg, losartan had a duration of action greater than 6 hours with a peak inhibition of 56% (Fig. 5), while after an i.v. dose of 1 mg/kg, losartan had a duration of action greater than 6 hours with a peak inhibition of 78% (Fig. 6) of the pressor response to an exogenous angiotensin II challenge. Further, losartan at 3 mg/kg i.v. produced a peak inhibition of 93% and had a duration greater than 24 hours, suggesting the duration of action was dose-related. The ED50 (dose that produces a 50% reduction in the angiotensin II response) for losartan p.o. and i.v. was 0.66 and 0.28 mg/kg, respectively. Losartan did not change either the basal b.p. or pressor responses to methoxamine. At 1 and 3 mg/kg, the inhibition of pressor response to angiotensin II was biphasic with a transient peak inhibition at 5 min followed by a subsequent gradual increase in blockade of the angiotensin II pressor response over 3 hours, suggesting the formation of one or more active metabolites.

Utilizing the same methods as described above, E-3174 at 0.1, 0.3 and 1 mg/kg i.v. and 0.3, 1, 3 and 10 mg/kg p.o. was evaluated for its effects on angiotensin II-induced (0.1 µg/kg, i.v.) pressor responses. Both oral and i.v. doses of E-3174 produced a dose-related inhibition of the pressor response to angiotensin II. Maximal inhibitory effect was evident at 5 min post-injection, and significant inhibitory effects were evident at 6 hours post-treatment with the 0.3 and 1 mg/kg i.v. doses and the 1-10 mg/kg p.o. doses, suggesting E-3174 is likely to contribute to the long duration of the angiotensin II inhibitory effect of losartan. E-3174 at these doses did not alter basal blood pressure and heart rate.

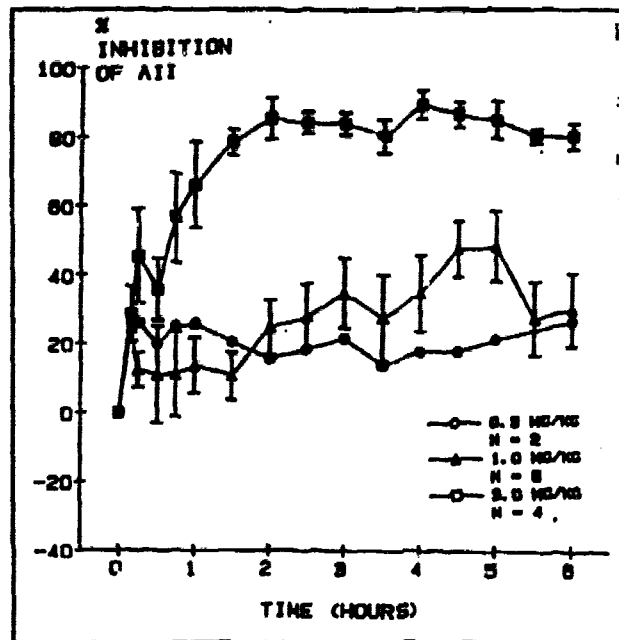
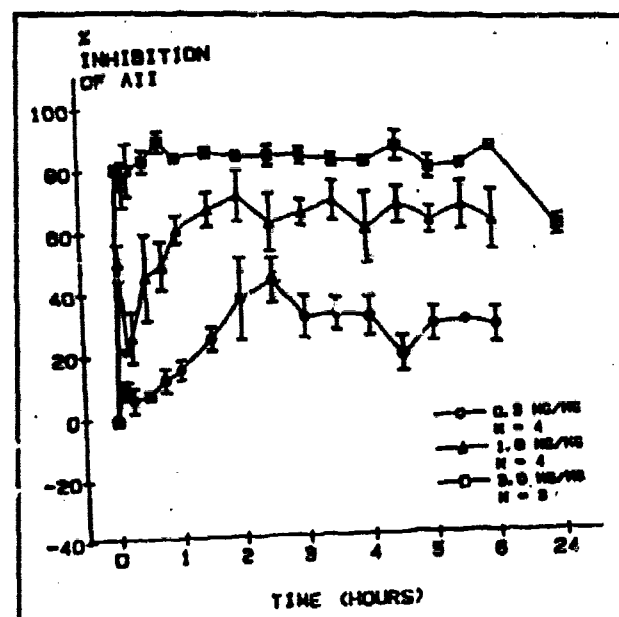


Fig. 5: Inhibition of the pressor response to angiotensin II after oral administration of losartan (0.3, 1, and 3 mg/kg) in conscious rats.



Since brain RAS appears to have an important physiological role in the regulation of b.p., losartan was evaluated for its ability to gain access to the brain angiotensin II receptors. In chronically catheterized conscious rats, angiotensin II was given at 0.35 μg in 10 μl of CSF intracerebroventricularly and i.v. (0.1 $\mu\text{g}/\text{kg}$) before and after the administration of losartan at 3.5 $\mu\text{g}/\text{rat}$ i.c.v. in 10 μl of CSF or 10 mg/kg p.o. Oral losartan at 10 mg/kg blocked pressor responses to i.v. angiotensin II but not to i.c.v. angiotensin II (up to 1 hr after administration). On the other hand, losartan given i.c.v. blocked the pressor responses to i.c.v. angiotensin II, suggesting that losartan at 10 mg/kg does not penetrate the brain. However, higher doses or longer periods of administration (over 3 hr) have not been explored by the sponsor.

In another study, conscious catheterized normotensive rats were made hypertensive by a constant infusion of angiotensin II (80 ng/kg/min). Thirtyfive minutes after the beginning of angiotensin II infusion, vehicle or losartan at 0.1, 1 or 10 mg/kg was given i.v. and its effect on blood pressure was monitored for another hour. The study demonstrated that without pretreatment losartan is still effective in antagonizing the angiotensin II-sustained blood pressure in a dose-dependent manner (Fig. 7). Rats treated with losartan at 10 mg/kg showed a small decrease in mean arterial pressure even after the angiotensin II infusion was stopped. Though the mechanism is not clear, the intrinsic influence of angiotensin II in the maintenance of vasoconstriction is implied.

The effect of losartan on angiotensin II-induced aldosterone release was studied in conscious normotensive rats that were surgically prepared with arterial and venous catheters one day before the experiment. The following day, the rats were given i.v. losartan (10 mg/kg) or saline vehicle 15 minutes before an i.v. infusion of angiotensin II (0.1 $\mu\text{g}/\text{kg}/\text{min}$) for 30 min. At the end of the infusion, rats were decapitated and serum aldosterone levels determined from aortic blood samples. Increases in blood pressure and aldosterone release by angiotensin II were effectively blocked by losartan at 10 mg/kg (Fig. 8).

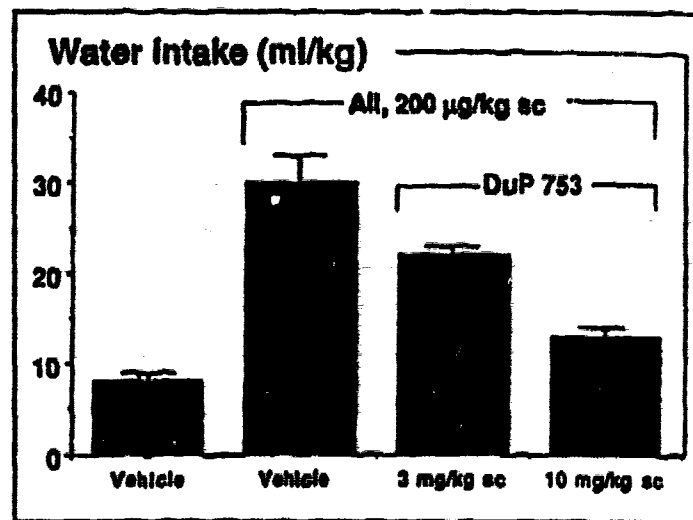


Fig. 9: Effects of losartan (3 and 10 mg/kg s.c.) on the drinking response to angiotensin II in conscious normotensive rats

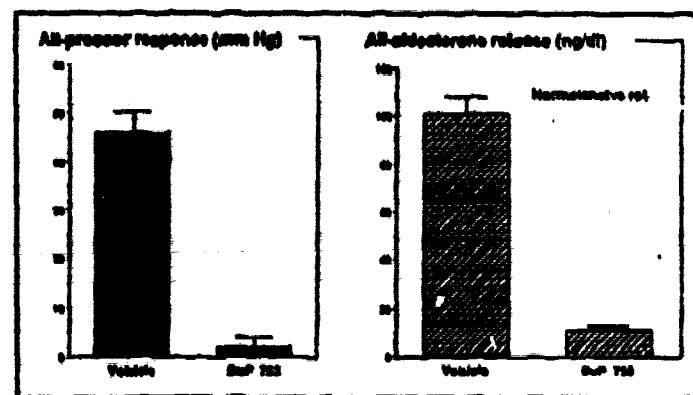


Fig. 8: Effects of losartan (10 mg/kg, i.v.) or the vehicle on the pressor (left) and aldosterone (right) responses to A-II (0.1 $\mu\text{g}/\text{min}$) in conscious rats

Systemic as well as central administration of angiotensin II has been demonstrated to stimulate water drinking in a variety of animals. After two days of habituation in metabolic cages, rats were given losartan 3 or 10 mg/kg or saline s.c. 1 hour before angiotensin II at 200 µg/kg s.c. Water intake was measured for 2 hours after the administration of angiotensin II or the vehicle. Angiotensin II-induced drinking response was blocked dose-dependently by losartan at 3 and 10 mg/kg s.c. (Fig. 9), suggesting that angiotensin II-induced drinking is mediated by its receptor activation. In a related study, losartan was given to a group of rats via the drinking water and liquid consumption and urinary output monitored. Losartan at 35 mg/kg/day had no effect on basal drinking behavior, urinary output or sodium and potassium excretions. Studies done by independent investigators (outside of Merck and DuPont Laboratories), while confirming the above observations, have also shown the specificity of this effect in the rat by demonstrating that losartan does not block the drinking response to isoproterenol, serotonin, 5-hydroxytryptophan, carbachol, hypertonic saline or polyethylene glycol. Further, these investigators have shown that losartan at 3 mg/kg p.o. for three days did not block the drinking response to i.c.v. angiotensin II (50 ng). In contrast, losartan administered centrally (10-100 ng) blocked the drinking response to angiotensin II at 0.1 ng i.c.v.

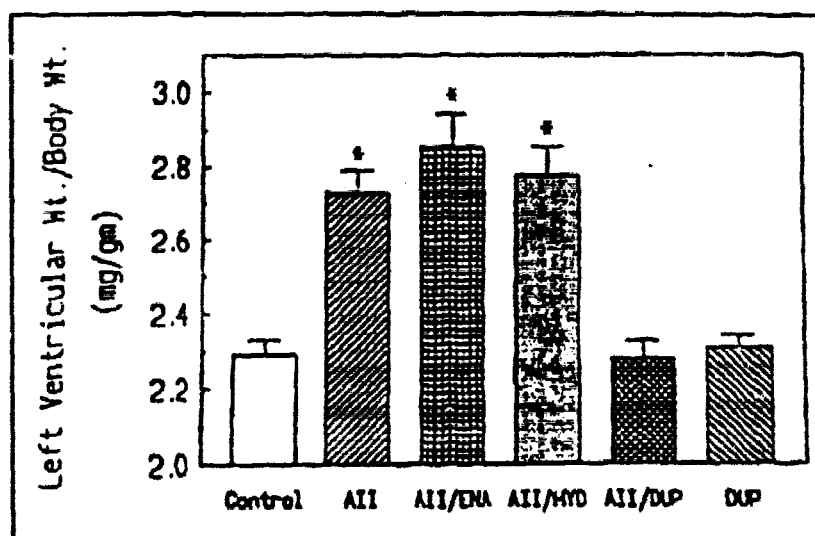


Fig.10: At 14 days, lv/bw ratios of AII±enalapril/hydralazine groups were significantly higher than control groups compared with groups receiving losartan ±AII

Angiotensin II has been reported to have positive chronotropic, inotropic and hypertrophic actions in cardiac tissue. The hypertrophic effects of the peptide have been described as direct wherein it stimulates the local release of growth factors from non-muscle cell types such as sympathetic neurons and fibroblasts in the heart. These factors could have a paracrine effect on cardiomyocytes to regulate or modulate growth-dependent mechanisms. Angiotensin II may also indirectly produce hypertrophy by increasing blood pressure (increased afterload) as a result of increase in vascular resistance. Cardiac hypertrophy was induced in conscious rats by infusing angiotensin II continuously (with the implantation of osmotic pumps on day 0 and day 7 of the experiment to deliver angiotensin II at a rate of 30 ng/min) throughout the 14-day time course of the experiment. Each rat was given 4 mg losartan (in 1 ml water) by gavage once a day. Enalapril maleate and hydralazine were administered in the drinking water at concentrations of 0.2 and 0.13 mg/ml, respectively. Blood pressure was monitored using a tail cuff method. The rats were killed on days 7 or 14 of the study and the atria and right and left ventricles removed. The tissue weights were indexed by dividing the weight of the tissue (in mg) by the body weight (in gm) of the animal.

The chronic infusion of angiotensin II significantly increased blood pressure (from 106 mm

Hg to 116 mm Hg, and from 108 mm Hg to 119 mm Hg, respectively, after 7 and 14 days) and left ventricular weight/body weight ratio (18.6% and 17.3% at 7 and 14 days, respectively). Animals with elevated blood pressure showed no significant correlation between increases in left ventricular mass and mean arterial pressure at 7 days, whereas at 14 days there was a correlation. This suggests that left ventricular hypertrophy induced by angiotensin II infusion is a result of hormonal rather than mechanical (afterload effect) mechanisms. Losartan completely prevented the rise in blood pressure and the cardiac hypertrophy (Fig. 10) at 14 days. The ACE inhibitor had no significant effect on either parameter. On the other hand, hydralazine (a vasodilator) normalized the blood pressure with no effect on the cardiac hypertrophy. These data provide evidence that the AT₁ cardiac receptor is mechanistically coupled to left ventricular muscle growth.

c) *Rhesus Monkeys:*

The effects of losartan on the pressor responses to angiotensin II following oral and i.v. administration were evaluated in conscious sodium/volume depleted rhesus monkeys. Chronic aortic catheters for recording mean blood pressure were placed in each monkey 2 weeks before the experiment. One week before the study monkeys were placed on a low sodium diet and 18 hours prior to the experiment given furosemide at 5 mg/kg i.m. On the days of study, monkeys were chair restrained and prepared with a saphenous or ulnar vein catheter for i.v. drug injection. Monkeys were initially challenged with methoxamine (50 µg/kg, i.v.), which was followed by bolus i.v. injections of angiotensin II (0.1 µg/kg) at times before and after losartan (3 and 10 mg/kg, p.o. or 0.3 and 1 mg/kg, i.v.) or its vehicle. Losartan at 3 and 10 mg/kg, p.o., produced peak effects of 22 ± 9 and 50 ± 7% inhibition, respectively. At 0.3 and 1 mg/kg, i.v., the peak effects were 49 ± 5 and 76 ± 9% inhibition, respectively. ED₅₀'s (95% confidence interval), based on the peak effect (i.e., percent inhibition of angiotensin II pressor response) for oral and i.v. administration were 10.22 (6.96-15.03) and 0.32 (0.18-0.58) mg/kg, respectively. The duration of action (the time from onset of activity to the last time point where inhibition of the angiotensin II was >30%) was 0.08 hr for the 0.3 mg/kg i.v. dose and 2.1 ± 0.9 hr for the 10 mg/kg p.o. dose.

d) *Chimpanzees:*

The potency and duration of action of losartan on angiotensin II-induced pressor effects was evaluated in anesthetized chimpanzees. Fasted adult male chimpanzees were anesthetized and cannulated for direct measurement of blood pressure and i.v. administration of drugs. Administration of angiotensin II (100 ng/kg bolus) or arginine vasopressin (AVP, 50 ng/kg bolus) elevated arterial pressure by 32 ± 4.7 and 52 ± 9.7 mm Hg, respectively. The duration of the pressor response was approximately 5 min with angiotensin II administration and approximately 10 min with AVP administration. Each chimpanzee was given repeated bolus i.v. injections of angiotensin II or AVP after 180 min of initial challenge. The chimpanzees were returned to their cages for recovery and were reanesthetized for study at 10 and 24 hr post drug effect. The pressor responses to AVP did not differ significantly from baseline throughout the studies, confirming the selectivity of the angiotensin II receptor antagonists for

angiotensin II-mediated increases in blood pressure, and verifying that the sensitivity of the chimpanzees to pressor stimuli was not altered. Losartan at 1 mg/kg i.v. significantly inhibited angiotensin II pressor responses for 10 hours after administration. Maximal inhibition ($93 \pm 4\%$) was obtained by 5 min post losartan. At 10 hours, inhibition of the angiotensin II response was $44 \pm 6\%$ and at 24 hours, the inhibition was not significant.

B. *In vivo* Inhibition of Endogenous Angiotensin II

a) *Hormonal Activity:*

The role of RAS in the control of blood pressure was studied in two models of hypertension. In the first study, SHR (11 week old) and age-matched WKY (normotensive rats) were dosed with losartan at 10 mg/kg/day by gavage for 14 days. Blood pressure and heart rate were monitored before, and after 7 and 14 days of treatment. At the end of 2 weeks of treatment, the rats were anesthetized and blood was withdrawn by aortic puncture for measuring plasma immunoreactive angiotensin I and angiotensin II, PRA, aldosterone and ACE.

TABLE 1.1.

Plasma components of the renin-angiotensin system and aldosterone in control and losartan-treated WKY and SHR.

	WKY		SHR	
	Control (n=6)	Losartan (n=6)	Control (n=7)	Losartan (n=8)
PRA (ng/ml per h)	3.85 ± 0.55	9.96 ± 1.40^a	3.18 ± 0.20	$21.24 \pm 3.16^{a,c}$
P-Ang I (pg/ml)	1.49 ± 0.18	3.37 ± 0.36^a	1.44 ± 0.10	$5.36 \pm 0.72^{a,c}$
P-Ang II (pg/ml)	6.85 ± 1.23	16.67 ± 2.49^a	3.65 ± 0.25^c	25.36 ± 3.59^a
ACE (U/ml)	76.8 ± 4.4	67.7 ± 3.2	56.7 ± 0.9	57.8 ± 1.7
Aldosterone (ng/dl)	40.5 ± 3.2	13.2 ± 1.7^b	72.7 ± 11.7^c	19.1 ± 6.0^a

Values are means $\pm$ S.E.M. PRA=plasma renin activity; ACE=angiotensin converting enzyme; P=plasma; ^aP<0.01; ^bP<0.001, compared with respective control groups; ^cP<0.05, compared with control WKY.

Losartan at 10 mg/kg p.o. produced a significant reduction in systolic blood pressure in SHR one week after the treatment, and a further decline in blood pressure was observed 2 weeks after the administration. This suggests a relatively slow onset of antihypertensive action of losartan and no tolerance to its antihypertensive effect. However, other reports suggest a marked fall in blood pressure within 15 to 30 min after a single oral administration of losartan in 18-21 week old SHR. The antihypertensive effect was not associated with a significant increase in heart rate. In contrast, losartan had no effect on the blood pressure of the normotensive rats. Compared with the control, the PRA and plasma levels of angiotensin I

and angiotensin II were markedly elevated in losartan-treated animals. The increase in these parameters tended to be greater in SHR than in the WKY. In contrast, losartan treatment significantly lowered aldosterone in both the SHR and WKY. No significant difference between the control and the drug-treated groups was found in plasma ACE activity (either SHR or WKY, Table 1.1). Additional *in vitro* studies have also shown the lack of effect of losartan (up to 0.1 mM) on plasma renin or ACE activities.

In the second study, the effects of losartan were studied in salt-depleted conscious dogs as the RAS is activated and the hypotensive response to blockers of the system is enhanced in this model. Beagle dogs prepared with chronic carotid arterial loops were each given a bolus i.v. dose of furosemide (5 mg/kg) on day 1 and placed on a low sodium diet (3 mmol/day) for 3 days. Blood pressure and heart rate were monitored continuously and arterial blood sampling was done at various intervals to measure plasma angiotensin II, renin and norepinephrine.

Infusion of losartan (30 µg/kg/min) over a period of 180 min produced a significant fall in systolic and diastolic blood pressure; both of which stabilized by 30 min. Mean arterial pressure also fell significantly from base line (110.9 ± 11.2 mm Hg to 95 ± 12.8 mm Hg). These changes were associated with a rise in heart rate from base line (84.6 ± 15.1 to 103 ± 15.2 beats per min). The heart rate response developed over a similar time course to the blood pressure changes. Using the same protocol, the effect of losartan on the MAP to pressor infusion of angiotensin II (54 ng/kg/min) was studied. During the control period (30 min before losartan administration), angiotensin II produced a 35.3 ± 11.6 mm Hg increase in MAP. This was significantly reduced at 15 min and at all points thereafter during constant infusion of the inhibitor (4.3 ± 3.3 mm Hg at 3 hr). There was no rebound response of blood pressure on stopping infusion of losartan, probably because its inhibitory effect persisted for several hours (approximately 30% recovery 2 hr after stopping drug infusion). It should be noted that in the dog there is only a limited conversion of losartan to its primary metabolite E-3174. This explains the shorter duration of action on MAP and may also play a part in the rise in heart rate in the dog. Circulating plasma angiotensin II (42.5 ± 11.8 pg/ml) and renin (64.5 ± 92.7 µ-units/ml) concentrations were elevated during the baseline D-glucose infusion (control period) in keeping with the sodium-deplete status of the animals. Infusion of losartan caused highly significant increases in plasma levels of angiotensin II (from 52.6 ± 22.2 pg/ml 30 min before the start of the losartan infusion to a maximum of 226 ± 70.5 pg/ml) and renin (average increase of 500 µ-units/ml). A large part of this response is thought to result from blockade of the inhibitory effect of angiotensin II on renin release, a calcium-mediated process at the renal juxtaglomerular cell. No significant change in plasma norepinephrine was noted throughout the 180 min losartan infusion.

b) Decreased Response to Sympathetic Nerve Stimulation:

It has been demonstrated that both exogenous and endogenous angiotensin II enhances noradrenergic transmission by acting at presynaptic sites in both isolated smooth muscle preparations and intact animals. The blockade of RAS results in the inhibition of the adrenergic facilitating effect of angiotensin II. Anesthetized, adrenalectomized, pithed and

artificially respirated rats were cannulated for arterial pressure measurement and i.v. drug injection. In addition, cardiac output, heart rate and total peripheral resistance (TPR) were measured.

Stimulation of sympathetic neurons or exogenous administration of norepinephrine (0.3-3 µg/kg, i.v.) in the pithed rat caused increases in blood pressure by increasing cardiac output and TPR. Losartan at 10 mg/kg i.v. (but not PD123177, an AT₂ receptor antagonist, at a dose of 100 mg/kg i.v.) significantly reduced the maximum change in arterial pressure and TPR while having little effect on the maximum change in cardiac output or heart rate in both maneuvers. This suggests that circulating angiotensin II gains ready access to the vascular but not to the cardiac sympathetic synapses in the pithed rat. Another explanation advanced in the literature is that the cardiac prejunctional angiotensin II receptor in rats may be absent or does not function *in vivo* since angiotensin II does not have a direct cardiac contractile effect. Similar experimental design has been used to study the effects of losartan on the renal vasoconstrictor responses to renal nerve stimulation and intraarterial injection of norepinephrine in anesthetized dogs. Both these studies suggest that the prejunctional angiotensin II receptors in the vasculature and renal adrenergic nerve are AT₁ receptors.

C. In vitro Inhibition of Exogenous Angiotensin II

a) Contraction:

Angiotensin II-induced contractions of isolated rabbit aortic strips were inhibited by losartan in a concentration-dependent manner. The rightward shift of the dose-response curve occurred in a parallel fashion with no changes in the maximum angiotensin II response (Figure 11). The pA₂ (defined as the negative logarithm of the concentration of antagonist required to shift the concentration/response curve two-fold to the right) of losartan was 8.48 (slope of the Schild plot was 0.9 ± 0.1). Further, losartan (10 µM) did not change the concentration-response curve for norepinephrine or KCl, nor did it (at 10 µM) cause contraction of rabbit aorta. These data are consistent with losartan being a selective, competitive angiotensin II receptor antagonist lacking partial agonist effects on the angiotensin II receptors.

In the same preparation, E-3174, at 10⁻¹⁰ to 10⁻⁶M, caused nonparallel shifts to the right of the angiotensin II concentration-response curves and reduced the maximal response to angiotensin II (Figure 12), suggesting E-3174 is a noncompetitive antagonist of angiotensin II. The estimated K_B (-log pA₂) value was 9.96. The reduction (25%) of the maximum contractile response to angiotensin II by E-3174 was reduced in the presence of increasing concentrations of losartan, indicating interaction with the same binding site. These results indicate (a) slow dissociation kinetics of E-3174, and (b) the existence of a saturable AT₁ receptor subpopulation sensitive to E-3174. E-3174 did not change the concentration-response curves for norepinephrine or KCl.

The extent of losartan specificity for the angiotensin II receptor was studied in a number of monoreceptor systems in a variety of preparations such as: aorta, jugular vein, and pulmonary

artery of the rabbit; stomach, urinary bladder, and portal vein of the rat; urinary bladder, colon, and ileum of the human; and the guinea pig ileum. In all these studies, the pA_2 values for losartan (against contractile responses to angiotensin I or angiotensin II) were 8.19 to 8.66. Losartan did not alter contractile responses to bradykinin, norepinephrine, substance P, neurokinin, bombesin, histamine, serotonin and acetylcholine. Further, in all of the above preparations, losartan (10 μ M) did not cause contraction by itself, suggesting that it lacks partial agonistic effects on the angiotensin II receptors.

b) *Functional Studies:*

The biochemical mechanism for the vasoconstrictor response to angiotensin II has been investigated extensively. It is now known that angiotensin II stimulates the phosphoinositide (PI) turnover signalling system by binding to specific cell surface receptors leading to the formation of second messengers, (a) inositol 1,4,5-triphosphate (IP_3) that mobilizes Ca^{++} from intracellular stores and stimulates the sodium-proton (Na^+/H^+) antiport, and (b) diacylglycerol that activates protein kinase C. Intracellular free calcium and stimulation of the Na^+/H^+ antiport function as intracellular signalling mechanisms for various cellular processes like vasoconstriction of vascular smooth muscle cells and cell growth (or hypertrophy of cells). The other major effect of angiotensin II on signal transduction pathways is the inhibition of adenylyl cyclase. Though both pathways (PI turnover and adenylyl cyclase inhibition) are mediated through activation of the AT_1 receptor, it is not yet clear whether different cellular responses are mediated through closely related subtypes of the AT_1 receptor.

The effect of losartan on angiotensin II-induced formation of IP_3 was evaluated in primary cultures of rat aorta vascular smooth muscle cells. In this study, losartan at 1 μ M completely inhibited the angiotensin II-induced elevation of IP_3 . Losartan at 0.1 μ M reduced the angiotensin II response from an increase of 390% to an increase of 150%. In isolated rat hepatocytes, angiotensin II stimulates both the labeling of phosphatidylinositol (resynthesis) and the release of inositol phosphates (breakdown). Both effects were blocked by losartan but not by PD123177 (an AT_2 receptor antagonist). Angiotensin II has no effect on the low levels of cAMP found in unstimulated membranes, but in membranes stimulated with GTP and lithium chloride angiotensin II can reduce the rate of production of cAMP. Losartan (10 μ M) shifted the angiotensin II-concentration-adenylyl cyclase inhibitory response curve in rat liver membranes, whereas PD123177 was without effect. No significant agonist activity was seen with losartan in both studies. The results indicate that the same receptor subtype, AT_1 , may couple uniquely to these two separate second messenger pathways, or the two subpopulations of the same receptor subtype, AT_1 , may couple independently to different transducing mechanisms, leading to different responses.

In vascular smooth muscle cells, angiotensin II induces vasoconstriction by facilitating the influx of extracellular Ca^{++} (by activating receptor-operated channels) and/or release of intracellular Ca^{++} . The latter event can be measured by monitoring the efflux of preloaded radiolabeled Ca^{++} (calcium mobilization) from rat aortic smooth muscle cells. Angiotensin II-induced $^{45}Ca^{++}$ efflux in these cells was inhibited in a concentration-dependent manner by

losartan with complete inhibition observed at concentration of 0.3 μM . Angiotensin II-induced release of calcium from intracellular stores (chiefly from endoplasmic reticulum) through the action of phosphoinositides (formation of second messenger IP_3) was studied as indicated by changes in Ca^{++} -Fura-2 fluorescence in rat aortic smooth muscle cells, liver cells and cardiomyocytes. In all these studies, angiotensin II (1 nM-1 μM) caused increases in $[\text{Ca}^{++}]_i$ in a concentration-dependent manner. Losartan inhibited this angiotensin II response in a concentration-dependent manner. Complete blockade was seen at a concentration of 1 μM . Losartan up to a concentration of 1 μM did not alter baseline levels of $[\text{Ca}^{++}]_i$ except in rat vascular smooth muscle cells, where 1 μM was shown to produce a small increase in $[\text{Ca}^{++}]_i$. By contrast, PD123177 (1 nM to 10 μM) did not effect the $[\text{Ca}^{++}]_i$ response of angiotensin II or the other agonists.

The effects of losartan on the cellular hypertrophy responses to angiotensin II were measured by studying the angiotensin II-induced changes in DNA and protein synthesis in cultures of rat aortic smooth muscle cells. In this study, angiotensin II (0.1 μM) provoked a 45% increase in protein synthesis and a 56% increase in DNA synthesis over the unstimulated control in a 24 hour period. Addition of losartan (10 μM) before the addition of angiotensin II to cells inhibited greater than 90% of angiotensin II-induced protein and DNA synthesis, while PD123177 (10 μM) was without any inhibitory effect. Increased protein synthesis is a hypertrophic response that contributes to cell growth in atherosclerosis. Both hypertension and atherosclerosis are the result of alteration in intracellular Ca^{2+} handling and abnormal growth of vascular smooth muscle cells. However, it should be noted that losartan is inactive against platelet-derived growth factor-induced cell protein synthesis, suggesting the specificity of action of losartan.

c) Receptor-mediated Release Studies:

Angiotensin II can release arachidonic acid metabolites both directly and indirectly via vasoconstriction (to release PGE_2) in coronary vessels, renal vessels, vas deferens and astrocytes. However, angiotensin II can exert vasodilatory effects presumably due to release of depressor prostaglandins (PGI_2) in cultured rat mesenteric and aortic smooth muscle cells. It has no stimulatory effect to release PGI_2 in cultured human vascular endothelial cells, porcine endothelial cells, bovine aortic and pulmonary arterial endothelial cells, and rat C₆ glioma cells and spleen macrophages. Thus, it could be concluded that angiotensin II release of prostacyclin (PGI_2) is cell type specific. Losartan (10 μM) but not PD123177 blocked these responses, characterizing the angiotensin II-stimulated prostaglandin formation as an AT_1 receptor-mediated event. According to the sponsor, losartan *per se* does not stimulate PGI_2 or PGE_2 release. However, two published reports describe a very significant release of PGI_2 or PGE_2 from porcine smooth muscle cells or human astrocytes by losartan. Additional studies are needed to clarify under what conditions, if any, losartan can release prostaglandin(s) directly.

The hypertensive action of angiotensin II is believed to be contributed to by its enhancing effect on sympathetic function. Enhancement of nerve-stimulated norepinephrine release and

the release of epinephrine from the adrenal medulla are believed to be major mechanisms by which angiotensin II acts to increase sympathetic activity. The effect of losartan to inhibit the actions of angiotensin II on norepinephrine release was evaluated in rat portal vein and guinea pig and rat adrenal medullary slices. In these studies, angiotensin II (10-100 nM) produced a dose-related increase in norepinephrine release, and losartan (1-3 μ M) significantly reduced (in some studies completely prevented) the effect of angiotensin II, suggesting an AT₁ receptor-mediated event.

The pharmacology of angiotensin II-stimulated aldosterone production was investigated in both rat and bovine adrenal glomerulosa cells. In these studies, angiotensin II-stimulated aldosterone production was inhibited completely by losartan and to a lesser extent or insignificantly by AT₂ antagonists.

D. *In vitro* Inhibition of Angiotensin II binding

The selectivity of losartan for angiotensin II receptors was evaluated by receptor binding techniques using the AT₁ receptor predominant rat aortic smooth muscle and adrenal cortical microsomes. In these preparations, losartan displaced ($IC_{50} = 19-20$ nM, $K_i \sim 19$ nM) specifically bound [¹²⁵I]angiotensin II in a monophasic manner. Similar binding results have been reported with losartan in adrenal cortex in rabbits and monkeys, glomerular, cortical tubular and outer medullary membranes from rat kidney, and human platelets. There are species differences in the relative abundance of losartan-sensitive angiotensin II receptors in kidney. In rat and rabbit, AT₁ predominates. In monkey kidney cortex, over half of the receptors are losartan-insensitive. Angiotensin II binding studies have also been carried out in fetal and adult human kidneys. In fetal kidney, AT₂ sites predominate. In adult kidney, losartan inhibits angiotensin II binding with high affinity.

In a rabbit left ventricular membrane preparation, losartan (as well as PD121981) displayed a shallow, biphasic curve with generally incomplete displacement of bound [¹²⁵I]angiotensin II (even at higher concentrations) with two K_i 's, 19 nM and 60 μ M. The K_i (the dissociation constant of an inhibitory nonradioactive ligand) for adrenal cortex in the same study was 14 nM. The biphasic displacement curve for losartan in the heart appears to have a smaller, higher affinity component as well as a larger, lower affinity one. These results suggest that cardiac angiotensin II receptors are functionally (and possibly structurally) different from angiotensin II receptors in the adrenal and vascular smooth muscle. If this is true, then losartan demonstrates some organ selectivity in binding well to adrenal and vascular smooth muscle cell receptors, but poorly to cardiac receptors. This means, losartan lowers blood pressure without affecting cardiac performance directly. From *in vitro* studies, the cardiac inotropic potency of angiotensin II (though mediated *via* AT₁ sites) is much less than the vasoconstrictor potency in vascular preparations. This suggests that angiotensin II in the plasma will affect b.p. before stimulating the heart. However, this needs substantiative proof. Similar results were reported in cardiac tissue from rat and monkey.

Angiotensin II acts on the brain to stimulate drinking, to increase sodium appetite, to increase

blood pressure, and to release pituitary hormones. The brain contains all the enzymes and precursors for angiotensin II synthesis and degradation. The angiotensin II receptor heterogeneity in the rat brain has been extensively studied using autoradiographic techniques and receptor ligand binding. Based on the differential sensitivities to losartan and PD123177, the midbrain, and thalamus-septum regions contain mostly AT₂ receptors and the hypothalamus contains a mixture of AT₁ and AT₂ receptors. The vascular organ of the lamina terminalis, subfornical organ, median preoptic nucleus, area postrema, and nucleus of the solitary tract contain exclusively AT₁ receptors. The pituitary gland contains mostly AT₁ sites. In the human brain there are many similarities with, but also important differences from, the rat brain. The similarities include the nucleus of the solitary tract and ventrolateral medulla, which contain AT₁ receptors, and the inferior olivary nucleus which contains AT₂ receptors in both species. Differences include locus ceruleus and subthalamic nucleus, which contain AT₂ receptors in rat brain, but contain exclusively AT₁ receptors in human brain. The subtype-specific receptor mapping is relevant to understanding the roles of angiotensin in the CNS and to central actions of angiotensin II receptor antagonists.

The specificity of the affinity of losartan for angiotensin II binding sites has been shown in binding assays with other ligands in various tissue preparations. Losartan had no affinity (at concentrations 10-100 μM) for binding to receptor sites for: α-adrenergic ligand, muscarinic ligand, nicotinic, serotonin, dopamine, glycine, phencyclidine, nitrendipine, neurotensin or opiates. Losartan is a weak inhibitor of the specific thromboxane A₂/prostaglandin H₂ receptor in human platelets. Inhibition of platelet aggregation was only observed at concentrations greater than 40 μM (i.e., greater than 1000-fold higher than required for angiotensin II inhibition).

1.1.2. Antihypertensive Effects

A. Renal Hypertension

The antihypertensive effects of losartan were evaluated in conscious rats with the right kidney intact and with the left kidney with a complete renal artery ligation. Six days after the ligation, the mean blood pressure and PRA were respectively elevated to 174 ± 7 mm Hg and 26.8 ng angiotensin I/ml/hr compared to 107 ± 3 mm Hg and 5.4 ng angiotensin I/ml/hr for sham operated rats. Hypertension in these animals is primarily due to the activation of the RAS. Given orally, losartan decreased blood pressure dose-dependently at 0.3 to 10 mg/kg (Fig. 13). The maximal hypotensive effect was achieved at 10 mg/kg. A dose of 100 mg/kg caused an earlier lowering of blood pressure but did not increase the magnitude of effect at 10

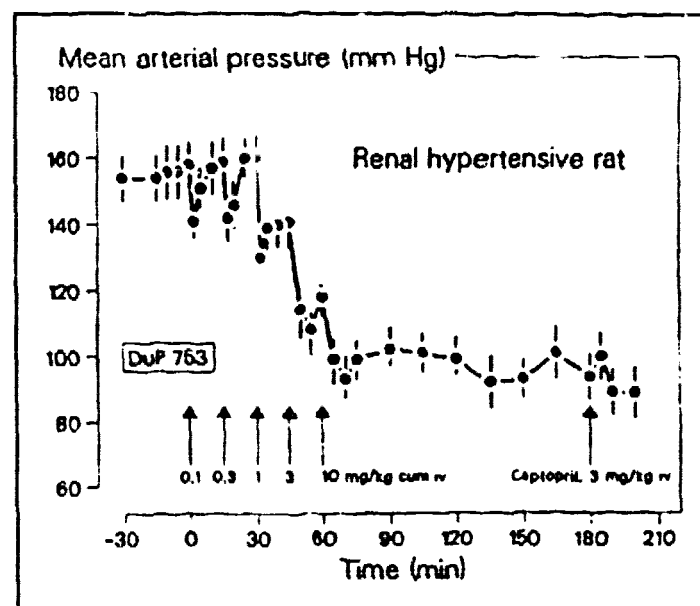


Fig. 14: Effects of losartan at 0.1, 0.3, 1, 3 and 10 mg/kg i.v. on mean arterial pressure in renal artery-ligated rats

mg/kg. The calculated oral ED30 for losartan was 0.59 mg/kg. A single oral dose of 3 mg/kg in renal artery-ligated rats produced a long duration of antihypertensive effect (at least 24 hr) with an onset of effect at 15-30 min and the maximal effect reached at 5-6 hr. None of the above doses increased heart rate compared to the vehicle control.

Cumulative i.v. injections of losartan (0.1 to 10 mg/kg) caused a dose-dependent decrease in mean arterial pressure in 6 day old renal artery ligated rats. At 10 mg/kg, losartan lowered mean blood pressure to a normotensive level and captopril, 3 mg/kg i.v., given after 180 min, did not further decrease mean arterial pressure (Fig. 14). When angiotensin II (0.1 µg/kg/min) was administered to renal artery-ligated rats before and after increasing doses of losartan, losartan at 0.03-3 mg/kg i.v. produced a dose-related decrease in the pressor response to angiotensin II (Fig. 15). Two hours following the injection of losartan (3 mg/kg i.v.), the *per se* effect on mean arterial pressure (Fig. 14) and the pressor response to angiotensin II (Fig. 15) were still markedly reduced. Losartan did not reduce the pressor response to vasopressin.

The selectivity and potency of E-3174 was evaluated in a series of renal hypertensive rats as described above for losartan. Cumulative i.v. injections of E-3174 at 0.003 to 0.3 mg/kg caused a dose-dependent decrease in mean arterial pressure. The calculated ED30 for E-3174 was 0.038 mg/kg (about 20 times more potent than losartan). Given orally, E-3174 was also effective in decreasing blood pressure dose-dependently at 0.3 to 10 mg/kg (Fig. 16). The calculated oral ED30 for E-3174 was 0.66 mg/kg. E-3174 did not alter heart rate when given either orally or intravenously.

Antihypertensive effects of losartan have also been evaluated in other renal hypertensive models such as 2-kidney 1-clip, 1-kidney 1-clip, reduced renal mass, aortic-coarctation renal hypertensive rats as well as renal hypertensive cynomolgus monkeys and dogs. Full reports of these studies are not available. To summarize, losartan prevented the development of hypertension in all of the above rat models. The antihypertensive efficacy of losartan studied in conscious instrumented 2-kidney 1-clip (Goldblatt hypertension) hypertensive cynomolgus monkeys indicated a markedly shorter duration of action (peak activity 1-2 hours, recovery 6 hours) compared to hypertensive rats (response > 24 hours). E-3174 dose-dependent reductions in mean arterial blood pressure, glomerular filtration rate and renal blood flow were observed in dogs which had been uninephrectomized and the remaining renal artery clamped to reduce renal blood flow by approximately 50%.

B. Genetic Hypertension

The antihypertensive effects of losartan were evaluated in conscious, catheterized (for measuring blood pressure and for drug administration) spontaneously hypertensive rats. Losartan given orally decreased mean arterial pressure in a dose-dependent manner at 3 and 10 mg/kg during a 3 hour observation period, while the vehicle had no effect (Fig. 17). Heart rate was not significantly changed. In a second experiment, losartan given intravenously at 3, 10 and 30 mg/kg caused a dose-dependent decrease in mean arterial pressure. The blood pressure lowering effects of losartan at these doses were sustained for at least 2 hours.

Losartan at 10 mg/kg i.v. significantly elevated basal PRA from 10.4 ± 1.2 to 63.1 ± 5.3 ng angiotensin I/ml/hr. In another study, losartan at 10 mg/kg i.v. reduced both mean arterial pressure and the pressor response to i.v. bolus injection of angiotensin II (0.1 μ g/kg). The maximum inhibition of the angiotensin II response was observed within 2 hours, whereas the maximum pressure reduction was observed at approximately 6 hours. Both parameters were still reduced after 24 hours. In another series of experiments using SHR, it was shown that losartan at 10 mg/kg i.v. significantly reduced the pressor response to angiotensin II (0.1 μ g/kg i.v.) but not to norepinephrine (0.3 μ g/kg i.v.). However, losartan increased the pressor response to vasopressin (0.03 I.U./kg i.v.) in SHR but did not affect the response to vasopressin in normotensive chimpanzees and dogs.

To study the chronic antihypertensive effect of losartan, SHRs were treated orally with losartan or vehicle for 4 days, and on the 5th day the rats were surgically prepared for blood pressure measurements. After the resting blood pressure (which was significantly lower for the losartan group than for the vehicle-treated group, 130 vs. 167 mm Hg) and heart rate were obtained, the animals were given the fifth dose (10 mg/kg p.o.) and the experiments were monitored for 3 hours. This dose caused a modest but significant decrease in mean blood pressure from 130 to 128, 122 and 120 mm Hg at 1, 2 and 3 hours postdose, respectively. Thus, no tolerance to the antihypertensive effect of losartan was noted as the 5th dose decreased blood pressure to a similar level as that of the single oral dose of 10 mg/kg of losartan. In two different studies losartan was administered chronically, in one case orally for 14 days, and in the other losartan was given at 15 mg/kg/day in the drinking water for 10 weeks. In both cases, no tolerance to the antihypertensive effect of losartan was seen. [Since losartan did not reduce blood pressure in WKY rats, these data suggest that RAS plays an important role in the control of blood pressure in SHRs.] As PRA is normal in the SHR, it is unlikely that circulating angiotensin II is responsible for the high blood pressure. On the other hand, vascular renin derived from the kidney contributes to the local generation of (tissue) angiotensin II for the maintenance of the vascular tone in SHRs.

The antihypertensive effects of losartan were evaluated in furosemide pretreated SHR. Furosemide-treated (10 mg/kg s.c. at 22 and 4 hours prior to dosing with losartan) SHR displayed significantly elevated levels of PRA (from 10.4 ± 1.2 to 24.9 ± 1.1 ng angiotensin I/ml/hours), resulting in the formation of circulating angiotensin II in addition to tissue angiotensin II. Thus, furosemide pretreatment enhanced the blood pressure lowering effect of losartan at 3 and 10 mg/kg i.v.

The removal of both kidneys reduced the PRA to almost undetectable levels. Losartan at 10 mg/kg i.v. had no significant effect on blood pressure in these low renin (bilateral nephrectomized) SHR.

Losartan was also evaluated in conscious, trained, genetically (Penn) hypertensive dogs with systolic blood pressure of 140 to 220 mm Hg and diastolic blood pressure >100 mm Hg. The animals were treated with losartan (1, 3, 10 or 30 mg/kg i.v.) over a period of 4 weeks. Parameters assessed were the pressor responses to angiotensin I (1.0 μ g/kg i.v.) and

angiotensin II (0.3 $\mu\text{g}/\text{kg}$), PRA and renal function (creatinine, PAH clearance).

Losartan caused a dose-related slight but significant reduction (40-70 mm Hg) in blood pressure response to angiotensin I (10 and 30 mg/kg) and angiotensin II (1-30 mg/kg). The reduction in blood pressure in hypertensive dogs is relatively small when compared to the antihypertensive effects described in other models of hypertension. Losartan dose-dependently increased glomerular filtration rate and effective renal plasma flow, while significantly reducing renal vascular resistance. All doses of losartan increased the fractional excretion of sodium while only higher doses (10 and 30 mg/kg) increased the fractional excretion of potassium. Although a trend towards an increase in PRA was observed at 45 to 75 min after administration of losartan, these increases were not statistically significant at any of the doses studied.

C. DOCA-Salt Hypertension

The antihypertensive effects of losartan were evaluated in conscious rats made hypertensive by implanting DOCA pellets subcutaneously and providing 0.1% saline for drinking for 7-8 weeks. Hypertension in this model is fully developed by 7-8 weeks (mean arterial pressure 156 ± 9 mm Hg) with low PRA (0.47 ± 0.44 ng angiotensin I/ml/hr), which in turn results in low levels of angiotensin II and a suppressed RAS. In this model, losartan at 10 mg/kg i.v. did not lower blood pressure. On the other hand, hydralazine (0.3 mg/kg i.v.), a direct acting vasodilator, lowered blood pressure in these rats.

1.1.3. Effects in Normotensive Animals

A. Studies in Conscious Rats

Since angiotensin II does not normally contribute to the maintenance of arterial pressure, an AT_1 angiotensin II receptor antagonist would not be expected to affect blood pressure in normotensive animals. Losartan (10 mg/kg p.o. or 1 to 100 mg/kg i.v.) had no acute effect on blood pressure of normotensive rats for 3 hours post-treatment. Though heart rate was more variable, no significant effect was observed. Chronic oral administration of losartan (10 mg/kg/day p.o.) for 14 days in normotensive Wistar-Kyoto (WKY) rats was shown to have no effect on systolic blood pressure, suggestive of lack of partial agonistic action at the AT_1 receptor. Additionally, losartan pretreatment blocked the pressor effect of saralasin (0.1 to 10 $\mu\text{g}/\text{kg}$ i.v.) indicating that saralasin exerts its agonist action at the AT_1 receptor.

In contrast, a single subcutaneous injection of losartan (10 mg/kg) significantly decreased systolic blood pressure of normotensive rats 6 hours post-treatment and after 21 days of daily treatment. Although the blood pressure had returned to control values by 24 hours post-injection on each day, the pressor response to an i.v. bolus injection of angiotensin II (0.1 $\mu\text{g}/\text{kg}$) was significantly attenuated in chronic losartan treated rats 24 hr after the last injection. The significant reduction in blood pressure in normotensive animals (with an intact sympathetic nervous system) would suggest that the RAS may play a more significant role in

blood pressure maintenance/regulation in the presence of a fully functional sympathetic nervous system than previously thought. The fact that blood pressure returned to normal levels 24 hours post-injection of losartan would suggest that compensatory actions of the sympathetic nervous system and/or other regulatory mechanisms have occurred.

B. Studies in Conscious Dogs

In conscious dogs with normal renin, losartan at 1 to 10 mg/kg i.v. produced a dose-dependent and transient decrease in blood pressure. E-3174 had no effect on the blood pressure. It is not clear from the studies whether the transient hypotensive effects of losartan are unrelated to angiotensin II receptor antagonism. This transient effect does not contribute to the blood pressure lowering or hemodynamic effects of losartan beyond the first few minutes postdose. In furosemide-treated dogs with high renin, both losartan (10, 30 mg/kg p.o. and 3, 10, 30 mg/kg i.v.) and E-3174 (3, 10, 30 mg/kg i.v. and 10 mg/kg p.o.) produced marked and long lasting reductions (more than 3 hours) in mean arterial pressure. The maximum reductions in blood pressure were dose-related.

1.2. *General Pharmacological Studies*

1.2.1. **Cardiovascular Effects**

A. Hemodynamic

Acute hemodynamic effects of losartan were evaluated in furosemide-treated (10 mg/kg i.m. at 18 and 2 hours before the experiment) anesthetized dogs. Losartan at 3 (and not at 1) mg/kg i.v. reduced mean arterial pressure and total peripheral resistance while having little effect on heart rate or cardiac output or dp/dt or blood flow in the coronary, renal, or iliac vascular beds. However, in sodium-deplete anesthetized dogs (animals maintained on low sodium diet for 7 days and treated with furosemide at 10 mg/kg i.m. for 4 days) with high PRA, losartan at 5 mg/kg i.v. decreased blood pressure, increased renal blood flow and decreased renal vascular resistance in a similar fashion. These effects were less pronounced in sodium replete anesthetized dogs with low PRA, suggesting the dependence of renal effects of losartan on the basal PRA. Thus, the potent action of losartan on renal function could be seen only in sodium-deplete anesthetized dogs.

The acute cardiovascular and autonomic effects of losartan were evaluated in anesthetized dogs. Losartan at 10 mg/kg i.v. antagonized the mean arterial pressure and heart rate response to angiotensin II but had no significant effects on mean arterial pressure, heart rate, lead II ECG recordings or meaningful effects on autonomic responses.

B. Cardiac

The direct effect of losartan on myocardial rate and force of contraction was evaluated in isolated guinea pig atrial preparations. Losartan at concentrations of 0.1 to 10 μ M did not

significantly alter atrial rate in spontaneously beating atrium and developed tension (inotropism) in left paced atrium.

The cardiac cell electrophysiologic effects of losartan and E-3174 were evaluated in left ventricular Purkinje fibers isolated from dogs. Both losartan and E-3174 (at concentrations 0.3 to 10 μ M) showed a lack of direct electrophysiological activity.

1.2.2. Renal Effects

The acute effects of losartan on renal function were assessed in anesthetized normotensive (WKY) and SHR and in a group of anesthetized euvolemic Munich-Wistar rats. The SHR and WKY were volume expanded with a 0.9% sodium chloride infusion of 100 μ l/min. The euvolemic rats were infused with 0.9% sodium chloride at a rate of 20 μ l/min. Losartan at 2 or 10 mg/kg i.v. had no effect on urine volume, sodium excretion, renal blood flow or glomerular filtration rate in WKY. In SHR, losartan at 2 mg/kg decreased urine flow (24%), increased renal blood flow (30%), but sodium excretion, GFR, and arterial pressure were not significantly altered. Losartan at 10 mg/kg i.v. significantly reduced arterial pressure, urine volume, and sodium excretion while significantly increasing renal blood flow (34%). In euvolemic rats, losartan at 2 mg/kg i.v. increased PRA, renal blood flow, urine flow, and sodium excretion, while mean arterial pressure and GFR were unaltered. It was concluded that the limited renal effects of losartan do not contribute to the initial antihypertensive action.

The renal effects of losartan were studied in anesthetized dogs maintained on either normal sodium diet (104 mEq/day) or on a low sodium diet (5 mEq/day, also received furosemide at 10 mg/kg i.v. on days 2 to 5). In sodium replete dogs (PRA 1.2 ± 0.3 ng angiotensin I/ml/hr), losartan at 5 mg/kg i.v. decreased mean arterial pressure, renal vascular resistance, and filtration fraction, and increased renal blood flow, urinary sodium, and potassium and urine volume. In sodium depleted dogs (PRA 21 ± 2.7 ng angiotensin I/ml/hr), losartan at 5 mg/kg i.v. produced significant reductions in arterial pressure, renal vascular resistance, and filtration fraction while increasing renal blood flow. The urinary excretion of sodium, potassium or water and GFR were not significantly altered. The data thus shows that losartan produces potent action on renal function only in sodium-deplete anesthetized dogs (which are RAS dependent since PRA levels are elevated).

Further, losartan has also been evaluated for its renal protective effect in SHR. Losartan at 1 and 10 mg/kg/day i.p. decreased urinary protein excretion to the same extent as enalapril. This suggests that losartan, like ACE inhibitors, is effective in models of renal failure.

1.2.3. Neuropharmacological Effects

Losartan administered orally to rats at doses ranging from 13 to 100 mg/kg, equivalent to 22 to 167 times its antihypertensive ED₃₀ in the rat (0.5 mg/kg p.o.) produced no overt signs. In mice, losartan at 100 mg/kg p.o. produced ptosis in 2 of 15 animals. No other symptoms were observed. In other studies in mice, it was found that losartan does not have analgesic,

neuroleptic, opiate antagonistic, anticonvulsant, or dopamine antagonistic activity. In the models of cognition, losartan at 1 and 30 mg/kg s.c. in the mouse, and 10 and 30 mg/kg s.c. in the rats reversed the scopolamine-induced deficit in the passive avoidance test. Also, at 3 mg/kg s.c. losartan reversed the deficit in the delayed-matching-to-position test (working memory task) induced by scopolamine. These effects are similar to that reported for ACE inhibitors.

Losartan at 3, 10, 25, 50 and 100 mg s.c. produced significant changes in the cortical EEG profile in conscious rats. The observed EEG changes were similar to those of a general vigilance-enhancing profile.

It is known that acute and chronic RAS inhibition do not always result in the same antihypertensive effect. When the ACE inhibitors are administered repeatedly over a long time, the reduction in blood pressure below the pretreatment level persists long after discontinuation of treatment. This "persistent" antihypertensive effect of ACE inhibition is of particular importance when the regimen is started before hypertension is completely established. In this regard, the effects of angiotensin II blockade by losartan on the development and maintenance of hypertension in stroke-prone SHR (SHR-SP) was evaluated. In this study animals were dosed with losartan (1 or 10 mg/kg in drinking water) at 5 to 13 weeks of age. Rats were sacrificed either at 13 or 29 weeks of age. Systolic blood pressure was measured by the tail-cuff method.

Losartan at 10 mg/kg/day like enalapril (3 mg/kg/day) inhibited the age-related development of hypertension in SHR-SP. Heart weight was significantly lower than the controls. In SHR-SP, PRA markedly increases in adults (from 16 to 29 weeks of age) with concomitant development of extremely high blood pressure, thereby suggesting that RAS plays an important role in the pathophysiology of this animal model. Losartan at 10 mg/kg significantly lowered PRA and immunoreactive renin content in the juxtaglomerular cells compared to controls. Thus, continuous inhibition of RAS from the pre-hypertensive stage of SHR-SP may be important for exerting the persistent antihypertensive effect. In SHR-SP, more than 80% of rats develop cerebral hemorrhage and/or infarction when the animals are somewhat over 20 weeks of age. Cerebrovascular lesions determined at the age of 29 weeks were significantly prevented by losartan. None of effects were observed at 1 mg/kg/day.

1.2.4. Gastrointestinal Effects

Losartan at 10 mg/kg s.c. had no effect on intestinal motility in conscious mice. In another study in mice, losartan at 10, 30 and 100 mg/kg p.o. showed no effect on intestinal propulsion. The effects of losartan on gastric secretion were evaluated in rats with pylorus ligation. In this study, 30 but not 3 mg losartan/kg, administered by oral gavage, significantly inhibited gastric secretion by 22%, and gastric output by 45%. In contrast, losartan at 10 mg/kg, administered directly into the stomach via the fistula cannula in dogs, did not significantly alter basal gastric acid secretion or that stimulated by exogenous gastrin.

1.2.5. Anti-inflammatory Effects

Losartan at 2 mg/kg i.p. showed no effects on inflammation induced by carrageenan in rat paw.

1.2.6. Effects on Platelet Aggregation

Aggregation of platelets induced by the addition of arachidonate *in vitro* was inhibited by losartan at a concentration of 1 mM. Losartan at 100 but not at 10 mg/kg p.o. significantly reduced arachidonate-induced, but not ADP-induced platelet aggregation *ex vivo* in rats.

2. PHARMACOKINETICS

2.1. Absorption and Pharmacokinetic Studies

2.1.1. Absorption and Pharmacokinetics of Losartan in Rats

Study Facility: E.I. duPont Pharmaceutical Labs, Wilmington DE

Study No: MP 89-033

Study Dates: Not stated; Report dated 5/10/89

GLP Compliance: Not indicated.

Animals: Male Sprague-Dawley rats (250-350 gm)

Procedure: Losartan was dissolved in sterile normal saline and administered intravenously (1.0 or 3.0 mg/kg) as a single bolus (4 rats/dose group) or administered orally (10 mg/kg) by gavage (3 rats). Samples of venous blood were obtained from rats via indwelling cannulas at 0, 5, 15, 30, 45 min, 1, 2, 3, 6 and 8 hours after IV administration and at similar intervals including 24 hours after oral administration. Plasma concentrations of losartan were measured by reverse phase HPLC; these measurements were used for calculating plasma half-life, clearance, volume of distribution and plasma AUC. Oral bioavailability was calculated according to:

$$\frac{\text{AUC}_{\text{oral}} \times \text{IV dose}}{\text{AUC}_{\text{iv}} \times \text{PO dose}} \times 100 = \% \text{ Oral Bioavailability}$$

Results: Plasma levels of losartan declined in an apparent biexponential fashion following IV administration with a terminal half-life of 100 to 113 min. The mean oral bioavailability was approximately 33% for a 10 mg/kg oral dose. The terminal half-life after an oral dose, 166 min, was longer than that observed after the IV doses. This could be due to the slow and continuous absorption of the oral dose or enterohepatic recirculation. Pharmacokinetic results are summarized as follows:

TABLE 2.1.1.1
PHARMACOKINETIC PARAMETERS FROM IV LOSARTAN

Parameter	1 mg/kg IV	3 mg/kg IV
Half-life (min)	100 +/- 17	113 +/- 7
Clearance (ml/min/kg)	6.2 +/- 0.7	7.8 +/- 0.3
V _{dss} (L/kg)	0.57 +/- 0.04	0.92 +/- 0.12
AUC _{0-inf} (ug.min/ml)	168.5 +/- 18.2	388.5 +/- 17.8

Values are the mean +/- SEM from 4 rats/dose group

V_{dss} = apparent volume of distribution at steady-state

AUC_{0-inf} = Area under the plasma concentration vs time curve

TABLE 2.1.1.2
PHARMACOKINETIC PARAMETERS FROM PO (10 MG/KG) LOSARTAN

Parameter	Mean +/- SEM
Half-life (min)	166 +/- 29
T _{max} (min)	130 +/- 61
C _{max} (ug/ml)	1.57 +/- 0.28
AUC _{0-inf} (ug.min/ml)	428.5 +/- 192.3
Clearance (ml/min/kg)	56.2 +/- 39.0
F (%)	33.4 +/- 14.9

Values are the mean +/- SEM from 3 rats

F = Oral bioavailability

2.1.2. Absorption and Pharmacokinetics of Losartan in Dogs

Study Facility: E.I. duPont Pharmaceutical Labs., Wilmington, DE

Study No: MP 89-032

Study Dates: Not stated; Report dated 5/10/89

GLP Compliance: Not stated.

Animals: Male Beagle dogs (7-10 kg)

Procedure: Losartan was dissolved in sterile normal saline and administered intravenously (3 mg/kg) as a single bolus (5 dogs) or administered

orally (5, 10 or 20 mg/kg) by gavage (4 dogs/dose group). Samples of venous blood were obtained from dogs by repeated venipuncture at 0, 5, 10, 15, 30 min, 1, 1.5, 2, 4, 6, 8 and 24 hours after dosing. Plasma concentrations of losartan were measured by reverse phase HPLC; these measurements were used for calculating plasma half-life, clearance, volume of distribution, C_{max}, T_{max} and plasma AUC.

Results: Plasma concentrations of losartan in dogs given a single 3 mg/kg IV bolus declined in a multiexponential fashion with a mean terminal plasma half-life of 41 min. After oral dosing there was a linear relationship between the dose and AUC or C_{max}. Pharmacokinetic results are summarized as follows:

TABLE 2.1.2.1.
PHARMACOKINETIC PARAMETERS FROM IV (3 MG/KG) LOSARTAN

Parameter	Mean +/- SEM
Half-life (min)	41 +/- 10
Clearance (ml/min/kg)	22.2 +/- 2.9
V _{dss} (L/kg)	0.30 +/- 0.03
AUC _{0-inf} (ug.min/ml)	144.5 +/- 18.3

V_{dss} = Apparent volume of distribution at steady state

AUC_{0-inf} = Area under the plasma concentration vs time curve

TABLE 2.1.2.2.
PHARMACOKINETIC PARAMETERS FROM PO LOSARTAN

Parameter	5 mg/kg PO	10 mg/kg PO	20 mg/kg PO
Half-life (min)	144 +/- 31	108 +/- 10	153 +/- 22
T _{max} (min)	25 +/- 12	45 +/- 9	53 +/- 8
C _{max} (ug/ml)	0.79 +/- 0.22	1.97 +/- 0.04	2.94 +/- 0.84
AUC _{0-inf} (ug.min/ml)	54.7 +/- 9.3	156.7 +/- 18.2	257.1 +/- 57.2
F (%)	22.5 +/- 0.6	33.2 +/- 1.7	25.7 +/- 2.2

Values are the mean +/- SEM from 4 dogs/dose group

F = Oral bioavailability

2.1.3. Oral Bioavailability of Losartan and Metabolite (L-158,641) in Adult Chimpanzees

Study Facility: MSD Research Laboratories, West Point, PA and New Iberia Research Center, New Iberia, LA

Study No: # 9201-805-062-0229

Study Dates: Not stated; Report dated 6/11/93

GLP Compliance: Not stated.

Subjects: Four adult chimpanzees (49-63 kg)

Procedure: Losartan and its metabolite were dissolved in sterile normal saline and administered intravenously (40 mg of losartan or 20 mg of L-158,641) as a single dose over 20 min or administered orally (100 mg of losartan or 100 mg of L-158,641) by nasogastric tube in a 4-way randomized, crossover design (each animal received each of the four doses in the crossover design). About six to seven days separated treatments. With IV administration, 6 ml venous blood samples were collected at 0, 10, 20, 25, 30 and 60 min and at 2, 3, 4, 6, 9, 16 and 24 hours after dosing. Six-ml venous blood samples were collected at 0, 20, 40 and 60 min and 2, 3, 4, 6, 9, 12, 16 and 24 hours after oral administration. Urine samples were collected from the animals in metabolism cages prior to dosing and at 0-12, 12-24, 24-36, 36-48 and 48-72 hr intervals. Blood and urine were assayed for parent drug and metabolite by HPLC and these measurements used in calculating the pharmacokinetic parameters summarized below.

Results: Based on a comparison of IV to PO AUCs, the absolute oral bioavailabilities of losartan and its metabolite, L-158,641, were 35% and 34%, respectively.

TABLE 2.1.3.1.
PHARMACOKINETIC PARAMETERS FROM IV ADMINISTRATION

Parameter	Losartan 40 mg IV		L-158,641 20 mg IV
	Losartan	L-158,641	
C max, ng/ml	2582*	165	4370*
Tmax, hr	NA	1.25	NA
AUC _{0-inf} , ng.hr/ml	1278	677	5267
t1/2, hr	1.02	NA	6.70
Vd _w , L	16.3	NA	15.1
CL, ml/min	619	NA	71
% Dose in urine	16%	2.3%	60%

NA = Not Applicable

* Concentrations immediately after drug administration.

TABLE 2.1.3.2.
PHARMACOKINETIC PARAMETERS FROM PO ADMINISTRATION

Parameter	Losartan 100 mg PO		L-158,641 100 mg PO
	Losartan	L-158,641	
C _{max} , ng/ml	189	66	966
T _{max} , hr	7.0	10.5	7.8
AUC _{0-inf} , ng.hr/ml	1392	998	13207
CL, ml/min	67	22	23
% Dose in Urine	4.3%	1.3%	17%
Oral Bioavailability	35.4%	NA	34.4%

NA= Not Applicable

2.1.4. Oral Bioavailability and Pharmacokinetics of Losartan and Metabolite (L-158,641) in Humans.

Study Facility: MSD Research Laboratories, West Point, PA and Jefferson Medical College, Clinical Research Unit, Philadelphia, PA

Study No: MA # 060

Study Dates: Not stated; Report dated 3/19/93

GLP Compliance: Not stated.

Animals: Six healthy, adult, male subjects

Procedure: ¹⁴C-losartan and its metabolite (non-radiolabelled) were dissolved in sterile normal saline and administered intravenously (30 mg of losartan or 20 mg of L-158,641) as a single dose over 20 min or administered orally (losartan only, 100 mg) as a single dose in a randomized, crossover design. Seven days separated adjacent treatments. With IV administration, 6 ml venous blood samples were collected at 0, 10, 20, and 30 min and at 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36 and 48 hours after dosing. Six-ml venous blood samples were collected at 0, 15, 30 and 45 min and 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36 and 48 hours after oral administration. Urine samples were collected prior to dosing and at 0-2, 2-4, 4-6, 6-8, 8-12, 12-18, 18-24, 24-36, 36-48, 48-72 and 72-96 hr intervals. Blood and urine were assayed for parent drug and metabolite by HPLC and resulting values used in calculating pharmacokinetic parameters summarized below.

Results: The observed and calculated pharmacokinetic values are summarized in the

tables below. A comparison of AUCs from oral and IV losartan showed that oral bioavailability of losartan in normal male subjects was 36.5%.

TABLE 2.1.4.1.
PHARMACOKINETIC PARAMETERS FROM IV ADMINISTRATION

Parameter	Losartan 30 mg IV		L-158,641 20 mg IV
	Losartan	L-158,641	
C max, ng/ml	1453*	149	3721*
Tmax, hr	NA	4.0	NA
AUC _{0-inf} , ng.hr/ml	851	1332	5969
t1/2, hr	3.2	5.3	6.3
Vd _d , L	46.6	NA	10.3
CL, ml/min	559	NA	47
% Dose in urine	11.5%	7.6%	55%

NA = Not Applicable

* Concentrations immediately after drug administration

TABLE 2.1.4.2.
PHARMACOKINETIC PARAMETERS FROM PO ADMINISTRATION

Parameter	Losartan 100 mg PO	
	Losartan	L-158,641
Cmax, ng/ml	659	653
Tmax, hr	0.46	2.3
AUC _{0-inf} , ng.hr/ml	1091	4072
CL, ml/min	64	27
% Dose in Urine	4.8%	7.6%
Oral Bioavailability	36.5%	NA

NA= Not Applicable

2.2. *Distribution Studies*

2.2.1. Tissue Distribution of Radiolabelled Losartan in Rats

Study Facility: E.I. duPont Research Labs, Wilmington, DE

Study No.: MP89-005

Study Dates: Not stated; Report date-2/02/89

GLP Compliance: Not indicated.

Animals: Male Sprague-Dawley rats (250-290 gm)

Procedure: ^3H -Losartan was prepared as an aqueous solution and administered orally at a dose of 10 mg/kg to 28 rats by gavage. Groups of 4 rats were sacrificed at 0.5, 1, 4, 8, 24, 48 and 96 hours after dosing. Whole blood was collected and major tissues and organs were removed and combusted in a tissue oxidizer. The trapped radioactivity was measured by liquid scintillation spectrometry.

Results: Absorption from the GI tract was rapid with peak blood and tissue levels appearing 30 to 60 min after dosing. Overall, 33% and 38% of the dose was contained in all tissues sampled at 30 and 60 min, respectively. Radioactivity in liver, lungs and kidney declined over the first 8 hours with half-lives of 3 to 4 hours. At 24 hours postdose all tissues, including blood, contained less than 1% of the dose. Tissues and organs containing > 0.5% of the administered dose at any sampling time are summarized below.

TABLE 2.2.1.1
MEAN % OF RADIOACTIVITY CONTAINED IN TISSUES AFTER 10 MG/KG ORAL LOSARTAN

Tissue	0.5 Hr	1 Hr	4 Hr	8 Hr	24 Hr
Kidney	0.86	0.52	0.25	0.11	0.02
Sm. Intest. Distal	0.18	1.56	12.2	0.77	BQL
Sm. Intest. Proximal	3.83	13.6	3.58	0.34	BQL
Stomach	1.33	0.71	0.11	0.03	BQL
Liver	19.7	15.5	9.56	4.67	0.47
Muscle	3.22	2.53	1.59	1.34	BQL
Skin	1.02	0.95	0.83	0.49	BQL
Plasma	2.34	2.51	1.44	0.48	0.16
Whole Blood	2.21	2.16	1.17	0.53	0.24

BQL= Below Quantifiable Limit (240 dpm)

2.2.2. Distribution of Radiolabelled Losartan in Rats

Study Facility: Tokai Research Laboratories, Daiichi Pure Chemical Co, Japan

Study No: AE-1565

Study Dates: 5/29/91 - 9/10/91

GLP Compliance: Not indicated.

Animals: Male Sprague-Dawley rats (185-249 gm)

Procedure: ^{14}C -Losartan was dissolved in phosphate buffer and administered intravenously (3 mg/kg; 15 rats) or orally (10 mg/kg; 21 rats) by gavage. The animals were kept in metabolism cages and urine and feces were collected up to 168 hours after dosing. Groups of 3 rats were sacrificed at 0.5, 1, 4, 8, 24 and 96 hours after oral administration and 0.25, 1, 8 and 48 hours after IV administration. Whole blood was collected and major tissues and organs were removed and combusted in a tissue oxidizer. The radioactivity was trapped and measured by liquid scintillation spectrometry. Radioactivity in urine and in acidified methanol extracts from feces was measured by liquid scintillation spectrometry.

Results: Tissues containing concentrations of radioactivity above 3 ug equivalent of losartan/gm are presented in the following tables. Negligible levels of radioactivity were detected in brain or fat tissue. The results of this study conducted by a Japanese pharmaceutical company are qualitatively similar (in terms of relative tissue concentrations) to those of the previous oral administration study conducted at duPont Research Labs.

TABLE 2.2.2.1.
CONCENTRATION OF RADIOACTIVITY (UG EQUIV. LOSARTAN/GM) CONTAINED IN TISSUES
AFTER 10 MG/KG ORAL LOSARTAN

Tissue	0.5 Hr	1 Hr	4 Hr	8 Hr	24 Hr
Kidney	10.1	11.6	3.42	3.48	0.08
Small Intestine	11.3	13.2	4.12	1.34	BQL
Stomach	16.6	20.7	1.66	1.54	BQL
Heart	4.40	1.32	0.30	0.31	BQL
Liver	72.4	61.0	36.2	40.7	0.65
U. Bladder	3.51	3.02	2.64	2.45	BQL
Trachea	3.48	1.16	0.69	0.75	BQL
Plasma	6.38	8.04	2.55	2.56	0.12
Whole Blood	3.71	4.54	1.40	1.41	BQL

BQL= Below Quantifiable Limit (240 dpm)

TABLE 2.2.2.2.
CONCENTRATION OF RADIOACTIVITY (UG EQUIV. LOSARTAN/GM) CONTAINED IN TISSUES
AFTER 3 MG/KG IV LOSARTAN

Tissue	0.25 Hr	1 Hr	8 Hr	48 Hr
Kidney	3.70	6.31	0.83	0.02
Small Intestine	2.10	1.55	0.59	BQL
Bone Marrow	1.24	2.15	0.15	BQL
Lung	0.49	1.30	0.18	0.02
Liver	41.7	60.3	13.0	0.09
U. Bladder	0.75	0.61	0.19	BQL
Cecum	0.24	0.46	2.80	0.01
Plasma	2.09	3.71	0.76	0.03
Whole Blood	1.23	2.26	0.44	BQL

BQL= Below Quantifiable Limit (240 dpm)

2.2.3. Transfer of Radiolabelled Losartan into Fetus and Milk in Rats

Study Facility: Tokai Research Laboratories, Ibaragi-ken, Japan

Study No: AE-1721

Study Dates: 5/28/92 - 9/22/92

GLP Compliance: Not stated; QA audit report included.

Animals: Pregnant and lactating Sprague Dawley rats (pregnant rats weighed 279-233gm and nursing rats weighed 320-347gm).

Procedure: ¹⁴C-Losartan was dissolved in distilled water and administered as a single oral dose (10 mg/kg) by gavage to 9 pregnant rats on days 18 of gestation or to 18 lactating rats on day 11 after delivery. Pregnant rats were sacrificed at 1, 8 and 24 hours (3 rats/time period). Maternal and fetal blood samples were collected in heparinized tubes. Maternal and fetal tissues and amniotic fluids in the same litter were pooled, solubilized using a tissue solubilizer and radioactivity measured by liquid scintillation spectrometry. In lactating rats, maternal blood was collected from the tail veins and milk was collected from the nipples at 0.5, 1, 2, 4, 8, 24 and 48 hours after dosing (3 rats/time period). Radioactivity in the milk and blood of lactating rats was measured by liquid scintillation spectrometry.

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TRADE NAME:

COZAAR (LOSARTAN POTASSIUM)

25/50 MG TAB

GENERIC NAME:

LOSARTAN POTASSIUM

Results: Radioactivity was detected in fetal tissue following administration of radioactive losartan to pregnant rats. Fetal concentration of radioactivity was barely detectable 1 hour after treatment of dams, but fetal radioactivity levels increased at 8 and 24 hours. The concentrations of radioactivity measured in maternal and fetal tissues are as follows:

TABLE 2.2.3.1.
RADIOACTIVITY CONCENTRATION (UG EQUIVALENT/GM) AFTER 10 MG/KG PO DOSE OF ¹⁴C-LOSARTAN

Tissue	1 hour	8 hours	24 hours
Maternal Plasma	3.8	0.79	0.08
Blood	2.5	0.51	0.05
Lung	1.1	0.25	0.05
Liver	84.7	22.0	2.36
Kidney	10.3	2.2	0.53
Uterus	1.0	0.28	0.09
Fetal Blood	0.02	0.14	0.18
Brain	BQL	0.01	0.01
Heart	BQL	0.04	0.05
Lung	BQL	0.05	0.05
Liver	0.04	0.17	0.15
Kidney	BQL	0.08	0.09
% of Dose/Fetus	0.00	0.01	0.01

BQL=Below quantifiable limit (<0.01 ug equiv/gm)

Radioactivity was detected in the milk of lactating rats as early as 30 min after dosing and the radioactivity levels increased up to 8 hours following the single 10 mg/kg dose. Radioactivity was still detected in the milk up to 48 hours after dosing.

TABLE 2.2.3.2.
RADIOACTIVITY CONCENTRATION (UG EQUIVALENT/ML) IN MATERNAL PLASMA AND MILK IN LACTATING RATS AFTER 10 MG/KG PO OF ¹⁴C-L OSARTAN.

Time (hr)	Maternal Radioactivity Concentration (ug/ml)	Milk Radioactivity Concentration (ug/ml)
0.5	0.03	1.26
1	0.04	1.02
2	0.09	1.01
4	0.16	1.18
8	0.30	0.76
24	0.11	0.33
48	0.05	0.11

2.2.4. Binding of Losartan to Rat, Dog and Human Plasma Protein:

Study Facility: Du Pont Haskell Research Center, Newark, NJ

Study No.: DMP 93-008

Study Dates: Not stated

GLP Compliance: Not indicated

Blood/Plasma: Fresh blood and plasma were obtained from male Sprague-Dawley rats and Beagle dogs. Human plasma was obtained from normal male volunteers.

Procedure: Plasma from Beagle dogs (n=4), human volunteers (n=4) or rats (n=4) were added to glass tubes containing ¹⁴C-losartan or ³H-carboxylic acid metabolite (E-3174) to give final concentrations of 0.5, 1.0, 2.0 and 5.0 ug/ml of losartan or 0.1, 1.0, and 10.0 ug/ml of E-3174. The samples (in triplicate) were mixed and incubated for 30 min at 37°C, centrifuged and aliquots of plasma analyzed by liquid scintillation spectrometry to determine the fraction of drug unbound to plasma protein. In a separate series of experiments, solutions of other drugs (aspirin, naproxen, warfarin, ibuprofen, diazepam) were added to plasma containing losartan or E-3174 to determine drug-drug interaction of plasma protein binding.

Results: Losartan binding to plasma protein was extensive in rat, human and dog plasma. Unbound fraction of losartan was lowest in the rat (0.7% to 1.0%), followed by human (1.3% to 1.4%) and then dog (2.7% to 3.1%). The fraction unbound appeared to be concentration-independent. Plasma binding of the pharmacologically active

metabolite, E-3174 (L-158,641), was greater than that of the parent compound.

TABLE 2.2.4.1.
PERCENT UNBOUND (FREE) FRACTION OF DRUG IN PLASMA

Concn ug/ml	Losartan			E-3174	
	Man	Dog	Rat	Man	Rat
0.1	ND	ND	ND	0.2	0.1
0.5	1.4	3.1	0.7	ND	ND
1.0	1.3	2.7	0.8	0.2	0.2
2.0	ND	2.9	1.0	ND	ND
5.0	1.2	ND	ND	ND	ND
10.0	ND	ND	ND	0.2	0.1

Neither losartan nor E-3174 was displaced *in vitro* from human plasma proteins by coincubation with pharmacologically relevant concentrations of naproxen (50 ug/ml), ibuprofen (20 ug/ml), diazepam (0.25 and 3.5 ug/ml) or warfarin (2 and 20 ug/ml). Suprapharmacologic concentrations of aspirin (300 and 3000 ug/ml), naproxen (500 ug/ml) and ibuprofen (200 ug/ml) increased the fraction of unbound losartan and metabolite 2- to 7-fold.

2.3. Metabolism

2.3.1. Metabolism of Losartan by Rat, Monkey and Human Liver Slices.

Study Facility: Merck Research Labs, Rahway, NJ

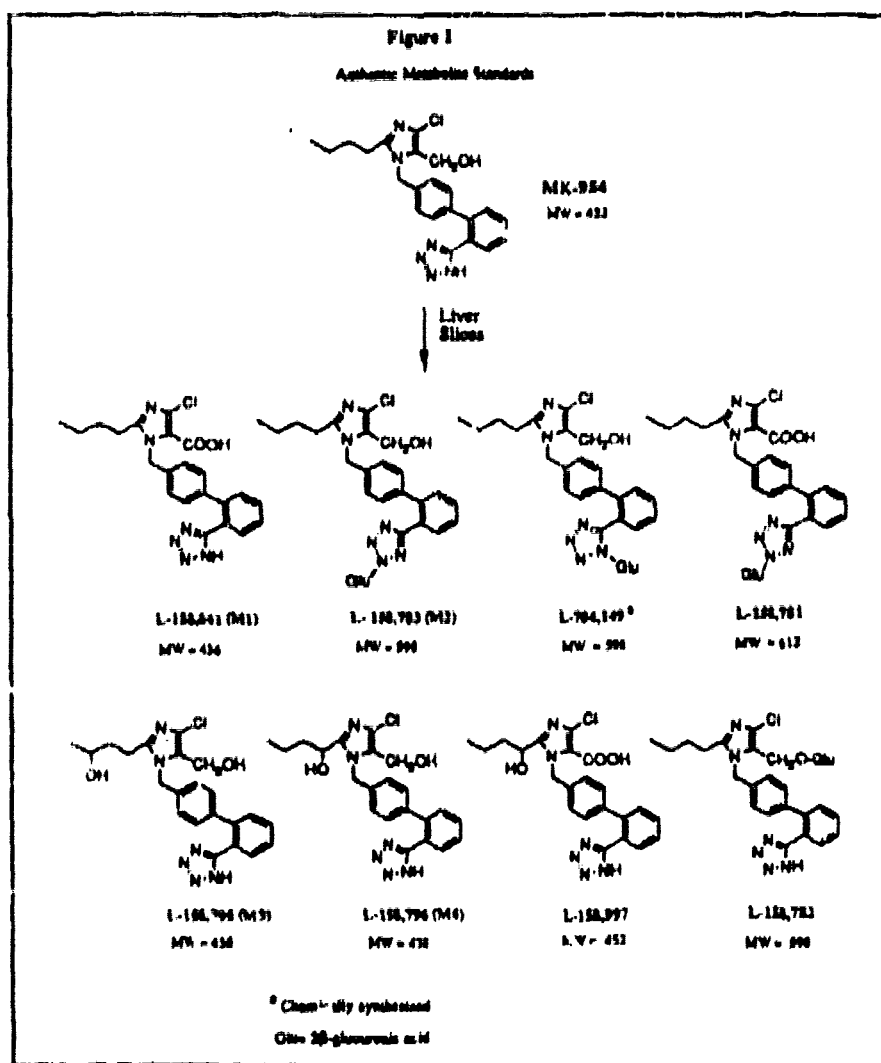
Study No: This is a report by RA Stearns et al published in DRUG METABOLISM AND DISTRIBUTION: Vol. 20: 281-287 (1992).

GLP Compliance: Not stated

Tissues: Rat livers were obtained from male Sprague-Dawley rats, monkey livers were obtained from control group Rhesus monkeys sacrificed in toxicology studies and normal human liver tissue was obtained as excess tissue surgically removed from patients with metastatic cancer.

Procedure: ³H-Losartan was dissolved in medium containing 3.7 gm wet weight of rat or monkey liver slices or 2.1 gm wet weight of human liver slices and incubated for 5 hr at 37°C. Aliquots of the incubation medium were removed and metabolites measured by HPLC. Radioactivity was also determined from aliquots of the incubation medium by liquid scintillation spectrometry.

Results: Incubation of radiolabelled losartan with rat liver slices resulted in the formation of 7 metabolites (designated M-1 to M-7). In rat liver, the primary route of hepatic metabolism was oxidative, leading to either monohydroxylated (M-1, M-2, M-5) or oxidized (carboxylic acid, M-6) metabolites and, to a lesser extent, the tetrazole-N-glucuronide (M-7). The M-6 metabolite accounted for about 25% of all metabolites in the rat liver incubation. The major metabolites formed with monkey liver slices, each accounting for 40% of the total radioactivity, were the tetrazole-N-glucuronide (M-7) and the hydroxymethyl-O-glucuronide (M-3). Incubation of losartan with human liver slices yielded six metabolites (M-3 excluded) an equal mixture of both oxidized and glucuronic acid conjugated metabolites. With the exception of M-3, the same metabolites isolated from incubations with rat and monkey slices were observed in human liver slices. The metabolism of losartan by human liver slices was characterized by an approximately equal distribution of both oxidized and glucuronidated metabolites.



2.3.2. Urinary Metabolites After Oral and IV Losartan in Rats

Note: A portion of this study was reviewed and described under Elimination.

Study Facility:

Study No: JDM#92-A6

Study Dates: 4/21/92 - 1/07/93

GLP Compliance: Not stated; QA audit report included.

Animals: Male and female Sprague-Dawley rats (165-240 gm)

Procedure: ¹²C-Losartan was dissolved in phosphate buffer (pH 7.4) and administered to rats orally (10 mg/kg) by gavage or intravenously (3 mg/kg) as single doses (3/sex/dose group). Samples of arterial blood (from cannulated carotid) were collected at intervals up to 48 hours after oral and IV administration. Urine and feces were collected at 8, 24 and 48 hours after dosing. Radioactivity in the biological samples was measured by liquid scintillation spectrometry; metabolites were measured by HPLC.

Results: Urinary excretion of drug related products with both routes of administration appeared to be higher in females than males. Urinary excretion of parent drug and metabolites in males was negligible; urinary excretion of losartan metabolites in females represented a small fraction of the drug-related excretory products.

TABLE 2.3.2.1.
LOSARTAN METABOLITES EXCRETED IN URINE AFTER IV AND ORAL DOSE IN RATS

Metabolite	% of Dose Excreted in Urine in 24 Hrs			
	Male		Female	
	IV	PO	IV	PO
Parent Drug	ND	0.28	13.1	8.1
1-hydroxylated	ND	ND	0.73	0.66
3-hydroxylated	0.18	ND	1.52	1.06
Carboxylic acid	ND	ND	ND	0.06
Others (Unknown)	3.9	2.9	3.0	1.7

ND= Not detected

2.3.3. Metabolism of Losartan in Dog Primary Cultured Hepatocytes

Study Facility:

Study No: 91-M018

Study Dates: 7/09/91 - 7/31/91

GLP Compliance: Not stated; QA audit report included.

Cell Culture: Isolated dog liver was digested with collagenase and dispersed cells were filtered, centrifuged and resuspended. Aliquots of the hepatocyte suspension were plated on growth media and incubated overnight for cell stabilization.

Procedure: Losartan was dissolved in DMSO in concentrations of 2.5 and 25 mM and 4 uL of the drug solution was added to the cell culture and incubated for 24 hours. Aliquots of the incubation medium were removed for measurement of losartan and metabolites by HPLC.

Results: Incubation of the higher concentration of losartan for 24 hours produced six detectable metabolites. The major metabolite was identified as the glucuronide of losartan; two other prominent metabolites were hydroxylated derivatives. Only a small amount of the carboxylic derivative (biologically active metabolite, L-158,641) was produced. The remaining metabolites were unidentified.

2.3.4. Metabolism of Losartan in Humans

Note: A portion of this study was reviewed and described under Absorption.

Study Facility: MSD Research Laboratories, West Point, PA and Jefferson Medical College, Clinical Research Unit, Philadelphia, PA

Study No: MA # 060

Study Dates: Not stated; Report dated 3/19/93

GLP Compliance: Not stated.

Animals: Six healthy, adult, male subjects

Procedure: ¹⁴C-Losartan and its metabolite (non-radiolabelled L-158,641) were dissolved in sterile normal saline and administered intravenously (30 mg of losartan or 20 mg of L-158,641) as single doses over 20 min or administered orally (100 mg of losartan) as single doses in a randomized, crossover design. Seven days separated

adjacent treatments. With IV administration, 6 ml venous blood samples were collected at 0, 10, 20, and 30 min and at 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36 and 48 hours after dosing. Six-ml venous blood samples were collected at 0, 15, 30 and 45 min and 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36 and 48 hours after oral administration. Urine samples were collected prior to dosing and at 0-2, 2-4, 4-6, 6-8, 8-12, 12-18, 18-24, 24-36, 36-48, 48-72 and 72-96 hr intervals. Feces were collected up to 168 hours after dosing. Blood, feces and urine were assayed for parent drug and metabolites by HPLC.

Results: Recovery of radioactivity following IV administration of losartan was 43.3% of the dose in urine and 49.5% of the dose in feces; following oral administration of losartan, recovery in urine and feces was 35.2% and 57.7%, respectively. Three major metabolites were identified in urine, L-158,795 (1-hydroxylated derivative), L-158,796 (3-hydroxylated derivative) and L-158,641 (biologically active carboxylic acid metabolite). The N2-glucuronide derivative was a minor metabolite in urine. In feces, the parent drug accounted for 7.8%-12.8% of the dose after IV administration of losartan; the hydroxylated derivatives were approximately equal and combined accounted for 16%-18% of the administered dose. The carboxylic acid metabolite was detected in feces as approximately 7%-13% of the IV dose. No metabolic profiling was conducted on feces following oral losartan.

2.4. Elimination

2.4.1. Urinary and Fecal Excretion of Radioactivity After Oral and IV ¹⁴C-Losartan in Rats

Study Facility:

Study No: JDM#92-A6

Study Dates: 4/21/92 - 1/07/93

GLP Compliance: Not stated; QA audit report included.

Animals: Male and female Sprague-Dawley rats (165-240 gm)

Procedure: ¹²C-Losartan was dissolved in phosphate buffer (pH 7.4) and administered to rats orally (10 mg/kg) by gavage or intravenously (3 mg/kg) as single doses (3/sex/dose group). Samples of arterial blood (from cannulated carotid) were collected at intervals up to 48 hours after oral and IV administration. Urine and feces were collected at 8, 24 and 48 hours after dosing. Radioactivity in the biological samples was measured by liquid scintillation spectrometry; metabolites were measured by HPLC.

Results: Radioactivity was predominantly eliminated via fecal excretion following

either oral or IV dosing. Approximately 80% and 82% of the radioactivity was eliminated by 24 hours following IV dosing in males and females, respectively; approximately 92% and 82% of the radioactive dose was eliminated in 24 hours after oral dosing in males and females, respectively. By 48 hours, elimination was essentially complete.

TABLE 2.4.1.1.
RADIOACTIVITY EXCRETED IN URINE AND FECES AFTER IV AND ORAL DOSE IN RATS

Parameter	% of Radioactive Dose Eliminated in 48 Hrs			
	Male		Female	
	IV	PO	IV	PO
Urinary Excretion	4.2	3.6	19.5	13.4
Fecal Excretion	89.9	93.3	68.7	80.2
Total Excretion	94.1	96.9	88.2	93.6

2.4.2. Urinary, Biliary and Fecal Excretion of Radioactivity After Oral and IV ³H-Losartan in Rats

Study Facility: E.I. duPont Research Labs, Wilmington, DE

Study No: MP-89-015

Study Dates: Not indicated; report date 3/29/89

G.P. Compliance: Not indicated.

Animals: Male Sprague-Dawley rats (250-300 gm)

Procedure: ³H-Losartan was prepared as an aqueous solution and administered intravenously (10 mg/kg) or orally (10 mg/kg) by gavage to intact rats (4/route); a separate group (4) of bile-duct cannulated rats was administered a single oral dose (10 mg/kg) by gavage. Animals were placed in individual metabolic cages and urine and feces were collected from 0-24 hr and 24-48 hr following dosing. Bile was collected from bile-duct cannulated rats at 24 hr intervals up to 144 hours postdose. Blood was drawn from all rats by cardiac puncture at termination of the study and radioactivity in urine, plasma and feces measured by liquid scintillation spectrometry.

Results: The excretion of radioactivity, reflecting the sum of all metabolites, as well as unchanged losartan, after a single oral or IV dose is summarized below. Recovery of radioactivity from feces and urine was somewhat lower than that noted in previously described studies and appears to be related to the use of the tritium as

the radiolabel. The investigators determined that some loss of radioactivity from the fecal and urine samples had occurred after the samples were lyophilized, indicating that exchange of the radiolabel had occurred, presumably forming tritiated water which was removed during lyophilization.

TABLE 2.4.2.1.
EXCRETION OF RADIOACTIVITY IN INTACT RATS AFTER IV OR ORAL (10 MG/KG) ³H-LOSARTAN

Sample	% of Administered Oral Dose		% of Administered IV Dose	
	0-24 Hr	24-48 Hr	0-24 Hr	24-48 Hr
Feces	67.3	3.9	54.8	8.9
Urine	2.3	0.1	4.9	0.1
TOTAL	73.7%		68.8%	

TABLE 2.4.2.2.
EXCRETION OF RADIOACTIVITY (% OF DOSE) IN BILE-DUCT CANNULATED RATS AFTER 10 MG/KG ORAL DOSE OF ³H-LOSARTAN

Time (Hr)	Bile	Urine	Feces	TOTAL
0-24	37.5	2.8	37.8	78.0
24-48	1.9	0.5	1.7	4.2
48-72	0.4	0.3	0.1	0.8
72-96	0.1	0.3	<0.1	0.4
0-96	39.9	3.9	39.6	83.8

2.4.3. Biliary Excretion of Radioactivity after Oral and IV ¹⁴C-Losartan in Rats

Study Facility:

Study No: JDM #91-A6

Study Dates: 8/12/91- 9/21/92

GLP Compliance: Not stated; QA audit report included.

Animals: Male and female Sprague-Dawley rats (156-228 gm)

Procedure: ¹⁴C-Losartan was dissolved in phosphate buffer (pH 7.4) and administered orally (10 mg/kg) by gavage to 3 male and 3 female bile-duct cannulated rats or intravenously (3 mg/kg) to male bile-duct cannulated rats. Bile was collected for up to 48 hours after dosing and metabolite identified by HPLC. Radioactivity was measured by liquid scintillation spectrometry.

Results: Radioactivity in the 48 hour bile samples was low and metabolites in these samples could not be identified. Thus, metabolite measurements are only for the 24-hour post-drug period. Metabolites found in the bile were 3-hydroxylated derivative (M-1), 1-hydroxylated derivative (M-2), carboxylic acid derivative (M-4) and N₂-tetrazole glucuronide derivative (M-5). M-5 was the predominant biliary excretory product with either route of administration of the parent drug. M-4 was also a main biliary excretion product following oral dosing but not following IV dosing.

TABLE 2.4.3.1
METABOLITE COMPOSITION IN BILE 24 HR AFTER IV OR ORAL ADMINISTRATION

Metabolite	Mean Percent of Biliary Excretion		
	IV Males	PO Males	PO Females
Parent Drug	14.6	11.9	12.3
M-1	12.1	9.6	5.2
M-2	7.1	4.0	6.4
M-4	26.6	29.2	36.7
M-5	7.8	23.4	26.9
Others	8.2	2.4	0.7
Adsorbed*	24.1	19.5	11.8

*Fraction not effectively eluted with methanol

2.4.4. Excretion of Radioactivity After Oral and IV ¹⁴C-Losartan in Dogs

Study Facility: Merck Research Labs, West Point, PA

Study No: None indicated; Report # G-34

Study Dates: Not indicated; report date 5/19/93

GLP Compliance: Not indicated

Animals: Male Beagle dogs (8-10 kg)

Procedure: ¹⁴C-Losartan was dissolved in phosphate buffer (pH 7.4) and administered as a single oral dose (10 mg/kg) to 3 dogs by gavage. Two weeks later the same animals were administered ¹⁴C-losartan intravenously (2 mg/kg) as a solution in DMSO. Urine and feces were collected at 24-hr intervals for 168 hours after dosing. Radioactivity in the urine and feces was measured by liquid scintillation spectrometry.

Results: Approximately 96% of the radioactivity was recovered within 120 hours after oral dosing and approximately 91% was recovered within 120 hours after intravenous dosing. Fecal elimination was the major route for the excreted products.

TABLE 2.4.4.1.
EXCRETION OF RADIOACTIVITY (% OF DOSE) AFTER ORAL AND IV ¹⁴C-LOSARTAN IN DOGS

Time (hr)	% of Total Oral Dose			% of Total IV Dose		
	Urine	Feces	Total	Urine	Feces	Total
0-24	10.5	79.7	90.2	18.6	64.0	82.6
24-48	0.4	4.5	4.9	0.4	7.4	7.8
48-72	0.05	0.6	0.65	0.05	0.5	0.6
72-96	ND	ND	-	0.05	0.13	0.18
96-120	ND	0.09	0.09	0.04	ND	0.04
120-168	ND	ND	-	ND	ND	-
TOTAL	11.0	84.9	95.9	19.1	72.0	91.2

ND=Not detected

3. TOXICOLOGY

3.1. Acute Toxicity Studies

3.1.1. Acute Oral Toxicity Study in Mice

Study Facility: E.I. du Pont de Nemours and Company, Wilmington, DE

Study Number: 88-4-5

Study Dates: 4/15/88-7/13/88

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: CF-1 mice (19M, 20F; 17-27gm)

Drug Administration: Losartan (Lot E-3340-9) was prepared as a solution in sterile water for injection and administered to mice as a single dose by gavage.

Dose Levels: 0 (vehicle), 500, 1000 and 2000 mg/kg (5/sex/group; only 4M in lowdose group).

Observations/Measurements: Mice were observed daily for 14 days for clinical signs of toxicity and mortality. Body weights were measured prior to dosing and on days 2, 7 and 14 after dosing. Gross examination was performed on all mice that died and those that survived to scheduled sacrifice.

Results:

TABLE 3.1.1.1
MORTALITY

Dose (mg/kg)	Dead/No. Males	Dead/No. Females
0	0/5	0/5
500	0/4	0/5
1000	0/5	1/5
2000	4/5	1/5

Deaths occurred within 3 hours after dosing with 2000 mg/kg and approx. 48 hours after dosing with 1000 mg/kg. Clinical signs of toxicity seen prior to death included decreased motor activity, ataxia, prostration, loss of righting reflex, enophthalmia and colored material around the mouth. Mice that survived treatment with 1000 mg/kg and

2000 mg/kg exhibited enophthalmia, decreased motor activity and perianal staining. Gross postmortem examination revealed discoloration of the stomach mucosa and/or red-colored contents in the intestinal tract of mice that died after a dose of 2000 mg/kg. Mice treated with 500 mg/kg showed no signs of toxicity. The acute oral no-observed-adverse-effect-level of losartan in mice was 500 mg/kg.

3.1.2. Acute Intraperitoneal Toxicity Study in Mice

Study Facility: E.I. du Pont de Nemours and Company, Wilmington, DE

Study Number: 88-10-5

Study Dates: 10/06/88 - 10/21/88

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: CF-1 mice (25M, 25F; 19-32 gm)

Drug Administration: Losartan (Lot No. E-3340-15) was dissolved in sterile water for injection and administered to the mice by intraperitoneal injection.

Dose Levels: 0 (vehicle), 25.6, 64, 160 and 400 mg/kg (5/sex/dose group)

Observations/Measurements: Mice were observed daily for 14 days for clinical signs of toxicity and mortality. Body weights were measured prior to dosing and on days 2, 7 and 14 after dosing. Gross examination was performed on all mice that died and those that survived to scheduled sacrifice.

Results:

TABLE 3.1.2.1.
MORTALITY

Dose (mg/kg)	No. Dead/No. Treated	
	Males	Females
0	0/5	0/5
25.6	0/5	0/5
64	0/5	0/5
160	0/5	0/5
400	4/5	5/5

Deaths occurred 1 to 3 days post-dose. Clinical signs of toxicity seen prior to death included ataxia, decreased motor activity, tremors, ptosis, perianal and urogenital staining and

decreased respiration. Doses of 160 mg/kg and lower produced no clinical signs of toxicity or treatment-related pathology on gross examination.

Note: A subsequent acute intraperitoneal study (IT#90-2649) in female mice only was conducted by MSD Research Labs using doses of 156, 312, 625, 1250, 2500 and 5000 mg/kg and a limited number (3) of mice per dose group. 3/3 mice died with doses = or > 625 mg/kg. No mortality occurred with doses of 156 or 312 mg/kg.

3.1.3. Acute Oral Toxicity Study in Rats

Study Facility: E. I. du Pont de Nemours and Co., Wilmington, DE

Study Number: 88-4-4

Study Dates: 4/14/88 - 7/13/88

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Sprague-Dawley rats (15M, 15F, 8 weeks old)

Drug Administration: Losartan (Lot E-3340-9) was prepared as a solution in sterile water for injection and administered to rats as a single dose by gavage.

Dose Levels: 0 (vehicle), 1000 and 2000 mg/kg (5/sex/group)

Observations/Measurements: Rats were observed daily for 14 days for clinical signs of toxicity and mortality. Body weight was measured predose, and on days 2, 7 and 14 after treatment. Gross examination was performed on all rats that died and those that survived to scheduled sacrifice.

Results:

TABLE 3.1.3.1.
MORTALITY

Dose (mg/kg)	No. Dead/No. Treated	
	Males	Females
0	0/5	0/5
1000	0/5	0/5
2000	3/5	0/5

Deaths occurred between two and five hours after dosing. Clinical signs of toxicity seen prior to death included decreased motor activity, loss of righting reflex, prostration, enophthalmus, loose stools, perianal staining and colored material around the mouth. Among surviving animals, 3/5 rats treated with 1000 mg/kg had loose stools on day 1; animals surviving the 2000 mg/kg dose exhibited decreased motor activity, enophthalmus, loose stools, facial and perianal staining. Fluid distention of the GI tract was noted in the 3 rats that died. No significant lesions or pathology were noted in surviving rats upon gross examination at scheduled sacrifice.

3.1.4. Acute Intraperitoneal Toxicity Study in Rats

Study Facility: E. I. du Pont de Nemours and Co., Wilmington, DE

Study Number: 88-10-4

Study Dates: 10/4/88 - 10/19/88

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Sprague-Dawley rats (25M, 25F, 8 weeks old)

Drug Administration: Losartan (Lot INE-3340-15) was prepared as a solution in sterile water for injection and administered to rats as a single intraperitoneal dose.

Dose Levels: 0 (vehicle), 25, 50, 100 and 200 mg/kg (5/sex/group)

Observations/Measurements: Rats were observed daily for 14 days for clinical signs of toxicity and mortality. Body weight was measured predose and on days 2, 7 and 14 after dosing. Gross examination was performed on all rats that died and those that survived to scheduled sacrifice.

Results: Deaths occurred between 3 and 5 days post-dose. Clinical signs of toxicity seen prior to death included ataxia, decreased motor activity, perianal and urogenital staining, colored material around eyes, nose, paws and mouth, soft stools, dehydration and labored respiration. Surviving rats treated with 200 mg/kg exhibited ataxia, decreased motor activity, perianal and urogenital staining and soft stools. One male treated with 100 mg/kg exhibited perianal staining and one male treated with 50 mg/kg exhibited soft stools. No other clinical signs of toxicity were noted with rats treated with 25-100 mg/kg of losartan. Gross examination revealed losartan-related distension and thickened walls of the jejunum and cecum in animals dosed with 200 mg/kg. The intraperitoneal no-observable-adverse-effect level in mice was considered to be 100 mg/kg.

TABLE 3.1.4.1
MORTALITY

Dose (mg/kg)	No. Dead/No. Treated	Females
0	0/5	0/5
25	0/5	0/5
50	0/5	0/5
100	0/5	0/5
200	3/5	1/5

3.2. SUBCHRONIC, CHRONIC AND CARCINOGENICITY STUDIES

Studies in Rats

3.2.1. Fourteen-Week Oral Range Finding Toxicity Study in Rats

Study Facility: MSD Research Laboratories, West Point, PA

Study No: TT #90-013-0

Study Dates: 1/25/90- 1/27/90

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Male and female Crl:CD(SD) BR rats (39 days old at initiation of study).

Drug Administration: Losartan (Lot # 005H004 and 005H010) was dissolved in deionized water and administered orally by gavage.

Dose Levels: 0 (vehicle), 50, 150, 250 and 450 mg/kg/day (15/sex/dose group)

Observations/Measurements: Rats were observed daily for mortality and clinical signs of toxicity. Food consumption was measured weekly and body weights were measured prior to treatment, during week 1 and twice weekly, thereafter. Ophthalmoscopic examinations were conducted on all surviving control and high dose rats during weeks 3 and 11 of treatment. Blood samples were obtained from the orbital sinus or tail vein during weeks 5, 8 and 13 for hematologic and serum chemistry measurements. Urine was collected from 10 rats/sex/group during treatment weeks 8 and 13 for urinalysis. Rats that survived to scheduled necropsy were weighed, sacrificed and examined for gross pathology. Major organs were removed and weighed. Sections of major organs and tissues from the control and high dose animals were fixed on slides, stained and examined for microscopic pathology.

Results: A total of 5 high dose rats died during the study (3F, 1M during week 5 and 1M during week 8 of treatment).

Some rats in the 150-450 mg/kg/day dose groups had occasional dyspnea which was associated with excessive salivation following dosing. Most high dose rats had excessive salivation following dosing that was gone within 1 hour.

Body weight gain was decreased in a dose-related and statistically significant manner; food consumption was not affected by treatment.

TABLE 3.2.1.1
MORTALITY

Dose (mg/kg/day)	# Doses/Treated	
	Males	Females
0	0/15	0/15
50	0/15	0/15
150	0/15	0/15
250	0/15	0/15
450	2/15	3/15

TABLE 3.2.1.2
BODY WEIGHT AND BODY WEIGHT GAIN

Dose (mg/kg/day)	% Difference from Control Weight (Wt. Gain)	
	Males	Females
150	-10 (-15)	-5 (-8)
250	-13 (-18)	-8 (-13)
450	-14 (-21)	-8 (-16)

Mean erythrocyte, hemoglobin and hematocrit values were decreased approximately 10% in drug weeks 5, 8 and 13 in males and females dosed with 450 mg/kg/day; mean erythroid values in rats treated with 250 mg/kg/day were slightly depressed during drug weeks 5, 8 and 13 and no effects on these parameters were noted in 50 and 150 mg/kg/day groups. Mean leukocyte counts were increased 20%-50% in drug weeks 5, 8 and 13 in high dose animals relative to controls.

Dose-related increases in mean serum urea nitrogen were observed in all dose groups (19% to 161% higher than concurrent control females and 15% to 229% higher than concurrent control males) in drug weeks 5, 8 and 13. Mean ALT value was increased 40% above concurrent control in the male high dose group in week 13 of treatment. Mean potassium values were significantly increased about 10% in high dose males and females in drug weeks 5 and 13. Mean glucose values tended to be lower (10%-20%) in both male and female high dose groups relative to controls in drug weeks 5, 8 and 13. There were no treatment-related effects on urinalysis parameters.

No treatment related ocular abnormalities were observed. Macroscopic examination revealed the presence of dark, red-brown foci in the glandular mucosa of the stomach. Most of these foci were confirmed microscopically as focal erosions of the glandular epithelium with adjacent hyperemia, hemorrhage and mild inflammation.

TABLE 3.2.1.3
INCIDENCE OF FOCAL EROSIONS IN STOMACH MUCOSA

Dose (mg/kg/day)	Incidence of Focal Erosions in Stomach	
	Males	Females
50	1/15	0/15
150	0/15	0/15
250	7/15	3/15
450	6/15	4/15

Absolute and relative heart weights were significantly decreased in females treated with 150, 250 and 450 mg/kg/day and males at all dose levels.

TABLE 3.2.1.4
EFFECTS ON ABSOLUTE AND RELATIVE HEART WEIGHTS

Dose (mg/kg/day)	% Difference from Control Absolute (Relative) Heart Weight	
	Males	Females
50	-16.4 (-12.5)	-3.7 (-2.8)
150	-24.0 (-15.6)	-12.0 (-8.3)
250	-26.9 (-15.6)	-13.9 (-5.6)
450	-23.4 (-6.2)	-15.7 (-8.3)

Microscopic examination revealed treatment-related hyperplasia of the JG apparatus of the kidneys in both males (3/15, 5/15, 8/15) and females (1/15, 1/15, 3/15) given 150, 250 and 450 mg/kg/day, respectively.

3.2.2. Fifty-three Week Oral Toxicity Study in Rats

Study Facility: MSD Research Labs, West Point, PA

Study No: 90-001-0

Study Dates: 1/02/90 - 1/04/91

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Crl:CD(SD) BR rats (M=118-182gm; F=114-165gm)

Drug Administration: Losartan (Lot # 005H002 and 005H010) was dissolved in deionized water and administered daily to rats orally by gavage.

Dose Levels: 0 (vehicle), 15, 45 and 135 mg/kg/day (30/sex/dose group)

Observations/Measurements: Animals were observed daily for mortality and clinical signs of toxicity. Body weights were obtained predose, once during week 1, twice weekly through week 13, then once weekly thereafter. Food consumption was measured weekly until week 34 then once every 4 weeks. Ophthalmoscopic exams were conducted on all rats in the control and high dose groups during weeks 12, 25, 39 and 51 of treatment. Blood samples were obtained during weeks 4, 12 and 25 by orbital puncture on 10 rats/sex/group (rats designated for interim necropsy) and on all surviving rats during weeks 39 and 51 for hematologic and serum biochemical exams. Urine was collected for urinalysis during weeks 12 and 25 on 10 rats/sex/group (rats designated for interim necropsy) and on all animals surviving during weeks 39 and 51. Ten rats/sex/dose group were preselected for a 27-week interim necropsy and the remaining rats were necropsied at the termination of the 53-week treatment. Following gross examination major organs were removed and weighed. Sections of major organs and tissues from control and high dose groups and from rats that died prior to scheduled necropsy were fixed on slides and examined for histopathology.

Results: Mortality among losartan-treated animals was not significantly different from control. Post-dose salivation was observed occasionally throughout the study in mid and high dose animals.

Treatment-related, statistically significant ($P \leq 0.05$) decrements in body weight and body weight gain were observed at the high-dose level in both male and female rats and at the middle dose level in female rats. Data summarizing body weight gains over the course of this 53-week study are shown in the following table 3.2.2.2.

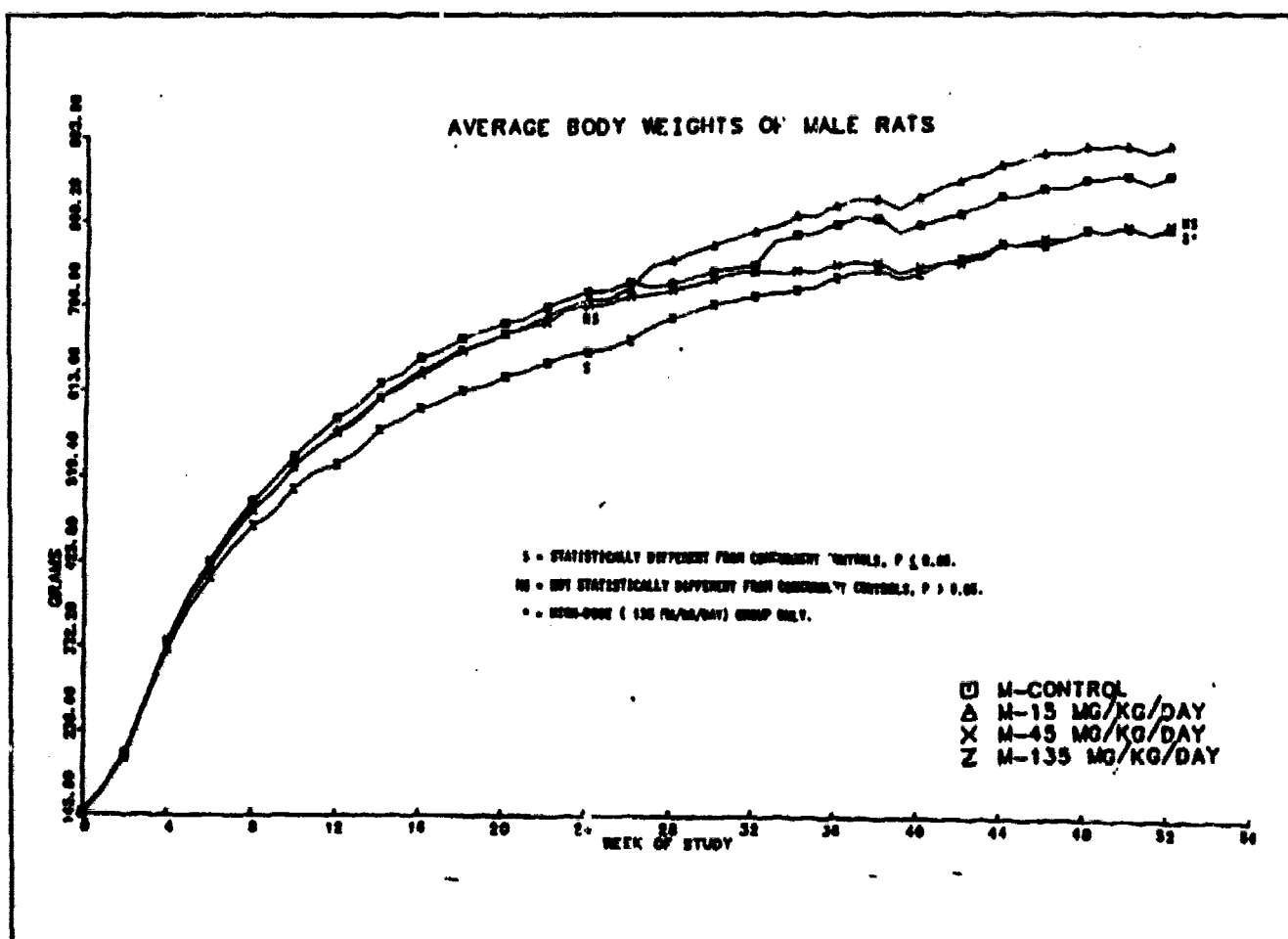
TABLE 3.2.2.1
MORTALITY

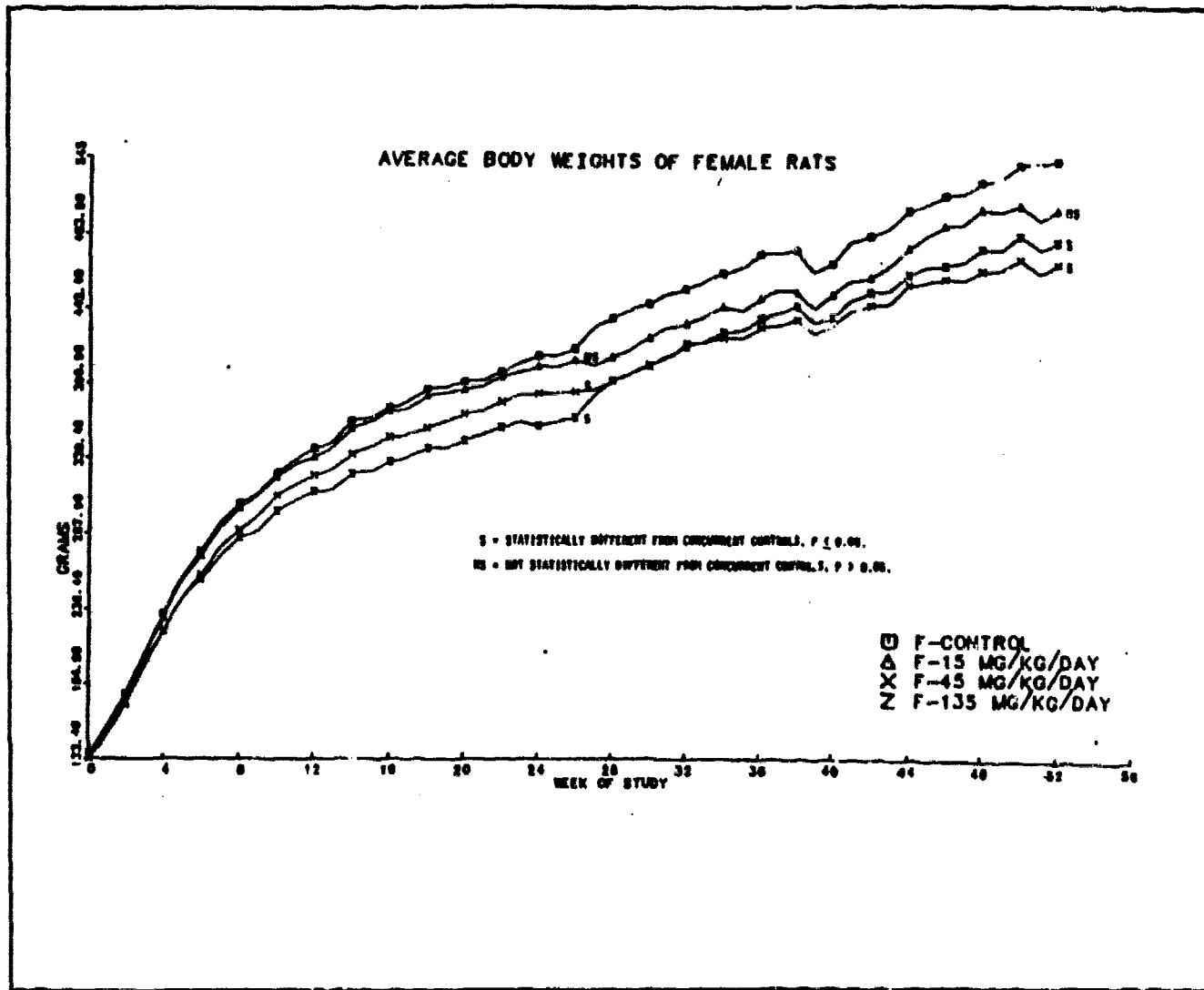
Dose (mg/kg/day)	# Dead Rats	
	Males	Females
0	2 (Wks 33-37)	3 (Wks 13-50)
15	3 (Wks 34-50)	0
45	4 (Wks 5-24)	2 (Wks 26-46)
135	3 (Wks 41-47)	2 (Wks 28-42)

TABLE 3.2.2.2
% CHANGE IN BODY WEIGHT (GAIN) VS. CONCURRENT CONTROLS
- DRUG WEEK 52

Dose	Males	Females
15 mg/kg/day	+4% (+4%)	-6% (-7%)
45 mg/kg/day	-6% (-9%)	-13%* (-16%)*
135 mg/kg/day	-7%* (-10%)*	-10%* (-14%)*

* P ≤ 0.05.





Significant, non-dose dependent decreases of -8% and -6% in food consumption were observed in female rats receiving the mid (45 mg/kg/day) and high (135 mg/kg/day) doses of losartan, respectively, through Study Week 26. By Study Week 50, a slight, but not significant decrease (5%), in food consumption was noted in high dose females; food consumption all other treated groups were comparable to control.

No treatment-related ocular effects were observed.

Losartan treatment caused statistically significant decreases in hemoglobin concentrations, hematocrit and erythrocyte counts in high dose males (treatment weeks 21, 39 and 51) and in high dose females (treatment weeks 39 and 51).

TABLE 3.2.2.3.
GROUP MEAN ERYTHROID VALUES IN RATS RECEIVING LOSARTAN

<i>MALES</i>									
Treatment Groups	DRUG WEEK								
	25			39			51		
	Hb ^a	Hct ^b	RBC ^c	Hb	Hct	RBC	Hb	Hct	RBC
Control	15.8	43	8.7	15.4	42	8.6	15.4	41	8.4
15 mg/kg/day	15.8	43	8.4	15.6	43	8.5	15.7	43	8.5
45 mg/kg/day	15.6	42	8.5	15.1	42	8.4	14.8	40	8.1
135 mg/kg/day	15.2*	41*	8.1*	14.8*	41*	8.1*	14.3*	39*	7.9*

<i>FEMALES</i>									
Treatment Groups	DRUG WEEK								
	25			39			51		
	Hb ^a	Hct ^b	RBC ^c	Hb	Hct	RBC	Hb	Hct	RBC
Control	15.1	41	7.6	15.2	41	7.7	14.6	40	7.4
15 mg/kg/day	15.4	41	7.6	15.2	41	7.6	14.9	40	7.5
45 mg/kg/day	15.5	42	7.8	15.0	41	7.4*	14.6	40	7.3*
135 mg/kg/day	15.2	41	7.6	14.8*	40*	7.3*	14.4*	39*	7.1*

a = g/dl, b = %, c = million/mm³

* Statistically different from concurrent controls at $P \leq 0.05$.

Higher than control levels of blood urea nitrogen (BUN) were observed in high-dose male rats throughout the study period, and in mid-dose male rats beginning during Drug Week 39. The greatest relative increase (100%) was observed in high-dose male rats during Drug Week 25. Similar, but less marked elevations were observed in high-dose female rats in Drug Weeks 4, 12, 25, and 39; these gradually declined to concurrent control levels by the last evaluation in treatment week 51.

TABLE 3.2.2.4.
GROUP MEAN BUN CONCENTRATIONS (MG/DL)

Treatment Groups	Males				
	Drug Week				
	4	12	25	39	51
Control	13	17	15	14	14
15 mg/kg/day	13	16	16	14	14
45 mg/kg/day	14	17	16	18(+28%)	17(+21%)
135 mg/kg/day	18(+38%)*	25(+47%)	30(+100%)	22(+57%)	25(+78%)

Treatment Groups	Females				
	Drug Week				
	4	12	25	39	51
Control	14	15	15	14	13
15 mg/kg/day	14	15	15	15	13
45 mg/kg/day	14	16	17(+13%)	15	13
135 mg/kg/day	19(+36%)*	18(+20%)	18(+20%)	16(+14%)	13

*Percent change from concurrent control value.

Treatment-related, dose-dependent decreases in average serum triglycerides were observed in female rats relative to concurrent control females. The following table summarizes the magnitude of this effect in female rats:

TABLE 3.2.2.5.
GROUP MEAN SERUM TRIGLYCERIDE CONCENTRATIONS IN FEMALE RATS (MG/DL)

Treatment Groups	Drug Week				
	4	12	25	39	51
Control	49	80‡	160‡	175	295
15 mg/kg/day	38(-22%)*	72(-10%)	106(-34%)	170(-3%)	257(-13%)
45 mg/kg/day	35(-29%)	54(-32%)	73(-54%)	117(-33%)	153(-48%)
135 mg/kg/day	31(-37%)	53(-34%)	57(-64%)	103(-41%)	132(-55%)

* Percent change from concurrent control value.

‡ Outlying values of 404 and 783 mg/dl in one control female (90-0055F) during Drug Weeks 12 and 25 were not included in average.

Slight, non-dose-dependent decreases (2%-7%) in urinary protein values were found in males and females at all dosage levels during treatment weeks 39 and 51.

Mean absolute heart weight and heart weight relative to brain weight were decreased at the interim necropsy in the high-dose males (16.9% and 17.2%) and females (14.6% and 10.3%) and in mid-dose males (9.2% and 10.3%). Statistically significant decreases in these parameters were observed only in mid-dose (9.6% and 8.7%) and high-dose males (15.5% and

15.2%) at the terminal necropsy. There was no histologic correlate. This effect on heart weight is attributed to the pharmacodynamic properties of losartan since similar decreases in heart weight have been observed following treatment with many other antihypertensive agents, including ACE inhibitors.

Juxtaglomerular cell hyperplasia, characterized by thickening of the afferent glomerular arterioles, was identified in 2/10 mid-dose and 5/10 high-dose males at the interim necropsy. At terminal sacrifice, very slight JG cell hyperplasia was identified in 14/20 low-dose, 17/18 mid-dose and 19/20 high-dose males and in 5/20 low-dose, 10/20 mid-dose and 12/20 high-dose females. Coincident with this effect on the JG apparatus were decreases in the incidence (29/40, 14/40, 9/38, 14/40 for control, low, mid and high dose groups respectively) and severity of chronic nephritis at all dosage levels of losartan.

Focal erosions of the glandular mucosa of the stomach were noted in one high-dose male at the interim necropsy and in 1 low-dose and 3 high-dose males among rats dying or necropsied at terminal sacrifice. No gastric lesions were found in concurrent control animals.

Gross and microscopic examinations revealed no other treatment-related pathologies.

3.2.3. One Hundred-Five Week Oral Carcinogenicity Study in Rats

Study Facility: MSD Research Laboratories, West Point, PA

Study No: TT #90-099-0

Study Dates: 7/11/90 - 7/13/92

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Male and female Sprague-Dawley Crl:CD (SD) BR rats (115-175 gm females, 119-194 gm males, 38 days old, housed individually).

Drug Administration: Losartan (Batch # 9, 10, 19 and 29) was dissolved in deionized water and administered orally by gavage once daily.

Dose Levels: 0 (Vehicle; 130/sex), 15, 45 and 135/270 mg/kg/day * (75/sex/group)

* *Note: High dose raised from 135 to 270 mg/kg/day in week 6 of treatment because previous dose did not appear (from 1-year chronic rat study) to be the maximally tolerated dose (MTD).*

Observations/Measurements: Animals were observed daily for mortality and observed weekly for clinical sign of toxicity. Rats were palpated for the presence of masses every 4th week beginning Drug Week 26. Body weights were recorded prior to study initiation, twice per week through Drug Week 13 and once weekly thereafter. Ophthalmologic examinations were conducted in Drug Weeks 52 and 102. A complete necropsy was performed on all animals. Sections of major tissues and organs were fixed on slides and examined microscopically. Treatment-related increases in tumor incidence was assessed by use of a trend test (Mantel-Haenszel procedure).

Results: *Mortality and Survival:* Two high dose rats (1M,1F) died and one high dose female was sacrificed between Drug Weeks 18 and 34 due to marked weight loss associated with cecal erosive inflammation. Two additional high dose rats were sacrificed (1F & 1M in Drug Weeks 49 and 70, respectively) due to marked weight loss with associated intestinal lesions. In addition, moderate to marked edema of the lungs, presumably due to hypotension, was the cause of death or sacrifice of a high dose female and 7 high dose males between Drug Weeks 25 and 92. Although these deaths were related to drug treatment, they did not significantly affect the overall incidence of mortality at termination of the study. In fact, there was a statistically significant decrease in mortality (increase in survival) in males with increasing dose.

TABLE 3.2.3.1.
ANIMAL SURVIVAL

Rat Sex	Percent Survival at Study Termination			
	Control	15 mg/kg	45 mg/kg	135/270 mg/kg
Females	28.5	26.7	26.7	25.3
Males	16.2	25.3	34.7	34.7

The incidence of chronic nephritis (moderate, marked or severe grades) as a specific cause of death in male rats not surviving to termination was considerably higher in control males (27%) than in low dose (16%), mid dose (8%) and high dose (8%) treated males.

Physical Signs: Excessive salivation immediately after dosing and lasting up to approximately 45 min was seen occasionally throughout the study in high dose rats. Tarry stools occurred in 3 high dose rats (1M, 2F) between Drug Weeks 18 and 34.

Body Weight: Male and female rats given 135 mg/kg/day for the first 5 weeks had body weights slightly below control values at the end of those 5 weeks (mean decrement less than 10%). After increasing the high dose to 270 mg/kg/day, body weight in this group was further reduced compared to controls. Body weight gains of high dose females were 10-23% less than controls from Drug Week 8 until termination. Body weight gain of high dose females at study termination was 18.5% less than control. High dose males had body weight gains 10-17% less than control from Drug Week 8 to Drug Week 83; after this time the decrease became less and at termination the body weight gains in high dose males were similar to control.

TABLE 3.2.3.2.
EFFECT ON MEAN BODY WEIGHT

Dose Group	Percent Difference From Control Weight									
	5 Wks		26 Wks		52 Wks		78 Wks		104 Wks	
	F	M	F	M	F	M	F	M	F	M
Low Dose	-1	-2	-3	-1	-1	+1	+3	+3	-4	+7
Mid Dose	-4	-5	-6	-5	-6	-2	0	+5	-7	+10
High Dose	-2	-5	-10	-11	-14	-11	-13	-8	-13	+4

Mean Pretest Weight: Control=147gm, Low Dose=145gm,
Mid Dose=143gm, High Dose=147gm

Ophthalmologic Effects: No treatment-related ocular effects were observed.

Gross Pathology: No evidence of treatment-related pathology on gross examination.

Microscopic Pathology:

Neoplastic Lesions: The sponsor's analysis revealed no evidence of a statistically significant increased trend in the incidence of any neoplasm in either sex of rat (Appendix I for tumor type and site). Summary of tumor incidence is as follows:

TABLE 3.2.3.3.
SUMMARY OF NEOPLASMS IN MALE RATS

	Number (% Incidence)			
	Control	Low Dose	Mid Dose	High Dose
# Rats with Neoplasms				
Malignant	28 (22)	24 (32)	23 (31)	20 (27)
Benign	91 (70)	59 (79)	63 (84)	49 (65)
Malignant or Benign	98 (75)	68 (91)	67 (89)	54 (72)
Total # of Neoplasms				
Malignant	30 (23)	25 (33)	24 (32)	21 (28)
Benign	170 (131)	105 (140)	116 (155)	95 (127)
Malignant or Benign	200 (154)	130 (173)	140 (187)	116 (155)

Control= 130 rats, Other Groups=75 rats

TABLE 3.2.3.4.
SUMMARY OF NEOPLASMS IN FEMALE RATS

	Number (% Incidence)			
	Control	Low Dose	Mid Dose	High Dose
# Rats with Neoplasms				
Malignant	42 (32)	26 (35)	29 (39)	13 (17)
Benign	126 (97)	68 (91)	70 (93)	65 (87)
Malignant or Benign	128 (98)	70 (93)	74 (99)	68 (91)
Total # of Neoplasms				
Malignant	45 (35)	30 (40)	31 (41)	14 (19)
Benign	261 (201)	144 (192)	135 (180)	129 (172)
Malignant or Benign	306 (235)	174 (232)	166 (221)	143 (191)

Control=130 rats, Other Groups=75 rats

Analysis of the tumor data By FDA Statistical Section (See Statistical Review and Evaluation) revealed a statistically significant trend (P value= 0.0084) in pancreatic acinar adenomas (0, 0, 0, 3 for control, low, mid and high dose groups, respectively) in female rats. The pairwise comparison (high dose vs. control) also showed a statistically significant (P value = 0.043) difference.

Non-Neoplastic Lesions: There was a treatment-related, dose-dependent increase

in the incidence of juxtaglomerular (JG) cell hyperplasia in the kidneys of both sexes. This effect was characterized by an increase in the size and number of the JG cells comprising the wall of the afferent arteriole of the glomerulus. Increased incidences of renal focal tubular hypertrophy were seen in male rats in the mid and high dose groups compared to controls.

TABLE 3.2.3.5
RENAL EFFECTS

Renal Effect		% Incidence			
		Control	Low Dose	Mid Dose	High Dose
JG Cell Hyperplasia	F	0	4.0	12	43
	M	0	11	43	71
Renal Tubular Hypertrophy	F	1.5	4.0	2.7	5
	M	2.3	1.3	7.1	15

A slight increase in the incidence of losartan-related cecal erosive inflammation was noted in high dose males (5%) and females (7%) compared to controls (1% and 0% for males and females, respectively). Also, an increased incidence of gastric lesions was noted in losartan-treated males.

TABLE 3.2.3.6
GASTROINTESTINAL EFFECTS

Gastric Lesion	% Incidence in Male Rats			
	Control	Low Dose	Mid Dose	High Dose
Fundus, Erosion/Ulcer	11	23	17	20
Pylorus, Erosion/Ulcer	8	15	5.3	15
Nonglandular Mucosa, Focal Hyperplasia	1.3	1.3	12	2.3

A non-dose-dependent increase in the incidence of focal vacuolation of the adrenal cortex was seen in rats in all losartan-treated groups. The incidence of this change was 22%, 45%, 44% and 51% for the control, low, mid and high dose groups, respectively. The change was characterized by the presence of one or more focal regions of cytoplasmic lipid-like vacuolation in the cortex, primarily in the zona fasciculata.

Appendix I

Primary Neoplasms in Rats

LOBARTAN: 105-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT #90-099-0
SUMMARY OF PRIMARY NEOPLASMS

NUMBER NECROPSIED	GROUP 1		GROUP 2		GROUP 3		GROUP 4	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
	130	130	75	75	75	75	75	75
STOMACH								
LEIOMYOMA	-	-	-	-	-	-	1	-
LEIOMYOSARCOMA	-	1	-	-	-	-	-	-
NONGLANDULAR MUCOSA, PAPILLOMA	-	1	-	-	-	-	1	-
NONGLANDULAR MUCOSA, SQUAMOUS CELL CARCINOMA	-	-	-	-	-	1	-	-
SMALL INTESTINE								
ADENOCARCINOMA	-	-	-	1	-	-	-	-
LEIOMYOMA	1	-	-	-	-	-	-	1
POLYP	1	-	-	-	-	-	-	-
LARGE INTESTINE								
FIBROMA	1	-	-	-	-	-	-	-
POLYP	-	1	-	-	-	-	-	1
LIVER								
BILE DUCT, CARCINOM.	-	-	-	-	-	1	-	-
HEPATOCELLULAR ADENOMA	4	4	1	2	3	2	3	4
HEPATOCELLULAR CARCINOMA	-	4	-	4	1	3	1	5
PANCREAS								
ACINUS, ADENOMA	-	4	-	2	-	-	3	5
ISLET, ADENOMA	10	20	10	10	9	14	3	6
ISLET, CARCINOMA	1	4	3	3	-	1	1	3
PERITONEUM								
LEIOMYOSARCOMA	1	-	-	-	-	-	-	-
BENIGN MESOTHELIOMA	-	-	-	-	1	-	-	-
MALIGNANT MESOTHELIOMA	1	-	-	-	-	-	-	-
OSTEOSARCOMA	-	1	-	-	-	-	-	-
ADRENAL								
CORTX, ADENOMA	4	1	2	1	2	-	2	2
CORTX, CARCINOMA	1	-	2	1	1	2	1	-
BENIGN PHEOCHROMOCYTOMA	4	16	3	7	1	7	1	4
MALIGNANT PHEOCHROMOCYTOMA	-	2	1	-	-	3	-	-
PARATHYROID								
ADENOMA	1	2	-	-	-	2	-	1

KEY: GROUP 1 = CONTROL
GROUP 2 = 15 MG/KG/DAY
GROUP 3 = 45 MG/KG/DAY
GROUP 4 = 135/270 MG/KG/DAY

CONTINUED
 LOSARTAN: 105-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT 870-099-0
 SUMMARY OF PRIMARY NEOPLASMS

	GROUP 1 FEMALES MALES		GROUP 2 FEMALES MALES		GROUP 3 FEMALES MALES		GROUP 4 FEMALES MALES	
PITUITARY								
ADENOMA	107	63	63	45	66	55	57	39
CARCINOMA	1	-	-	-	-	-	-	-
THYROID								
FOLLICULAR CELL, ADENOCARCINOMA	-	2	1	-	1	3	-	1
PARAFOLLICULAR CELL, ADENOMA	16	15	7	11	7	3	3	7
FOLLICULAR CELL, ADENOMA	4	4	-	1	-	4	-	3
PARAFOLLICULAR CELL, CARCINOMA	1	-	-	-	1	1	-	1
BENIGN GANGLIONEUROMA	1	-	-	-	-	-	-	-
KIDNEY								
TUBULAR ADENOMA	1	-	-	-	-	1	-	2
HEMANGIOMA	-	-	-	-	-	-	-	1
BENIGN MESENCHYMAL TUMOR	-	-	-	2	1	-	-	-
URINARY BLADDER								
TRANSITIONAL CELL CARCINOMA	-	-	-	-	-	1	-	-
OVARY								
BENIGN SERTOLI CELL TUMOR	1	-	-	-	-	-	-	-
UTERUS								
FIBROMA	-	-	1	-	1	-	-	-
LEIOMYOSARCOMA	-	-	1	-	1	-	-	-
POLYP	2	-	6	-	-	-	1	-
ENDOMETRIAL STROMA, SARCOMA	-	-	-	-	1	-	-	-
VAGINA								
LEIOMYOSARCOMA	-	-	-	-	1	-	-	-
TESTIS								
LEYDIG CELL, ADENOMA	-	11	-	4	-	3	-	3
BENIGN MESOTHELIONA	-	-	-	2	-	-	-	-
PROSTATE								
CARCINOMA	-	-	-	-	-	1	-	-
SKIN								
FIBROMA	5	6	2	1	1	4	2	3
FIBROSARCOMA	1	1	-	2	-	-	2	1
HEMANGIOMA	-	-	1	-	-	-	-	-
MALIGNANT FIBROUS HISTIOCYTOMA	-	-	-	-	1	-	-	-
BENIGN KERATOCYCLICOMA	-	4	1	2	-	1	-	2

KEY: GROUP 1 = CONTROL
 GROUP 2 = 15 MG/KG/DAY
 GROUP 3 = 45 MG/KG/DAY
 GROUP 4 = 135/270 MG/KG/DAY

CONTINUED

LOGARIN: 105-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT #90-099-0
 SUMMARY OF PRIMARY NEOPLASMS

	GROUP 1		GROUP 2		GROUP 3		GROUP 4	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
SKIN								
LEIOMYOMA	1	-	-	-	-	-	-	-
LIPOMA	5	4	3	1	1	3	-	2
LIPOSARCOMA	-	-	-	1	-	-	-	-
NEUROFIBROMA	-	-	-	-	-	1	-	-
PAPILLOMA	-	3	-	2	2	2	-	3
RHABDOMYOSARCOMA	-	1	-	-	-	-	-	-
UNDIFFERENTIATED SARCOMA	-	-	-	-	-	-	-	1
MALIGNANT SCHWANNOMA	-	1	-	-	-	-	-	-
SEBACEOUS ADENOMA	-	-	-	-	-	2	-	-
BENIGN TRICHOEPITHELIOMA	-	2	-	1	-	-	-	-
MAMMARY GLAND								
ADENOCARCINOMA	27	-	15	1	18	1	5	2
ADENOLIPOMA	1	-	-	-	-	-	-	-
ADENOMA	9	-	5	1	3	-	3	-
FIBROADENOMA	78	3	37	7	37	6	45	4
LUNG								
ADENOCARCINOMA	-	-	-	-	-	-	-	1
ADENOMA	-	-	-	1	-	1	2	-
PLEURA								
MALIGNANT HIBERNOMA	-	-	1	-	-	-	-	-
HEART								
ATRIUM, EPITHELIAL, BENIGN MESOTHELIOMA	-	-	-	-	-	1	-	-
SPLEEN								
HEMANGIOMA	-	-	-	1	-	-	-	-
HEMANGIOSARCOMA	-	1	-	-	-	-	-	-
LEIOMYOMA	-	-	1	-	-	-	-	-
LYMPH NODE								
HEMANGIOMA	-	5	1	-	-	-	1	1
THYROID								
BENIGN THYROID	1	-	-	-	-	-	1	-
BONE								
OSTEOSARCOMA	3	1	-	1	-	-	-	-
SCAPULAR MUSCLE								
FIBROSARCOMA	-	-	1	-	-	-	-	-

KEY: GROUP 1 = CONTROL

GROUP 2 = 15 MG/KG/DAY

GROUP 3 = 45 MG/KG/DAY

GROUP 4 = 135/270 MG/KG/DAY

CONTINUED

LOSARTAN: 105-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT #90-099-0
SUMMARY OF PRIMARY NEOPLASMS

	GROUP 1		GROUP 2		GROUP 3		GROUP 4	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
BRAIN								
MALIGNANT GLIOMA	4	1	1	-	1	-	1	-
BENIGN GRANULAR CELL TUMOR	3	1	-	1	-	4	-	1
MALIGNANT MENINGIOMA	-	-	-	-	-	1	-	-
EAR								
ZYMBAL'S GLAND, CARCINOMA	1	1	1	-	-	1	1	1
MALIGNANT SCHWANNOMA	-	-	1	-	-	-	-	1
PRIMARY SITE UNDETERMINED								
ADENOCARCINOMA	-	1	-	-	-	-	-	-
HISTIOCYTIC SARCOMA	1	4	1	3	-	3	-	2
GRANULOCYTIC LEUKEMIA	-	-	-	-	-	-	-	1
LYMPHOMA	2	4	1	8	4	1	2	1

KEY: GROUP 1 = CONTROL

GROUP 2 = 15 MG/KG/DAY

GROUP 3 = .5 MG/KG/DAY

GROUP 4 = 135/270 MG/KG/DAY

Studies in Mice

3.2.4. Fourteen-Week Oral Range Finding Toxicity Study in Mice

Study Facility: MSD Research Laboratories, West Point, PA

Study No: TT #90-058-0

Study Dates: 3/12/90- 7/13/90

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Male and female Crl:CD-1 (ICR) BR mice (39 days old at initiation of study).

Drug Administration: Losartan (Lot # 005H010) was dissolved in deionized water and administered orally by gavage.

Dose Levels: 0 (vehicle), 50, 250 and 500 mg/kg/day (15/sex/dose group)

Observations/Measurements: Mice were observed daily for mortality and clinical signs of toxicity. Body weights were measured prior to treatment, once during week 1 of treatment and twice weekly, thereafter. Food consumption was measured weekly. Urine was collected from mice during week 13 of treatment for urinalysis. At termination of the study, surviving mice were anesthetized with ether and blood was withdrawn from the vena cava for hematological and serum biochemical analyses. All animals were examined for gross pathology; sections of major organs and tissues from control and high dose animals were sectioned, fixed on slides and examined microscopically.

Results: One high dose (500 mg/kg/day) female mouse died on day 3 of treatment. Food consumption was decreased by 10% in high dose females; there was no effect on food consumption in male mice. Body weight gain was significantly lower in high dose males and females and in mid dose males compared to controls.

TABLE 3.2.4.1
EFFECT ON BODY WEIGHT AND BODY WEIGHT GAIN IN MALE MICE

Dose (mg/kg/day)	Starting Weight (gm)	Terminal Weight (gm)	% Difference from Final Control Weight	% Difference from Control Weight Gain
0	29.6	40.4		
50	29.1	38.3	-5.2	-16
250	28.1	35.5	-12.1	-31*
500	29.6	36.6	9.4	-35*

*Indicates statistically significant difference from control

TABLE 3.2.4.2
EFFECT ON BODY WEIGHT AND BODY WEIGHT GAIN IN FEMALE MICE

Dose (mg/kg/day)	Starting Weight (gm)	Terminal Weight (gm)	% Difference from Final Control Weight	% Difference from Control Weight Gain
0	23.5	30.3		
50	22.9	29.9	-1.3	+3
250	23.8	29.9	-1.3	-10
500	23.8	28.8	-5.0	-25*

*Indicates statistically significant difference from control

Mean erythrocyte, hemoglobin and hematocrit values were decreased from concurrent control by 8% to 10% in high dose females. These erythroid parameters were generally unaffected by 50 or 250 mg/kg/day doses of losartan.

Serum urea nitrogen values in mid and high dose females, respectively, were 25% and 154% higher than concurrent control values. Serum urea nitrogen in high dose males was only 10% above control. Other serum biochemical parameters were unaffected by treatment.

Urinalysis revealed a decrease in urine volume in high dose females compared to control (0.8 ml vs. 1.9 ml) as well as an increase in specific gravity (1.032 vs. 1.020). These effects were not seen in male mice or in lower dose female groups. No other urinalysis parameter was affected by treatment.

Treatment-related decreases in absolute and relative heart weights were observed with mid and high dose males and females. There were no gross or microscopic changes to account for these decreases in heart weights.

TABLE 3.2.4.3.
EFFECT ON ABSOLUTE AND RELATIVE HEART WEIGHT

Dose Group (mg/kg/day)	% Difference from Control Absolute/Relative Heart Weight	
	Males	Females
50	-2 (+4)	-7 (-4)
250	-16 (-4)	-14 (-13)
500	-20 (-12)	-14 (-9)

Microscopic examination revealed treatment related renal effects which consisted of hyperplasia of the juxtaglomerular apparatus and focal basophilia of the renal tubules. The incidence of these renal effects are as follows.

TABLE 3.2.4.4.
RENAL HISTOPATHOLOGIC EFFECTS

Effect	Incidence							
	Control		Low Dose		Mid Dose		High Dose	
	M	F	M	F	M	F	M	F
JG Hyperplasia	0	0	0	2	7	7	13	11
Tubular Focal Basophilia	2	0	0	1	5	5	11	11

No other gross or microscopic effects were associated with losartan treatment.

3.2.5. Ninety-Two Week Oral Carcinogenicity Study in Mice

Study Facility: MSD Research Laboratories, West Point, PA

Study No: TT #90-133-0

Study Dates: 8/20/90 - 5/20/92

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Male and female Crl:CD-1(ICR)BR mice (22.6-32.7 gm males, 17.7-27.0 gm females; 36 days old; housed 2-3/cage)

Drug Administration: Losartan (Batch # 086-005H-010 and 086-005H-019) was dissolved in deionized water and administered orally by gavage once daily.

Dose Levels:

Vehicle Control 1		50M, 50F
Vehicle Control 2		50M, 50F
Losartan 20 mg/kg/day	(Low Dose)	50M, 50F
Losartan 100 mg/kg/day	(Mid Dose)	50M, 50F
Losartan 300/200 mg/kg/day	(High Dose, Males)	50M
Losartan 500/300/200 mg/kg/day	(High Dose, Females)	50F

Note: Due to treatment-related decreases in body weight gain and increases in mortality, the dosage level for the high dose females was lowered from 500 to 300 mg/kg/day in Drug Week 28 and the dosage level for the high dose males and females was lowered from 300 to 200 mg/kg/day in Drug Week 43. An additional 5/sex/group were used as replacement animals for mice that died of causes unrelated to treatment, such as dosing accidents, during the first 8 weeks of the study. After 8 weeks, the remaining animals in these groups were discarded.

Observations/Measurements: Mice were observed daily for mortality and weekly for clinical signs of toxicity. The animals were palpated for masses every 4 weeks beginning in Drug Week 26. Body weights were measured pretest, once in Drug Week 1, twice weekly in Drug Weeks 2 through 13, and once weekly thereafter. Ophthalmoscopic examinations were conducted on all animals prior to treatment and in Drug Weeks 52 and 89. At scheduled sacrifice, mice were anesthetized with ether and venous blood was obtained from the vena cava for hematologic examination. Caval blood samples were obtained at unscheduled necropsies to aid in the diagnosis of leukemias and lymphomas. All animals were necropsied and sections of major organs and tissues were fixed on slides for microscopic examination. The incidences of various tumor types were analyzed for statistically significant trend ($P < 0.05$) with adjustments made for variations in mortality.

Results:

Mortality and Survival: A higher than expected occurrence of early deaths/early sacrifices (due to gastrointestinal lesions or to undetermined causes) was noted among high dose females prior to Drug Week 28 and in high dose males prior to Drug Week 43, prompting the sponsor to reduce the dosage levels for high dose males and females. At study termination, the number of male and female control and high dose mice which died or were killed were similar. The incidences of early sacrifices (ES) and early deaths (ED) among low and mid dose treated mice were lower than control.

TABLE 3.2.5.1.
INCIDENCE OF EARLY SACRIFICES/EARLY DEATHS

Dose Group	No. of Early Sacrifices/Early Deaths	
	Females	Males
Control 1	26	30
Control 2	29	30
Low Dose	16	23
Mid Dose	21	25
High Dose	33	29

TABLE 3.2.5.2.
GI AND UNDETERMINED CAUSES OF EARLY SACRIFICES/EARLY DEATHS

Dose Group	No. of Early Sacrifices/Early Deaths				
	GI Lesions		Undetermined		Total
	F	M	F	M	
Control 1	0	0	0	0	0
Control 2	0	1	0	0	1
Low Dose	0	1	0	0	1
Mid Dose	0	2	0	2	4
High Dose	5	4	4	7	20

Physical Signs: Dyspnea, decreased locomotor activity, weakness, pallor and abdominal distension were observed in several mid and high dose animals prior to early death or early sacrifice. These signs were often associated with treatment-related gastrointestinal effects (intestinal distension, gastritis and ulcers).

Body Weight: Statistically significant ($P < 0.05$) reductions in body weight gain, as compared to the average of combined concurrent control values, were observed after 91 weeks of treatment in high dose males and in females of all dose groups. Body weights and body weight gains in high dose females were reduced after Drug Weeks 27 and 42 and in high dose males after Drug Week 42. These body weight decreases, in conjunction with the increase in early mortalities and GI toxicity, prompted the lowering of the dosage level for the high dose animals.

TABLE 3.2.5.3
EFFECT ON BODY WEIGHT AND BODY WEIGHT GAIN

Dose Group	Sex	Percent Change from Control Wt. (Wt. Gain)		
		27 Weeks	42 Weeks	91 Weeks
Low Dose	M	0	0	-4
	F	-6	-8	-4 (-10)
Mid Dose	M	-1	-2	0
	F	-6	-10	-9 (-22)
High Dose	M	-5 (-12)	-8 (-23)	-6 (-22)
	F	-13 (-39)	-15 (-40)	-13 (-34)

*Average of 2 concurrent control group values used in calculating change.

Ophthalmoscopic Effects: No treatment-related ocular effects were observed.

Hematological Effects: There were no treatment-related effects on hematologic parameters in animals that died or those sacrificed at termination of the study.

Gross Pathology: Except for the gastrointestinal lesions (gastric fundic erosions, ulceration or hemorrhage of the small and/or large intestine) observed primarily in high dose animals that died or were sacrificed prior to study termination, no treatment-related gross pathology was seen at necropsy.

Microscopic Pathology:

Neoplastic Lesions: There were no significant differences in the number of mice with neoplasms or total neoplasms between losarten-treated groups and concurrent controls.

TABLE 3.2.5.4
SUMMARY OF NEOPLASMS IN MALE MICE

	Number of Incidence				
	Control 1	Control 2	Low Dose	Mid Dose	High Dose
# Mice with Neoplasms					
Malignant	8	11	16	9	15
Benign	19	19	14	22	16
Malignant or Benign	25	23	25	28	26
Total # of Neoplasms					
Malignant	8	12	17	11	20
Benign	25	22	18	29	19
Malignant or Benign	33	34	35	40	39

TABLE 3.2.5.5
SUMMARY OF NEOPLASMS IN FEMALE MICE

	Number or Incidence				
	Control 1	Control 2	Low Dose	Mid Dose	High Dose
# Mice with Neoplasms					
Malignant	12	12	8	11	7
Benign	14	16	18	11	7
Malignant or Benign	23	26	23	20	13
Total # of Neoplasms					
Malignant	14	14	10	11	7
Benign	15	18	20	13	9
Malignant or Benign	29	32	30	24	16

A statistically significant ($P < 0.05$) increased trend in the incidence of lung adenocarcinomas was seen in male mice. No statistically significant increased trend in the incidence of lung adenocarcinomas was seen in female mice and no increase was observed in either sex for lung adenomas.

TABLE 3.2.5.6
INCIDENCE (%) OF PULMONARY ADENOMAS AND ADENOCARCINOMAS

	Percent Incidence				
	Control 1	Control 2	Low Dose	Mid Dose	High Dose
Male Mice					
Adenoma	14	12	18	18	12
Adenocarcinoma	4	6	6	6	16
Adenoma or Adenocarcinoma	18	18	24	24	28
Female Mice					
Adenoma	20	10	14	14	10
Adenocarcinoma	6	8	2	0	4
Adenoma or Adenocarcinoma	26	18	16	14	14

Although the incidence of lung adenocarcinoma in high dose males was significantly increased above concurrent control, the sponsor dismisses this finding based on the fact that this incidence is within their range of historical control values. In the 9 most recent carcinogenicity studies from the same laboratory (studies of similar duration with 18 control groups of 50 male mice/group), the sponsor has observed the following mean incidences and ranges for pulmonary neoplasms (individual study results shown in Appendix II).

TABLE 3.2.5.7
HISTORICAL INCIDENCE OF PULMONARY TUMORS IN MALE MICE

	Mean	Median	Range
Adenoma	15%	20%	8-34%
Adenocarcinoma	6.6%	6.0%	0-24%

There was no statistically significant increased trend in the incidence of neoplasms in any other organs or tissues in this study (Appendix III).

Non-Neoplastic Lesions: As previously described, treatment-related gastrointestinal (GI) lesions were observed in several mice of both sexes, primarily in the high dose group but also in some males in the mid dose group. The types and incidences of GI lesions observed are as follows:

TABLE 3.2.5.8
TREATMENT-RELATED GASTROINTESTINAL LESIONS

GI Effect	Incidence (# mice)										
	C-1		C-2		Low		Mid		High		
	F	M	F	M	F	M	F	M	F	M	
Stomach											
Distension	0	0	0	0	0	0	0	0	1	1	
Necrotizing Gastritis	0	0	0	0	0	0	0	0	1	0	
Sm. Intestine											
Distension	0	0	0	1	0	0	0	3	5	3	
Ulcer	0	0	0	0	0	1	1	2	1	2	
Lge. Intestine											
Distension	0	0	0	0	0	0	0	1	3	1	
Ulcer	0	0	0	0	0	0	0	0	0	2	

A dose-related occurrence of renal juxtaglomerular (JG) cell hyperplasia was seen in all losartan-treated groups. The lesions were characterized by an increase in the number and size of these specialized cells comprising the wall of the afferent arteriole of the glomeruli. A slightly higher incidence of chronic nephritis was seen in mid and high dose females and in high dose males.

TABLE 3.2.5.9
RENAL EFFECTS

Pathology		Incidence (# mice)				
		C-1	C-2	Low	Mid	High
JG Cell Hyperplasia	F	0	0	10	22	24
	M	0	0	8	15	32
Chronic Nephritis	F	24	31	29	43	42
	M	30	34	28	36	42

Appendix II

Historical Incidence of Benign and Malignant Pulmonary Tumors in Control Male CD-1 (ICR)BR Mice from Nine Recently Conducted Carcinogenicity Studies

Study	Group	Malignant Adenocarcinoma		Benign Adenoma	
		Incidence*	% Incidence	Incidence*	% Incidence
1	C-1	0/50	0	11/50	22
	C-2	0/50	0	8/50	16
2	C-1	12/50	24	4/50	8
	C-2	7/49	14	8/49	16
3	C-1	0/50	0	10/50	20
	C-2	0/50	0	6/50	12
4	C-1	1/50	2	9/50	18
	C-2	2/50	4	8/50	16
5	C-1	5/50	10	17/50	34
	C-2	6/50	12	10/50	20
6	C-1	5/50	10	8/50	16
	C-2	7/50	14	9/50	18
7	C-1	3/50	6	8/50	16
	C-2	3/50	5	12/50	24
8	C-1	2/50	4	11/50	22
	C-2	4/50	8	10/50	20
9	C-1	1/50	2	11/50	22
	C-2	1/47	2	10/47	21

All groups on study for 92 weeks except groups from study #7 which were on study for 73 weeks. *Represents # mice with tumor/# mice necropsied

Appendix III

Primary Neoplasms in Mice

LOREARTAN: 92-WEEK ORAL CARCINOGENICITY STUDY IN MICE. TT 890-133-0
SUMMARY OF PRIMARY NEOPLASMS

NUMBER NECROPTED	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5		GROUP 6	
	F	M	F	M	F	M	F	M	F	M	F	M
	50	50	50	50	50	50	50	50	-	50	50	-
STOMACH												
NONGLANDULAR MUCOSA, PAPILLOMA	-	-	-	-	1	-	-	-	-	-	-	-
SMALL INTESTINE												
ADENOCARCINOMA	-	-	-	-	-	-	1	-	-	-	-	-
HEMANGIOMA	-	-	-	1	-	-	-	-	-	-	-	-
POLYP	-	-	1	1	-	-	-	1	-	-	-	-
LARGE INTESTINE												
ANKIE, SQUAMOUS CELL CARCINOMA	-	-	-	-	-	-	1	-	-	-	-	-
LIVER												
HEMANGIOMA	-	-	3	-	1	-	-	-	-	-	-	-
HEMANGIOSARCOMA	-	1	-	1	-	1	-	-	-	-	-	-
HEPATOCELLULAR ADENOMA	-	6	1	3	1	2	-	5	-	6	-	-
HEPATOCELLULAR CARCINOMA	4	3	-	6	-	8	-	4	-	7	-	-
PANCREAS												
ISLET, ADENOMA	-	-	-	1	-	-	-	-	-	-	-	-
ADRENAL												
CORTEX, ADENOMA	-	2	-	1	-	1	-	-	-	-	-	-
MALIGNANT PHEOCHROMOCYTOMA	1	-	-	-	-	-	-	-	-	-	-	-
BENIGN SPINDLE CELL TUMOR	1	-	-	-	-	-	1	-	-	-	1	-
PITUITARY												
ADENOMA	2	-	-	-	-	-	1	1	-	-	-	-
THYROID												
FOLLICULAR CELL, ADENOMA	-	2	-	1	-	-	1	-	-	1	-	-
KIDNEY												
PELVIC EPITHELIUM, TRANSITIONAL CELL CARCINOMA	-	-	-	-	-	-	1	-	-	-	-	-
OVARY												
PAPILLARY ADENOMA	-	-	-	-	1	-	-	-	-	-	-	-
BENIGN GRANULOSA CELL TUMOR	-	-	1	-	-	-	1	-	-	-	-	-
MALIGNANT GRANULOSA CELL TUMOR	-	-	-	-	1	-	-	-	-	-	-	-

KEY: GROUP 1 = CONTROL 1

GROUP 2 = CONTROL 2

GROUP 3 = 20 MG/KG/DAY

GROUP 4 = 100 MG/KG/DAY

GROUP 5 = 500/300 MG/KG/DAY

GROUP 6 = 500/300/200 MG/KG/DAY

LOREANIN (CONTINUED): 92-WEEK ORAL CARCINOGENICITY STUDY IN MICE. TT #90-133-0
SUMMARY OF PRIMARY NEOPLASMS

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5		GROUP 6	
	F	M	F	M	F	M	F	M	F	M	F	M
UTERUS												
HEMANGIOMA	-	-	-	-	1	-	-	-	-	-	1	-
LEIOMYOMA	-	-	-	-	2	-	-	-	-	-	-	-
POLYP	1	-	2	-	3	-	1	-	-	-	-	-
ENDOMETRIAL STROMA, SARCOMA	1	-	-	-	-	-	-	-	-	-	1	-
VAGINA												
LEIOMYOSARCOMA	1	-	-	-	-	-	-	-	-	-	-	-
TESTIS												
RETE TESTIS, ADENOMA	-	1	-	-	-	-	-	-	-	-	-	-
HEMANGIOMA	-	-	-	1	-	-	-	-	-	-	-	-
BENIGN INTERSTITIAL CELL TUMOR	-	1	-	1	-	1	-	2	-	1	-	-
EPIDIDYMIS, LEIOMYOSARCOMA	-	-	-	-	-	-	-	-	-	1	-	-
SEMINAL VESICLE												
PAPILLARY ADENOMA	-	1	-	-	-	-	-	-	-	-	-	-
SKIN												
HEMANGIOMA	-	-	1	-	-	-	-	-	-	-	-	-
HEMANGIOSARCOMA	-	1	-	-	-	-	-	-	-	-	-	-
BENIGN XIBEROMA	-	-	-	-	-	-	-	1	-	-	-	-
LIPOMA	-	-	-	1	-	-	-	-	-	-	-	-
OSTEOGENIC SARCOMA	-	1	-	-	-	-	-	-	-	-	-	-
RHABDOMYOSARCOMA	-	-	-	-	2	-	-	-	-	-	-	-
MAMMARY GLAND												
MALIGNANT ADENOCARCINOMA	1	-	2	-	-	-	-	-	-	-	-	-
ADENOCARCINOMA	2	-	3	-	1	-	1	-	-	-	1	-
LUNG												
ADENOCARCINOMA	3	2	4	3	1	3	-	3	-	8	2	-
ADENOMA	10	7	5	6	7	9	7	9	-	6	5	-
OSTEOMA	1	-	-	-	-	-	-	-	-	-	-	-
HEART												
HEMANGIOMA	-	-	1	-	-	-	-	-	-	-	-	-
SPLEEN												
HEMANGIOSARCOMA	-	-	-	1	-	-	-	1	-	-	-	-
KIDNEY												
OSTEOMA	-	-	1	-	-	-	-	-	-	-	-	-
OSTEOSARCOMA	-	-	1	-	-	-	-	-	-	-	-	-

KEY: GROUP 1 = CONTROL 1

GROUP 2 = CONTROL 2

GROUP 3 = 20 MG/KG/DAY

GROUP 4 = 100 MG/KG/DAY

GROUP 5 = 300/200 MG/KG/DAY

GROUP 6 = 500/300/200 MG/KG/DAY

1-158,046 (CONTINUED): 92-WEEK ORAL CARCINOGENICITY STUDY IN MICE, TT #90-133-0
 SUMMARY OF PRIMARY NEOPLASMS

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5		GROUP 6	
	F	M	F	M	F	M	F	M	F	M	F	M
SKELETAL MUSCLE												
HIBRANTIOCARCIN.												
	-	-	-	-	-	1	-	-	-	-	-	-
RABDOMYOSARCOMA												
	1	-	-	-	-	-	1	-	-	-	-	-
NERVE												
MALIGNANT SCHWANNOMA												
	-	-	-	-	-	-	-	-	-	1	-	-
EYE												
HARDERIAN GLAND, ADENOMA												
	-	5	2	5	3	5	1	10	-	5	2	-
PRIMARY SITE UNDETERMINED												
HISTIOCYTIC SARCOMA												
	1	-	1	1	-	1	1	-	-	1	1	-
MYELOID LEUKEMIA												
	-	-	-	-	-	1	-	-	-	-	-	-
LYMPHOMA												
	1	-	3	-	5	2	4	3	-	2	2	-
MALIGNANT PLASMA CELL MYELOMA												
	-	-	-	-	-	-	1	-	-	-	-	-

KEY: GROUP 1 = CONTROL 1

GROUP 5 = 300/200 MG/KG/DAY

GROUP 2 = CONTROL 2

GROUP 6 = 500/300/200 MG/KG/DAY

GROUP 3 = 20 MG/KG/DAY

GROUP 4 = 100 MG/KG/DAY

Studies in Dogs**3.2.6. One Month Oral Toxicity Study in Dogs**

Location of Data: Vol. 13, Tab B-5

Testing Facility: Toxicology Section, Experimental Station, Pharmaceuticals and Biotechnology R & D Division, E. I. du Pont de Nemours and Company, Medical Products Department, Wilmington, DE.

Study No.: 88-7-3

Study Dates: Initiated: July 26, 1988
Terminated: August 26, 1988

GLP Compliance: Studies were done in accordance with GLP regulations.

Animals: Beagle dogs (both sexes, approximately 9-13 months of age, 7.1 to 11.7 kg)

Drug Administration: Losartan (Lot # INE-3340-15) was prepared fresh daily as an aqueous solution in sterile water for injection and administered orally by gastric intubation.

Dose Levels: 0 (vehicle), 15, 45, and 135 mg/kg (4/sex/dose).

Observations/Measurements: All dogs were observed once daily for mortality and clinical signs of toxicity. Body weights were measured twice before treatment, on study day 1 prior to dosing and twice weekly during the dosing period. A final body weight was measured prior to scheduled sacrifice. Food consumption was measured daily one week before commencement of treatment and daily throughout the dosing period. Stool samples were analyzed for occult blood for approximately one week before treatment and then daily during the dosing period. Body temperatures and respiratory rates were recorded and neurologic reflexes evaluated during the pretest period, and within two hours after dosing during the last week of the study. Electrocardiographic tracings were recorded pretest and predose and within two hours after dosing just prior to termination of the study. Ophthalmoscopic examinations were performed once pretreatment and during the last week of the dosing period. Blood for hematology and clinical chemistry measurements was collected from all dogs twice pretest and once after approximately two weeks of dosing. Urinalysis was performed on urine collected from all dogs pretest and after 4 weeks of dosing. The concentration of losartan in plasma was determined from blood samples collected from all dogs approximately 45 min after dosing on dose days 1, 14, and 30. Necropsy was performed on all animals at the end of treatment. Liver, heart, kidneys, testes, adrenals and brain from all animals were weighed and organ-to-terminal body weight ratios calculated. Major tissues/organs collected from all animals were fixed for histopathological evaluation.

Results: No treatment-related deaths occurred. There was one non-scheduled kill in the high dose group. Within one hour after receiving its fifth dose, the high dose male became ataxic, displayed reduced motor activity, increased salivation and shortly later, red material was observed in the animal's vomitus. Within 90 min of dosing, the animal was prostrate and had labored breathing, cyanotic membranes and no pupillary response. The animal was sent to necropsy as a moribund kill. This animal had moderate hemorrhage, congestion, necrosis and edema of the lungs.

The most prominent clinical findings, observed at all dose levels were adverse gastrointestinal effects, as evidenced by emesis, mucoidal, soft or watery stool, and red material under the cage (not otherwise described). These signs were considered to be losartan-induced effects since they were not seen in control animals. The frequency and severity of these observations were dose-dependent and considered to be dose-limiting in the high dose group. These clinical observations occurred sporadically and were relatively mild in nature in low dose group animals. In the 45 mg/kg/day dosage group, the onset for these effects ranged from study day 2 to study day 21. At 135 mg/kg/day, these clinical signs generally occurred as soon as study day 1, shortly after dosing. The total number of occurrences or frequency of all but one clinical sign (soft stool) was 1.3- to 4.6-fold greater for the high dose group than for the mid-dosage group. Occult blood was infrequently observed for all low dosage group animals. However, repeated (for at least three consecutive days) occurrences of fecal occult blood in animals from both mid and high dosage groups suggests a dosage dependent relationship between gastrointestinal effects and losartan administration.

There were no treatment-related effects on body weight gain, food consumption or ophthalmoscopic and E.C.G. examinations. Slight but statistically significant differences (from control) in group mean serum chemistry parameters (including aspartate aminotransferase, alanine aminotransferase, sodium and inorganic phosphorus) were observed sporadically at various dosage levels during the study period. These changes were not considered to be treatment-related since they were minor and non-dose dependent. There were no treatment-related effects on urinalysis profiles or organ weights for any of the dose groups. Gross and histopathological examination revealed no treatment-related abnormalities. The numerous occurrences of emesis might suggest an irritation of gut mucosa, but histopathological findings did not indicate that losartan was irritating to the mucosal wall.

In conclusion, clinical signs suggestive of gastrointestinal effects were the most prominent findings at all dose levels. The severe emetic episodes that occurred in animals receiving losartan at 135 mg/kg/day were considered to be dose limiting.

Plasma concentrations of losartan increased dose-dependently but not in proportion to the dose administered as shown in Table 3.2.6.1.

TABLE 3.2.6.1
PLASMA CONCENTRATIONS ($\mu\text{g/ml}$)[@] OF LOSARTAN FREE ACID. STUDY # 88-7-3.

Dose (mg/kg/day)		Day 1	Day 14	Day 30
15	M	2.63 $\pm$ 1.83	2.88 $\pm$ 1.63	2.76 $\pm$ 1.69
	F	2.14 $\pm$ 0.76	2.23 $\pm$ 0.97	2.47 $\pm$ 0.30*
45	M	6.54 $\pm$ 3.16	8.74 $\pm$ 3.83	7.62 $\pm$ 3.81
	F	4.00 $\pm$ 2.90	12.46 $\pm$ 4.19	8.51 $\pm$ 2.46
135	M	10.54 $\pm$ 5.30	25.17 $\pm$ 10.40*	19.86 $\pm$ 10.79*
	F	22.38 $\pm$ 8.36	31.47 $\pm$ 10.28	27.54 $\pm$ 12.84

Values: Mean $\pm$ S.D. (n=4); @: measured 45 min after dosing; *: mean data from three animals.

3.2.7. Three Month Oral Toxicity Study in Dogs

Location of Data: Vol. 13, Tab B-6

Testing Facility: Toxicology Section, Experimental Station, Pharmaceuticals and Biotechnology R & D Division, E. I. du Pont de Nemours and Company, Medical Products Department, Wilmington, DE.

Study No.: 89-5-6

Study Dates: Initiated: May 31, 1989
Terminated: September 1, 1989

GLP Compliance: Studies were done in accordance with GLP regulations.

Animals: Beagle dogs (Males, 8.2 - 11.4 kg; Females, 6 - 10.7 kg) were approximately 9-13 months of age at initiation of treatment.

Drug Administration: Losartan (Lot # INE-3340-19M) was prepared fresh daily as an aqueous solution in sterile water for injection and administered via liquid-filled gelatin capsules.

Dose Levels: 0 (vehicle), 5, 25, and 125 mg/kg (5/sex/dose).

Observations/Measurements: All dogs were observed once daily for mortality and clinical signs of toxicity. Body weights were measured before treatment and twice weekly during the dosing period. A final body weight was measured prior to scheduled sacrifice. Food consumption was measured daily and stool samples were analyzed for occult blood for one week before commencement of treatment and daily throughout the dosing period. Body temperatures and respiratory rates were recorded and neurologic reflexes evaluated during the pretest period, and once monthly during the dosing period. Electrocardiographic tracings were recorded twice during the pretest period, prior to dosing and approximately two hours after

dosing during study weeks 1, 4, 7-8, and 13. Ophthalmoscopic examinations were performed pretreatment and during the last week of the dosing period. Blood and urine samples were collected from all dogs twice pretest and once at approximate monthly intervals during the dosing period for hematology and blood chemistry, and urinalysis. The concentration of losartan in plasma was determined from blood samples collected from all dogs approximately 45 min after dosing on dose days 1, 7, 31, 59, and 84. Necropsy was performed on all animals at the end of treatment. Liver, heart, kidneys, testes, adrenals, pituitary and brain from all animals were weighed and organ-to-terminal body weight ratios calculated. Major tissues/organs collected from all animals were fixed for histopathological evaluation.

Results: No deaths occurred. The most prominent clinical findings observed in high dose animals were vomiting, increased salivation and fecal abnormalities, which included positive fecal occult blood. With the exception of emesis, the onset and total incidence of these signs were similar among both sexes of the high dose group. Emesis, however, occurred with a greater frequency in (all) high dose female dogs following dosing on study day 1 and continued to be observed throughout the study. The onset of emesis was within 15 minutes of dosing. In the high dose males, the onset of the emetic response to losartan was not observed until study day 12, with 4 of 5 males vomiting during the study period. The total frequency (days) of emesis observed with each of the dogs ranged from 24 to 32 days for females and 5 to 15 days for the males during the 3-month study period. In the 25 mg/kg/day group, the clinical sign profile suggested a trend toward increased salivation, and increased incidence of emesis. However, the incidences are not considered to be of toxicological significance due to their relatively mild and sporadic occurrence. Fecal abnormalities, including abnormal consistency and/or color of the stool(s) were observed at a much greater frequency in the high dose group. Four of 5 high dose males and 3 of 5 high dose females tested positive for fecal occult blood (at least three consecutive days) five or more times during the study. Animals from other dose groups including control did not test positive for fecal occult blood for at least three consecutive days.

There were no treatment-related effects on body weight gain, food consumption or ophthalmoscopic and E.C.G. examinations. A slight but statistically significant increase in the serum creatinine level for the 125 mg/kg/day female group (relative to concurrent control) was observed at the two month sampling interval. However, the elevation was considered to be minor, of no biological significance, and unrelated to losartan treatment. Also noted in the high dose males was a slight decrease in erythroid parameters (RBC, hematocrit, and hemoglobin) at the one- and two-month intervals when compared to control. This too was not considered by the sponsor to represent a biologically adverse effect of treatment.

A statistically significant decrease in the mean absolute adrenal weight was found for the 5 and 25 mg/kg/day male groups. However, the mean absolute adrenal weight for males receiving 125 mg/kg/day was comparable with that of the control male group. There were no other significant differences in organ weights between vehicle control and losartan treated groups. The only histopathological finding of note was moderate lymphocytic infiltration of the gastric mucosa of a 125 mg/kg/day female dog, which was compatible with gastric

irritation. The emetic response induced by losartan may be attributed, in part, to a direct irritation of the gastric mucosa. Similarly, the fecal abnormalities observed were consistent with a treatment-induced irritation of the gastrointestinal tract. The no observable effect level was 5 mg/kg/day.

The plasma concentrations of losartan increased dose-dependently and appeared to increase in proportion to the dose administered in both male and female dogs. Losartan concentration and variabilities were similar in both male and female dogs at each dosage level.

TABLE 3.2.7.1
PLASMA CONCENTRATIONS ($\mu\text{g/ml}$)[@] OF LOSARTAN FREE ACID, STUDY #89-5-6.

Dose (mg/kg/day)		Day 1	Day 7	Day 31	Day 59	Day 84
5	M	0.79 $\pm$ 0.56 ⁴	1.02 $\pm$ 0.17 ²	0.27 $\pm$ 0.39	0.57 $\pm$ 0.37 ⁴	0.50 $\pm$ 0.72 ²
	F	0.70 $\pm$ 0.42 ⁴	0.71 $\pm$ 0.43 ⁴	0.45 $\pm$ 0.42 ³	0.66 $\pm$ 0.44 ⁴	0.72 $\pm$ 0.47 ⁴
25	M	3.57 $\pm$ 2.59	5.37 $\pm$ 4.64	3.89 $\pm$ 3.13	3.28 $\pm$ 1.94	4.21 $\pm$ 2.05
	F	4.05 $\pm$ 2.04	5.98 $\pm$ 3.24	2.16 $\pm$ 0.96	4.25 $\pm$ 2.42	3.02 $\pm$ 1.14
125	M	17.90 $\pm$ 8.45	21.98 $\pm$ 4.60	18.00 $\pm$ 6.70	19.27 $\pm$ 5.18	18.89 $\pm$ 3.50
	F	9.81 $\pm$ 5.66	18.94 $\pm$ 7.74	18.67 $\pm$ 6.33	16.09 $\pm$ 6.07	26.05 $\pm$ 7.08

Values: Mean $\pm$ S.D; @ measured 45 min after dosing; N=5 unless otherwise specified by a superscript number which denotes the sample size for a given interval of time and dose.

3.2.8. Fifty-Three-Week Oral Toxicity Study in Dogs with a 27-Week Interim Necropsy

Location of Data: Vol. 14, Tab B-7

Testing Facility: Department of Safety Assessment, Merck Sharp & Dohme Research Laboratories, Merck & Co., Inc., West Point, PA

Study No.: TT #90-028-0

Study Dates: Initiated: February 26, 1990
Interim necropsy: August 27 and 28, 1990
Terminal necropsy: February 25 and 26, 1991

GLP Compliance: Studies were done in accordance with GLP regulations.

Animals: Beagle dogs (32 Males, 8.9-14.9 kg; 32 Females, 6.9-16.2 kg) were 32-59 weeks of age at initiation of treatment.

Drug Administration: Losartan (Lot # 010) was prepared fresh daily as an aqueous solution in

deionized water and administered by orogastric gavage (5 ml/kg).

Dose Levels: 0 (vehicle), 5, 25, and 125 mg/kg, (8/sex/dose).

Observations/Measurements: All dogs were observed once daily for mortality and clinical signs of toxicity. Body weights were measured before treatment and once weekly during the dosing period. Food consumption was measured daily (4 days/week) through drug week 27 and then every fourth week (4 days/week) thereafter and drug weeks in which hematological, serum biochemical, and urinalysis parameters were evaluated. Ophthalmic and electrocardiographic examinations were performed pretreatment and in drug weeks 12, 24 or 25, 39, and 52. Blood for hematological and biochemical examinations was collected from the jugular vein of each animal (fasted) pretest and on all surviving animals during drug weeks 4, 12, 25, 39, and 51. In addition, alkaline phosphatase, ALT, and AST were determined on all dogs in drug week 17. Urinalyses were performed pretest and during drug weeks 12, 25, 39, and 51.

Four dogs/sex from the control and the 5 and 125 mg/kg/day dose groups and 3 females and 4 males from the 25 mg/kg/day dose group were sacrificed in drug week 27. The remaining animals were sacrificed in drug week 53. At both the interim and terminal necropsies, detailed gross examinations were performed on all dogs, including one mid dose female dog that died of an intubation accident in drug week 6. The weights of brain, spleen, heart, kidney, liver, adrenal, pituitary, thyroid, lung, testes, prostate, ovary and uterus were recorded. Major tissues/organ samples collected from all animals were preserved in appropriate solutions. Histopathological evaluations were performed on all control and high dose group dogs as well as the mid dose female dog which did not survive to scheduled necropsy. In addition, specimens of all gross lesions (from all dogs) were examined.

Results: No treatment-related deaths occurred. A female dog from the 25 mg/kg/day group died in drug week 6 due to an intubation accident. Mild, transient, treatment-related predose and/or postdose hypersalivation was observed frequently at the high dose and infrequently at the mid and low doses and not at all in control animals. Post dose hypersalivation generally lasted 10-30 minutes. Occasional treatment-related emesis and changes in stool consistency (unformed or loose) and color (yellow) were more frequently observed in high dose dogs compared to control animals. However, these signs were not considered significant given their mild and sporadic nature and the lack of histomorphologic changes in the gastrointestinal tract. The incidence of emesis in dogs given 5 and 25 mg/kg/day was not appreciably greater than that observed with control animals.

There were no treatment-related effects on body weight gain, food consumption, ophthalmoscopic and E.C.G. examinations, or hematologic and urinalysis parameters. Throughout the study, there were recurrent increases in serum ALT values for one mid dose male dog, and two female and one male high dose dogs when compared to pretest and historical control values (Table 3.2.8.1). However, the magnitude of the increases was not dose- or time-dependent and there was no histomorphological evidence of hepatic injury in

these animals. The recurrent increases in ALT as noted in this study are, nevertheless, attributed to treatment.

There were no organ weight or histopathologic findings that could be attributed to treatment.

TABLE 3.2.8.1
INDIVIDUAL SERUM ALT (U/L) VALUES. STUDY #90-028-0

Dose mg/kg/day	Pretest -1 week	Drug week					
		4	12	17	25	39	51
25/Male	28	34	73*	83*	99*	-	-
125/Female	36	41	46	49*	167*	86*	199*
125/Female	27	88*	91*	25	37	-	-
125/Male	31	26	43	32	32	49*	46*

* Values outside 95% limits for 3 year control values

- = Sacrificed at interim necropsy

In conclusion, with the exception of mild clinical signs of gastrointestinal toxicity and sporadic, isolated increases in serum ALT in one mid and three high dose dogs, oral administration of losartan at dosages levels up to 125 mg/kg/day for 53 weeks was well tolerated.

Studies in Monkeys

3.2.9. 14-Week Oral Toxicity Study in Monkeys

Study Facility: MSD Research Laboratories, West Point, PA

Study No: 90-193-0

Study Dates: 12/13/90 - 3/14/91

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Rhesus monkeys (16M, 16F; 2.3-3.3 kg)

Drug Administration: Losartan (Lot # 10) was dissolved in deionized water and administered orally once daily by nasogastric tube.

Dose Levels: 0, 20, 100 and 300 mg/kg/day (4/sex/dose group)

Observations/Measurements: Animals were observed daily during treatment for clinical signs of toxicity and mortality. Body weights were measured pretest and weekly during the study. Ophthalmoscopic exams were performed pretest and in weeks 5 and 11 of treatment. Blood was obtained via a femoral vein pretest and in weeks 4, 8 and 11 of treatment for hematology and serum biochemistry analyses. Urine was collected pretest and in weeks 2, 4, 8 and 11 of treatment for urinalysis. Prior to scheduled sacrifice and 24 hours after dosing, blood was obtained from all control and high dose animals for measurement of plasma angiotensin II levels. Blood samples were also obtained from 3 losartan-treated females/group during Drug Week 13 at 0.25, 0.5, 1, 2, 4, 6, 8 and 24 hours after dosing for measurement of parent drug and carboxylic acid metabolite levels. Monkeys were sacrificed at termination of the study and examined for gross pathology. Sections of major organs and tissues were fixed on slides for histopathologic examination.

Results:

Mortality: There were no treatment-related deaths. One mid dose male was killed for humane reasons in Drug Week 3 due to a fracture of the right humerus, with associated soft-tissue damage.

Clinical Signs: No clinical signs of toxicity were observed.

Body Weight: No treatment-related effects on body weights were observed.

Ophthalmoscopy: No treatment-related changes were seen on ophthalmologic examinations.

Hematology: Slightly lower (up to 5%) erythroid parameters (erythrocyte count, hematocrit and hemoglobin concentrations) compared to control occurred in monkeys given 300 mg/kg/day in weeks 8 and 11 of treatment.

Serum Biochemistry: No treatment-related effects were seen in the biochemical parameters measured. Angiotensin II levels in the high dose group (49.6 pg/ml) were approximately 5-fold higher than in the control group (11.8 pg/ml) 24 hours after losartan administration.

Urinalysis: No treatment-related effects on urinalysis parameters were observed.

Organ Weights: There were no treatment-related differences in organ weights.

Gross Pathology: Tarry intestinal contents and small depressed, reddened foci were noted in the stomachs and/or intestines in 4 high dose monkeys.

Histopathology: No microscopic effects related to losartan treatment were observed. No gastrointestinal lesions were observed in the high dose monkeys to correlate with the reddened foci noted during gross examination.

Plasma Drug Levels: Parent compound was detected in monkey plasma in only a few sampling periods after oral dosing at 20 mg/kg/day during Drug Week 13. Female monkeys did not extensively metabolize losartan to its acid metabolite or to its N2-tetrazole glucuronide. The acid metabolite was not detected in any sample after the 20 mg/kg/day dose and plasma samples were consistently less than 1.3 ug/ml for the 100 to 300 mg/kg/day dosage groups. Also, systemic exposure (AUC) to the acid metabolite increased in a near dose-proportional manner in the 100 and 300 mg/kg/day range and represented less than 20 percent of the systemic exposure to drug.

TABLE 3.2.9.1
LOSARTAN AND ACID METABOLITE PHARMACOKINETICS AFTER ORAL LOSARTAN IN FEMALE MONKEYS *

Dose Group (mg/kg/day)	AUC ₀₋₂₄ (ug.hr/ml)	Losartan C _{max} (ug/ml)	T _{max} (hr)	Acid Metabolite AUC ₀₋₂₄ (ug.hr/ml)
20	ND	0.29-0.65	0.5-2.0	ND
100	6.55	1.8	0.5	1.05
300	28.1	5.0	3.0	3.76

*N=3. ND= Drug not detected in sufficient number of intervals to calculate AUC value.

3.3. GENOTOXICITY

3.3.1. Bacterial Reverse Mutation Assay (Ames Test) #1

Study Facility: Haskell (du Pont) Laboratory, Newark, NJ

Study Number: 88-4-8

Study Dates: 7/06/88 -8/16/88

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Bacterial Strains: *Salmonella typhimurium* strains TA97, TA98, TA100 and TA1535.

Procedure: Losartan (Lot#E-3340-14) was dissolved in distilled-deionized water and added directly to the plate medium at concentrations of 0 (vehicle), 50, 100, 500, 1000 and 5000 ug/plate in the presence and absence of metabolic activation with S-9 fraction obtained from livers of Aroclor 1254-treated rats. Sodium azide, 2-aminoanthracene, 2-nitrofluorene and acridine (concentrations not stated) were used as positive controls. The numbers of revertant colonies per plate were determined for controls (vehicle and positive) and losartan-treated plates. Each strain was tested in 2 experiments, each using 2 plates/dose group. The criteria for a positive mutagenic effect required (1) an increase (at least 2X or greater) in the average number of revertant colonies at one or more drug concentrations over the average number of revertant colonies in the solvent control and (2) that the drug-related increase in revertant colonies be dose-related.

Results: In each of the four tester strains, losartan did not significantly increase the number of revertant bacterial colonies above vehicle control, either in the presence or absence of metabolic activation. The positive controls that were included in each test showed consistent positive mutagenic effects.

TABLE 3.3.1.1
MICROBIAL MUTAGENESIS ASSAY WITH S. TYPHIMURIUM

Treatment (µg/plate)	S-9	Mean # Revertants/plate			
		TA97	TA98	TA100	TA1535
Vehicle	-	125	30	114	19
	+	142	31	134	22
Losartan 50	-	127	20	123	16
	+	153	30	132	17
100	-	142	19	124	20
	+	149	32	121	15
500	-	137	19	119	21
	+	150	33	137	19
1000	-	141	24	135	16
	+	165	31	127	16
5000	-	143	21	126	14
	+	138	28	119	12
NAAZ	-			969	695
2-AA	+	1708	2106	2193	349
ACR	-	2184			
2-NF	-		1508		

NAAZ= Sodium azide; 2-AA= 2-aminoanthracene; ACR=acridine; 2-NF= 2-nitrofluorene

3.3.2. Bacterial Reverse Mutation Assay #2

Study Facility: MSD Research Laboratories, West Point, PA

Study Number: 90-8011

Study Dates: 5/16/90 - 5/18/90

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Bacterial Strains: *Escherichia coli* strains WP2, WP2 uvrA, WP2 uvrA pKM101

Procedure: Losartan (Lot# 005H010) was dissolved in DMSO and added directly to the plate medium at concentrations of 0 (vehicle), 100, 300, 1000, 3000 and 10,000 µg/plate in the presence and absence of metabolic activation with S-9 fraction obtained

from livers of Aroclor 1254-treated rats. Methyl methanesulfonate (2ug/plate), 2-aminoanthracene (2, 5, 10 ug/plate), and hydrazine sulfate (500 and 1000 ug/plate) were used as positive controls. The number of revertant colonies per plate were determined for controls (vehicle and positive) and losartan-treated bacterial plates. Losartan was tested in triplicate against each bacterial strain. The criteria for a positive mutagenic effect required 1) an increase (at least 2X or greater) in the average number of revertant colonies at one or more drug concentrations over the average number of revertant colonies in the solvent control and 2) that the drug-related increase in revertant colonies be dose-related.

Results: In each of the 3 bacterial strains, losartan did not significantly increase the number of revertant bacterial colonies above vehicle control, either in the presence or absence of metabolic activation. The positive controls that were included in each test showed consistent positive mutagenic effects.

TABLE 3.3.2.1
MICROBIAL MUTAGENESIS ASSAY WITH E. COLI

Treatment (µg/plate)	S-9	Mean # Revertants/plate		
		WP2	WP2uvrA	WP2uvrApK
Vehicle	-	32	10	63
	+	36	13	80
Losartan 100	-	35	13	61
	+	33	11	82
300	-	35	10	65
	+	35	16	86
1000	-	32	11	65
	+	30	9	81
3000	-	26	8	65
	+	38	11	82
10000	-	36	11	60
	+	34	10	85
MMS, 2 µl	-	14x*	45x*	33x*
2AA 5 µg	+		31	585
	+		37	739
HS 500 µg	+	206		
	+	369		

*Indicates the fold increase from vehicle (0) control.

MMS=methyl methanesulfonate; 2-AA= 2-aminoanthracene; HS= hydrazine sulfate

3.3.3. Bacterial Reverse Mutation Assay #3

Study Facility: MSD Research Laboratories, West Point, PA

Study Number: 92-8086 and 92-8088 (replicate test)

Study Dates: 11/30/92 - 3/01/93

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Bacterial Strains: *Salmonella typhimurium* strains TA97, TA98, TA100 and TA1535.
Escherichia coli strains WP2, WP2 uvrA, WP2 uvrA pKM101

Procedure: Losartan (Lot# 005H019) was dissolved in DMSO and added directly to the plate medium at concentrations of 0 (vehicle), 100, 300, 1000, 3000 and 10,000 ug/plate in the presence and absence of metabolic activation with S-9 fraction obtained from livers of Aroclor 1254-treated rats. Methyl methanesulfonate (2ug/plate), sodium azide (1.5u g/plate) and daunomycin (5 ug/plate) were used as positive controls for the *Salmonella* strains; hydrazine sulfate (500 and 1000 ug/plate) was used for *E. coli* WP2 strain and 2-aminoanthracene (2, 5 and 10 ug/plate) was used for *Salmonella* and *Escherichia* strains. The numbers of revertant colonies per plate were determined for controls (vehicle and positive) and losartan-treated bacterial plates. Losartan was tested in triplicate against each bacterial strain. The criteria for a positive mutagenic effect required 1) an increase (at least 2X or greater) in the average number of revertant colonies at one or more drug concentrations over the average number of revertant colonies in the solvent control and 2) that the drug-related increase in revertant colonies be dose-related.

Results: Losartan, up to the highest tested concentration of 10000 ug/plate did not produce any two-fold or greater increases in revertant colonies above vehicle control in any of the tester strains, either with or without metabolic activation. The positive controls that were included in each test showed the expected strain-dependent, positive mutagenic effects.

TABLE 3.3.3.1.
MICROBIAL MUTAGENESIS ASSAY WITH S. TYPHIMURIUM AND E. COLI

Treatment (µg/plate)	S-9	Mean # Revertants/plate						
		TA97	TA98	TA100	TA1535	WP2	WP2uvrA	WP2 uvrApK
Vehicle	-	136	18	100	12	37	31	66
	+	144	21	100	16	33	24	59
Losartan 100	-	130	15	112	16	30	30	72
	+	150	26	100	13	33	30	55
300	-	134	16	96	13	32	27	57
	+	148	21	101	20	34	24	58
1000	-	124	19	105	13	36	28	66
	+	144	18	96	15	26	25	57
3000	-	130	15	96	10	33	23	70
	+	164	16	98	16	35	22	68
10000	-	103	14	113	13	31	27	57
	+	144	17	93	13	34	30	59
2AA 10 ug	+	1360	1332	1796	218		67	363
HS 1000 ug	+					241		
NAAZ 1.5ug	-			4.8x*	43x*			
MMS 2 ul	-	2.4x*	2.1x*	15x*	8.1x*	9.6x*	21x*	22x*

*Indicates the fold increase from vehicle (0) control.

2-AA= 2-aminoanthracene; HS= hydrazine sulfate; NAAZ=sodium azide; MMS= methyl methanesulfonate

3.3.4. Bacterial Reverse Mutation Assay with Primary Metabolite (L-158,641)

Study Facility: MSD Research Laboratories, West Point, PA

Study Number: 92-8021

Study Dates: 7/25/90 - 7/27/90

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Bacterial Strains: *Salmonella typhimurium* strains TA97, TA98, TA100 and TA1535.
Escherichia coli strains WP2, WP2 uvrA, WP2 uvrA pKM101

Procedure: L-158,641 (Lot# 002X001) was dissolved in DMSO and added directly to the plate medium at concentrations of 0 (vehicle), 100, 300, 1000, 3000 and 10,000 ug/plate in the presence and absence of metabolic activation with S-9 fraction obtained from livers of Aroclor 1254-treated rats. Methyl methanesulfonate (2ug/plate), sodium azide (1.5u g/plate) and daunomycin (5 ug/plate) were used as positive controls for the *Salmonella* strains; hydrazine sulfate (500 and 1000 ug/plate) was used for *E. coli* WP2 strain and 2-aminoanthracene (2, 5 and 10 ug/plate) was used for *Salmonella* and *Escherichia* strains. The number of revertant colonies per plate were determined for controls (vehicle and positive) and L-158,641-treated bacterial plates. L-158,641 was tested in triplicate against each bacterial strain. The criteria for a positive mutagenic effect required 1) an increase (at least 2X or greater) in the average number of revertant colonies at one or more drug concentrations over the average number of revertant colonies in the solvent control and 2) that the drug-related increase in revertant colonies be dose-related.

Results: L-158,641 up to the highest tested concentration of 10000 ug/plate did not produce any two-fold or greater increases in revertant colonies above vehicle control in any of the tester strains, either with or without metabolic activation. The positive controls that were included in each test showed the expected strain-dependent, positive mutagenic effects.

TABLE 3.3.4.1.
MICROBIAL MUTAGENESIS ASSAY WITH S. TYPHIMURJUM AND E. COLI

Treatment (µg/plate)	S-9	Mean # Revertants/plate						
		TA97	TA98	TA100	TA1535	WP2	WP2uvrA	WP2 uvrApK
Vehicle	-	175	22	172	39	33	11	134
	+	188	25	195	36	30	11	97
L-158,641 100	-	193	20	166	40	31	9	123
	+	194	28	198	31	36	13	90
300	-	178	23	170	34	28	9	148
	+	174	21	198	36	28	9	87
1000	-	167	23	176	40	35	7	138
	+	188	26	188	30	35	9	94
3000	-	170	22	169	41	34	10	140
	+	198	20	191	30	28	9	103
10000	-	162	23	171	34	36	10	139
	+	156	22	224	50	28	7	108
2AA 5 µg	+	1359	1439	1832	209		40	901
HS 500 µg	+					201		
NAAZ 1.5µg	-			2.8x*	9.3x*			
MMS 2 µl	-	2.6x*	2.6x*	8.9x*	2.2x*	11x*	51x*	17x*

*Indicates the fold increase from vehicle (0) control.

2-AA=2-aminoanthracene; HS=hydrazine sulfate; NAAZ= sodium azide; MMS= methyl methanesulfonate.

3.3.5. Chinese Hamster Lung Cell Forward Mutation Assay:

Study Facility: MSD Research Laboratories, West Point, PA

Study Number: 91-8501

Study Dates: 1/23/91 - 2/08/91

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Procedure: This assay measures forward mutations at the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus as resistance to the purine analog 6-thioguanine (6-TG). Cells that have lost functional activity of the salvage enzyme

HGRPT are resistant to 6-TG and form mutant colonies. This assay measures forward mutations such as deletions, nonsense, missense, base-pair substitutions or frame shift mutations. Losartan (Lot# 005H010) was dissolved in DMSO and added to the Chinese hamster lung cell culture at concentrations of 0 (vehicle), 0.05, 0.1, 0.5, 1, and 2 mM (in duplicate) with and without metabolic activation using S-9 fraction obtained from the livers of Aroclor 1254-treated rats. 3-Methylcholanthrene (37.3uM) and 1-methyl-1-nitrosourea (100uM) were used as positive controls. Cells were exposed to compound for 3 hours at 37°C. The drug medium was replaced with growth medium, cells were incubated for 6-7 days for expression and then treated with 6-TG for mutant selection. The number of mutant colonies were counted for each concentration and compared to vehicle control. The criteria for a positive mutagenic effect required 1) an increase in the mutant frequency of 2.21X the standard deviation of the vehicle control frequency, 2) an increasing mutant frequency trend over 3 concentrations of drug and 3) positive mutagenic effects observed in a replicate assay.

Results:

TABLE 3.3.5.1
CHINESE HAMSTER LUNG MUTAGENESIS ASSAY

Treatment	S-9	Mean Mutant Fraction	Significance Level
Vehicle	-	2.32	
	+	2.32	
Losartan 0.05 mM	-	-	N.S.
	+	1.42	
0.1 mM	-	1.98	N.S.
	+	1.50	N.S.
0.5 mM	-	2.43	N.S.
	+	1.50	N.S.
1.0 mM	-	1.27	N.S.
	+	1.96	N.S.
2.0 mM	-	2.75	N.S.
	+	-	
3-MC*	+	54.06	p<0.0001
1-M-1-N*	-	54.63	p<0.0001

*3-MC = 3 methylcholanthrene, 1-M-1-N = 1 methyl-1-nitrosourea

At non-cytotoxic concentrations (80% cytotoxicity was noted with losartan concentrations >1 mM with S-9 and >2 mM without S-9), losartan did not induce

mutations in Chinese hamster lung cells in the presence or absence of metabolic activation.

Note: In replicate study (# 92-8558), losartan up to the same maximum concentrations produced no mutagenic effects in Chinese hamster lung cells.

3.3.6. Alkaline Elution/Rat Hepatocyte Genotoxicity Assay

Study Facility: MSD Research Laboratories, West Point, PA

Study Number: 90-8311; 92-8516 and 92-8531 (replicate assays)

Study Dates: 2/27/90 - 2/28/90 (Study # 90-8311) 11/04/92 - 12/3/92 (Study # 92-8516 and 92-8531)

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Procedure: This assay measures drug-induced DNA strand breaks in cultured rat hepatocytes. The assay sensitively detects small changes in molecular weight by measuring the rate at which single alkali-denatured strands of DNA elute through 2 u pore filters. Measurements by alkaline sucrose gradients show that low molecular weight DNA elutes first, followed by DNA of successively higher molecular weight. The amount of DNA in each elution fraction is measured fluorometrically. Losartan (Lot #005H009) was dissolved in DMSO and added to the hepatocyte cell culture plates at concentrations of 0 (vehicle), 1.0, 1.7, 2.4, 3.1 and 3.8 mM in Study # 90-8311 and 0, 0.6, 1.2, 1.8, 2.4, 3.0 and 3.6 mM (2 plates/conc.) in the replicate assays. These concentrations were selected from prior cytotoxicity tests; concentrations producing less than 70% relative cell viability were not used for mutagenicity assessment. Aflatoxin B1 (1uM) was used as the positive control. The cells were incubated with drug or vehicle for 3 hours, removed from the culture plates, tested for cell viability by trypan blue exclusion and then prepared for elution. For each drug concentration/plate, a 5 ml aliquot of cell suspension (approx. 1×10^6 cells) was placed on a 2 u polycarbonate filter and lysed with a lysing solution. An alkaline solution (pH 12.1) was added to the DNA held on the filter and 3 fractions of 3-hrs elution time were collected. The DNA from each fraction was trapped on other (0.2 u) polycarbonate filters and the amount of DNA on each filter was measured as the fluorescent product of 3,5-diaminobenzoic acid and deoxyribose. The rate of elution was calculated from a semi-log plot of the fraction of DNA retained against the time of elution. The mean slope of the plotted line from 3 to 9 hrs of elution was taken as the elution rate. The criteria used for defining a positive genotoxic effect are 1) induction of an elution slope (treatment slope-negative control slope) which is equal to or greater than 0.034 and 2) relative cytotoxicity <30% (i.e. relative cell viability >70%) because DNA strand breaks are also produced as a result of cytotoxicity and cell death.

Results:

TABLE 3.3.6.1
RAT HEPATOCYTE GENOTOXICITY ASSAY

Treatment	Assay #	Relative Cell Viability (%)	Mean Elution Slope
Vehicle	1	100	0.001
Losartan			
1.0 mM		90	0.002
1.7 mM		80	0.002
2.4 mM		64	0.024
3.1 mM		42	0.070
3.8 mM		15	N.D.*
Aflatoxin B1		98	0.051
Vehicle	2	100	0.006
Losartan			
0.6 mM		84	0.006
1.2 mM		80	0.005
1.8 mM		41	0.01
2.4 mM		61	0.032
3.0 mM		33	0.054
3.6 mM		17	0.087
Aflatoxin B1	99	0.149	
Vehicle	3	100	0.004
Losartan			
0.6 mM		94	0.004
1.2 mM		90	0.002
1.8 mM		92	0.010
2.4 mM		83	0.048
3.0 mM		60	0.111
3.6 mM		34	0.188
Aflatoxin B1	97	0.129	

*N.D. = Not determined due to extreme cytotoxicity.

Losartan did not induce an elution slope equal to or greater than 0.034 at concentrations that did not affect cell survival except in one assay (Study # 92-8516) in which a concentration of 2.4 mM of losartan induced an increase in the elution slope (0.048) although the relative cell viability at this concentration was 83% and did not satisfy the exclusion criteria. However, this concentration produced higher levels (>30%) of cytotoxicity in the other two assays (Study # 90-8311 and 92-8531) and produced elution slopes less than the required 0.034 for acceptance as positive mutagenic activity. At concentrations of 3.0 mM and higher, the mean elution slopes were above the minimum criteria of 0.034; however, these concentrations were

associated with appreciable cytotoxicity. It is concluded that losartan is not mutagenic in this assay.

3.3.7. Alkaline Elution/Rat Hepatocyte Genotoxicity Assay with Metabolite L-158,641

Study Facility: MSD Research Laboratories, West Point, PA

Study Number: 90-8317 and 90-8319 (replicate assay)

Study Dates: 3/14/90 - 3/27/90

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Procedure: L-158,641 (Lot #002X001) was dissolved in DMSO and added to the hepatocyte cell culture plates at concentrations of 0 (vehicle), 1.6, 2.3, 3.0, 3.7, 4.4 and 5.1 mM in Study # 90-8317 and 0, 5, 6, 7, 8 and 9 mM (2 plates/conc.) in the second assay. These concentrations were selected from prior cytotoxicity tests; concentrations producing less than 70% relative cell viability were not used for mutagenicity assessment. Aflatoxin B1 (1 μ M) was used as the positive control. The cells were incubated with drug or vehicle for 3 hours, removed from the culture plates, tested for cell viability by trypan blue exclusion and then prepared for elution. For each drug concentration/plate, a 5 ml aliquot of cell suspension (approx. 1×10^6 cells) was placed on a 2 μ polycarbonate filter and lysed with a lysing solution. An alkaline solution (pH 12.1) was added to the DNA held on the filter and 3 fractions of 3-hrs elution time were collected. The DNA from each fraction was trapped on other (0.2 μ) polycarbonate filters and the amount of DNA on each filter was measured as the fluorescent product of 3,5-diaminobenzoic acid and deoxyribose. The rate of elution was calculated from a semi-log plot of the fraction of DNA retained against the time of elution. The mean slope of the plotted line from 3 to 9 hrs of elution was taken as the elution rate. The criteria used for defining a positive genotoxic effect are 1) induction of an elution slope (treatment slope-negative control slope) which is equal to or greater than 0.034 and 2) relative cytotoxicity <30% (i.e. relative cell viability >70%) because DNA strand breaks are also produced as a result of cytotoxicity and cell death.

Results: L-158,641 did not induce an elution slope equal or greater than 0.034 at any of the concentrations tested. It is concluded that the losartan metabolite L-158,641 is not mutagenic in this assay.

TABLE 3.3.7.1
RAT HEPATOCYTE GENOTOXICITY ASSAY

Treatment	Assay #	Relative Cell Viability (%)	Mean Elution Slope
Vehicle	1	100	0.002
L-158,641			
1.6 mM		93	0.006
2.3 mM		90	0.006
3.0 mM		94	0.007
3.7 mM		97	0.006
4.4 mM		93	0.008
5.1 mM		92	0.007
Aflotoxin B1		96	0.067
Vehicle	2	100	0.002
L-158,641			
5 mM		92	0.005
6 mM		90	0.006
7 mM		93	0.012
8 mM		88	0.006
9 mM		83	0.005
Aflotoxin B1		101	0.234

3.3.8. Chromosomal Aberrations in Chinese Hamster Ovary Cells:

Study Facility: MSD Research Labs, West Point, PA

Study Number: 90-8622 and 90-8629 (replicate assay)

Study Dates: 3/01/90 - 6/11/90

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Cell Culture: Chinese hamster ovary cells

Procedure: This mammalian cell assay measures breaks or rearrangements in chromatids or chromosomes in post-treatment metaphase cells *in vitro* as a means of assessing genotoxicity. Losartan (lot #005H010) was dissolved in DMSO and added to the cell culture at concentrations of 0 (vehicle), 0.125, 0.25, 0.5, 1, 2, 4, 6, 8 and 10 mM (Study # 90-8622) and 0, 1, 1.5, 2.25, 2.5, 2.75, 3, 3.25 and 2.5 mM (Study #90-8629) and incubated for a period of 3 hours in the presence and absence of metabolic activation with S-9 fraction obtained from the livers of Aroclor 1254-treated

rats. Cyclophosphamide (2.5 and 5 μM) and mitomycin-C (0.25, 0.35 and 0.5 μM) were used as positive controls. After treatment the cells were washed free of drug and incubated for 17 hours to permit cell division. Cells were then fixed on slides and 200 metaphase spreads per treatment were scored for chromosomal aberrations (gaps, deletions, exchanges and translocations). Cells exposed to low concentrations of drug were examined by inverted microscope before harvest for frequency of mitotic cells and were not scored if they appeared healthy with no apparent reduction in mitotic frequency. A significant increase ($p < 0.05$) in chromosomal aberrations at two or more dose levels with less than 50% cytotoxicity was judged to be a positive effect. A positive result at one dose level was considered equivocal until repeated in another assay.

Results: The concentrations of losartan scored for aberrations in Study #90-8622 were 1 and 2 mM with and without S-9. Doses above 2 mM were cytotoxic (> 50%). Losartan, with or without metabolic activation, did not cause a significant increase in the proportions of cells with chromosomal aberrations above concurrent solvent controls. The concentrations tested in the second assay were chosen to provide a range between concentrations that caused little cytotoxicity and those that produced severe cytotoxicity (>50%). There were no significant increases at losartan concentrations of 2.5 mM or less. At a concentration of 3 mM with and without metabolic activation, losartan caused significant increases in chromosomal aberrations. Cytotoxicity at this concentration (3 mM) was 47% and 49% (very close to the exclusion level of 50%) with and without S-9, respectively. At a slightly higher concentration of 3.25mM, losartan was extremely cytotoxic (64%-85%); thus, significant increases in chromosomal aberrations were not seen at two or more dose levels for losartan to satisfy the criteria for a positive effect. Therefore, losartan is judged as negative in this chromosomal aberration assay.

TABLE 3.3.8.1
CHROMOSOMAL ABERRATIONS IN CHO CELLS (TEST #1)

Treatment	S-9	Cell Viability (% control)	Chromosomal Aberrations/100 Cells
Vehicle	-	100	2.5
	+	100	2.0
Losartan 0.125 mM	-	99	N.D.
	+	114	
0.25 mM	-	86	N.D.
	+	121	
0.50 mM	-	88	N.D.
	+	124	
1.0 mM	-	103	2.5
	+	84	
2.0 mM	-	85	1.0
	+	75	
4.0 mM	-	22	N.S.
	+	21	
6.0 mM	-	19	N.S.
	+	13	
8.0 mM	-	24	N.S.
	+	11	
10.0 mM	-	25	N.S.
	+	N.D.	
Cyclophosphamide			
2.5 µM	+	82	11.5*
5.0 µM	+	63	23.0*
Mitomycin C			
0.25	-	90	14*
0.35	-	N.D.	7*
0.50	-	82	N.D.

*Statistically significant (P<0.05) increase compared to vehicle control
 N.D. = Not done
 N.S. = Not scored due to excessive toxicity

TABLE 3.3.8.2
CHROMOSOMAL ABERRATIONS IN CHO CELLS (TEST #2)

Treatment	S-9	Cell Viability (% control)	Chromosomal Aberrations/100 Cells
Vehicle	-	100	2.0
	+	100	2.5
Losartan 1.0 mM	-	93	N.D.
	+	78	N.D.
1.5 mM	-	88	N.D.
	+	83	N.D.
2.0 mM	-	75	N.D.
	+	78	N.D.
2.25 mM	-	87	3.0
	+	62	2.5
2.5 mM	-	69	1.5
	+	56	4.0
2.75 mM	-	67	N.D.
	+	42	N.S.
3.0 mM	-	51	10.0*
	+	53	14.5*
3.25 mM	-	36	N.S.
	+	15	N.S.
3.5 mM	-	27	N.S.
	+	29	N.S.
Cyclophosphamide			
2.5 µM	+	78	15*
5.0 µM	+	73	48*
Mitomycin C			
0.25 µM	-	94	N.D.
0.35 µM	-	N.D.	11.0*
0.50 µM	-	91	19.0*

*Statistically significant ($P < 0.05$) increase compared to vehicle control

N.D. = Not done

N.S. = Not scored due to excessive cytotoxicity

3.3.9. Chromosomal Aberration Assay with Losartan Metabolite (L-158,641) in Chinese Hamster Ovary Cells

Study Facility: MSD Research Labs, West Point, PA

Study Number: 90-8628

Study Dates: 3/13/90 - 3/20/90

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Cell Culture: Chinese hamster ovary cells

Procedure: This mammalian cell assay measures breaks or rearrangements in chromatids or chromosomes in post-treatment metaphase cells *in vitro* as a means of assessing genotoxicity. L-158,641 (Lot #002X001) was dissolved in DMSO and added to the cell culture at concentrations of 0 (vehicle), 0.125, 0.25, 0.5, 1, 1.5, 2, 2.5, and 3 mM in the presence of metabolic activation (S-9 fraction obtained from the livers of Aroclor 1254-treated rats) and concentrations of 0, 1, 1.5, 2, 2.5, 3, and 3.5 mM without metabolic activation. Cyclophosphamide (2.5 and 5 μ M) and mitomycin-C (0.25, 0.35 and 0.5 μ M) were used as positive controls. Following 3 hours of drug exposure, the cells were washed free of drug and incubated to permit cell division. Cells were then fixed on slides and 200 metaphase spreads per treatment were scored for chromosomal aberrations (gaps, deletions, exchanges and translocations). Cells exposed to low concentrations of drug were examined by inverted microscope before harvest for frequency of mitotic cells and were not scored if they appeared healthy with no apparent reduction in mitotic frequency. A significant increase ($p < 0.05$) in chromosomal aberrations at two or more dose levels with less than 50% cytotoxicity was judged to be a positive mutagenic effect. A positive result at one dose level was considered equivocal until repeated in another assay.

Results: L-158,641 formed a fine precipitate at concentrations of 1.5 mM and higher with S-9; therefore, the top concentration level scored for chromosomal aberrations with S-9 was 1.0 mM. L-158,641 did not cause a significant increase above vehicle control in the number of Chinese hamster ovary cells with chromosomal aberrations. Cyclophosphamide and mitomycin-C elicited the expected positive genotoxic effects.

TABLE 3.3.9.1
CHROMOSOMAL ABERRATIONS IN CHO CELLS

Treatment	S-9	Chromosomal Aberrations (% cells)
Vehicle (DMSO)	-	1.5
	+	2.5
L-158,641	-	N.D.
	+	2.5
0.125 mM	-	N.D.
	+	2.5
0.25 mM	-	N.D.
	+	3.0
0.5 mM	-	N.D.
	+	2.5
1.0 mM	-	N.D.
	+	2.0
1.5 mM	-	N.D.
	+	N.S.
2.0 mM	-	N.D.
	+	N.S.
2.5 mM	-	2.0
	+	N.S.
3.0 mM	-	1.0
	+	N.S.
3.5 mM	-	3.0
	+	N.S.
Mitomycin C	-	
	-	
0.25 µM	-	8.0*
0.50 µM	-	21.0*
Cyclophosphamide	-	
	-	
2.5 µM	+	10.5*
5.0 µM	+	40.0*

* Statistically significant ($P < 0.05$) increase compared to vehicle control

N.D. = Not done

N.S. = Not scored due to precipitate

3.3.10. Chromosomal Aberrations in Male Mouse Bone Marrow

Study Facility: MSD Research Labs, West Point, PA

Study Number: 90-8635

Study Dates: 5/15/90 - 6/07/90

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Male Crl:CD-1 [ICR] BR mice (20-29 gm)

Procedure: This mammalian cell assay measures chromosomal aberrations from treated mice by examining mitotically active cells from the marrow of the femurs which have been arrested at metaphase. Chromosomal aberrations, such as structural changes and rearrangements, can be observed microscopically and serve as possible indicators of mutagenic potential of test compounds. Losartan (Lot # 005H010) was dissolved in water and administered to mice orally by gavage at doses of 0 (vehicle), 150, 500 and 1500 mg/kg (24/dosegroup for low and mid dose; 30/high dose and 36/vehicle group). The high dose is approx 2/3 of the LD₅₀. Mitomycin-C (3.5 mg/kg and 1 mg/kg; 4 and 8/dose, respectively) was used as the positive control. One-third of vehicle and losartan-treated mice were sacrificed at 6, 24 and 48 hours after treatment. Mice treated with the positive control were sacrificed 24 hours after treatment. Mice were dosed with colchicine 2 mg/kg 2.5-3.5 hours prior to sacrifice to arrest cells in metaphase. Both femurs of each animal were removed, the bone marrow harvested and marrow cells fixed on slides for measurement of mitotic activity and chromosomal aberrations. In this assay, at least 50 metaphase spreads per animal are scored with the aim of achieving at least 300 metaphases/dose group. Chromosomes and chromatids are scored for gaps, deletions, exchanges and translocations. The assay is considered positive if a significant increase in aberration frequencies ($p < 0.05$) above vehicle control occurs at a minimum of two dose levels; either two at a given sacrifice time or one dose at each of two sacrifice times. A significant increase at a single dose level at one sacrifice time would be considered equivocal and would require replication in a repeat assay.

Results: Five of 30 mice treated with 1500 mg/kg died within 5 hours after treatment. Losartan caused no significant increases in chromosomal aberrations above vehicle control with any dose tested (150 - 1500 mg/kg) or after any sacrifice time.

TABLE 3.3.10.1
CHROMOSOMAL ABERRATIONS IN MALE MOUSE BONE MARROW

Treatment	Hours Postdose	Chromosomal Aberrations (% cells)
Vehicle	6	0.50
Losartan		
150 mg/kg	6	0.00
500 mg/kg	6	0.00
1500 mg/kg	6	0.50
Vehicle	24	0.83
Losartan		
150 mg/kg	24	0.50
500 mg/kg	24	1.00
1500 mg/kg	24	1.00
Mitomycin C		
1 mg/kg	24	2.21
3.5 mg/kg	24	46.50 **
Vehicle	48	0.67
Losartan		
150 mg/kg	48	1.32
500 mg/kg	48	0.52
1500 mg/kg	48	0.25

** Statistically significant (P<0.001) increase compared to vehicle control

3.3.11. Chromosomal Aberrations in Female Mouse Bone Marrow

Study Facility: MSD Research Labs, West Point, PA

Study Number: 93-8601

Study Dates: 1/21/93 - 4/15/93

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Female Crl:CD-1 [ICR] BR mice (17.6 - 25 gm)

Procedure: This mammalian cell assay measures chromosomal aberrations from treated mice by examining mitotically active cells from the marrow of the femurs which have been arrested at metaphase. Chromosomal aberrations, such as structural changes and rearrangements, can be observed microscopically and serve as possible indicators of mutagenic potential of test compounds. Losartan (Lot # 005H009) was

dissolved in water and administered to mice orally by gavage at doses of 0 (vehicle), 150, 500 and 1500 mg/kg (24/dosegroup for low and mid dose; 30/high dose and 36/vehicle group). The high dose is approx 2/3 of the LD₅₀. Mitomycin-C (3.5 mg/kg and 1 mg/kg; 4 and 8/dose, respectively) was used as the positive control. One-third of vehicle and losartan-treated mice were sacrificed at 6, 24 and 48 hours after treatment. Mice treated with the positive control were sacrificed 24 hours after treatment. Mice were dosed with colchicine 2 mg/kg 2.5-3.5 hours prior to sacrifice to arrest cells in metaphase. Both femurs of each animal were removed, the bone marrow harvested and marrow cells fixed on slides for measurement of mitotic activity and chromosomal aberrations. In this assay, at least 50 metaphase spreads per animal are scored with the aim of achieving at least 300 metaphases/dose group. Chromosomes and chromatids are scored for gaps, deletions, exchanges and translocations. The assay is considered positive if a significant increase in aberration frequencies ($p < 0.05$) above vehicle control occurs at a minimum of two dose levels; either two at a given sacrifice time or one dose at each of two sacrifice times. A significant increase at a single dose level at one sacrifice time would be considered equivocal and would require replication in a repeat assay.

Results: Three of 30 female mice treated with 1500 mg/kg of losartan died within 24 hours after treatment. Losartan caused no significant increase in chromosomal aberrations above vehicle control with any dose tested (150 - 1500 mg/kg) or after any sacrifice time.

TABLE 3.3.11.1
CHROMOSOMAL ABERRATIONS IN FEMALE MOUSE BONE MARROW

Treatment	Hours Postdose	Chromosomal Aberrations (% cells)
Vehicle	6	0.67
Losartan		
150 mg/kg	6	0.25
500 mg/kg	6	0.75
1500 mg/kg	6	0.50
Vehicle	24	1.33
Losartan		
150 mg/kg	24	0.00
500 mg/kg	24	1.25
1500 mg/kg	24	1.25
Mitomycin C		
1 mg/kg	24	3.5*
3.5 mg/kg	24	41.6*
Vehicle	48	1.5
Losartan		
150 mg/kg	48	0.00
500 mg/kg	48	1.75
1500 mg/kg	48	0.25

* Statistically significant ($P < 0.05$) increase compared to vehicle control

3.4. REPROTOXICITY

3.4.1. Oral Fertility Study in Male Rats

Location of Data: Vol 18, Tab C-1

Testing Facility: 1

Study No.: TT #90-9807

Study Dates: Initiated: May 8, 1990
Terminated: August 15, 1990

GLP Compliance: Studies were done in accordance with GLP regulations.

Animals: Sprague-Dawley (CrI:CD BR) rats from Charles River Laboratories; Males were approximately 8 weeks of age and weighed 270-339 gm at initiation of the study.

Methods and Observations: Dosage levels of 25, 50, and 150 mg/kg/day were given orally by gavage daily to three groups of 25 males each for 70 days prior to and during cohabitation with untreated mature females of the same strain until confirmation of mating. An additional group of 25 males received the vehicle (water) at a dosing volume of 5 ml/kg and served as the control. The mating period was limited to 12 nights. On day 20 of gestation, females were sacrificed and their reproductive status was recorded. Fetuses were weighed, sexed, and examined for external abnormalities. After necropsy of females, all males were sacrificed and examined for gross abnormalities of the thoracic and abdominal viscera.

Results: There were no treatment-related deaths or physical signs of toxicity observed in males. The average body weight gains between dosing days 1 and 8 were significantly ($P \leq 0.05$) lower in the 50 (12%) and 150 (16%) mg/kg/day dose groups than in the control group. The body weights in treated groups between days 8 and 70 were comparable to or greater than that of controls.

No drug-related gross changes were observed at necropsy. Reproductive performance of mated males, as evidenced by time to mating, mating index (mean of $1/(\text{time to mating})$) for mated females and zero for females that did not mate), incidence of mating (percent mated females/females cohabited), and fecundity (percent pregnant females/mated females) and fertility (percent pregnant females/female cohabited) indices, was not affected by drug treatment. Also, there was no effect on the reproductive status of pregnant females or on the average body weight of live fetuses. No drug-related external abnormalities were observed in fetuses. In conclusion, losartan administered to male rats at dosage levels up to 150 mg/kg/day for 70 days prior to mating and throughout mating had no effects on reproductive

performance and fertility, and the prenatal development of the F₁ generation.

3.4.2. Oral Fertility Study in Female Rats

Location of Data: Vol 18, Tab C-2

Testing Facility: Department of Safety Assessment, Merck Sharp & Dohme Research Laboratories, Merck & Co., Inc., West Point, PA

Study No.: TT #90-708-0

Study Dates: Initiated: February 19, 1990
Terminated: July 28, 1990 (date of last F₁ necropsy)

GLP Compliance: Studies were done in accordance with GLP regulations.

Animals: Sprague-Dawley (CrI:CD BR) rats from Charles River Laboratories; Females were approximately 11 weeks of age and weighed 224-292 gm at initiation of the study.

Mode of Administration/Dosage Levels: Dosage levels of 25, 100, and 300/200 mg/kg/day were given orally by gavage daily to three groups of 40 females each (the high dose was initially 300 mg/kg/day and was lowered to 200 mg/kg/day at the start of mating due to excessive toxicity as reflected in severe loss of body weight). An additional group of 40 females received the vehicle (water) at a dosing volume of 5 ml/kg and served as the control. The females were given either water or test drug for 15 days prior to mating, during mating (with untreated mature males of the same strain), and through days 0 to 19 of gestation (cesarean-sectioned animals) or through day 20 of lactation (natural delivery females).

Observations/Measurements: All animals were observed for physical signs once daily (1-5 hr postdosing) from initiation to sacrifice. Body weights were recorded on days 1, 8, and 15 of the pre-mating period, weekly during mating and on days 0, 6, 12, 16, 18, 20, 22, 24 of gestation and on days 0, 3, 7, 10, 14, 17 and 21 of lactation. Food consumption was recorded on days 1 to 5 and 8 to 12 of the pre-mating period, days 1 to 5, 8 to 12, and 15 to 19 of gestation, and days 1 to 5 and 8 to 12 of lactation.

Females killed on day 20 of gestation (19-20/group) were examined for reproductive status, corpora lutea and implants were counted and the latter were classified as live fetus, dead fetus, or resorption. All fetuses were weighed, sexed, and examined externally. One-third of the fetuses from each litter were given a visceral examination, and heads of these fetuses were fixed in Bouin's solution for examination by free-hand coronal sectioning. All except two fetuses were fixed, cleared, and stained with alizarin red for subsequent skeletal examinations. One fetus from control and another from the 100 mg/kg/day group were submitted for histological analysis of the perineal region.

Females assigned for natural delivery were observed for parturition from day 21 until completion of delivery. Dams were killed between days 23 and 27 postpartum and the uterus of each female was examined to count metrial glands. A gross examination of thoracic and abdominal viscera was also performed. The F_1 pups were counted, examined externally, and sexed on postnatal day 0. All litters were reduced to 4 males and 4 females on lactation day 3. Two male and two female pups from each litter were examined for surface righting reflex on postnatal days 2, 4, and 6 and auditory response on postnatal days 11, 13, and 15. These pups were separated from dams on postnatal days 23 to 26 and housed individually until mating. They were observed daily for mortality and twice weekly for physical signs. Body weights were recorded once a week until breeding (in females) or sacrifice (in males). Testicular descent was recorded on postnatal day 39 and preputial separation on postnatal days 39, 43 and 47. Vaginal canalization was recorded on postnatal days 31, 34, and 37. Tests for behavioral assessment (open field activity and swimming maze) were performed on 1 male and 1 female animal from each litter during postnatal days 54-71. One female and one male of the same dose group but of different litters were mated between postnatal weeks 10 and 12. F_1 females which mated were weighed on days 0, 7, 14, and 20 of gestation, and after natural delivery on day 0 of postpartum. Approximately half of the F_1 males and females that were not needed for mating were sacrificed and discarded (without further examination) prior to F_1 mating. All F_1 males used for mating were killed after most females had completed delivery, and only the testes and epididymides were examined for gross changes. Histomorphologic examination was performed on testes and epididymides from the control and 300/200 mg/kg/day groups. F_1 females which delivered were killed within 1 week after delivery and the uterus of each animal was examined to count metrial glands. No gross necropsy was done.

The F_2 pups were counted, weighed, sexed, examined for external malformations on day 0 postpartum. All pups were killed within 3 days of delivery and discarded without further examination.

Results: There were no treatment-related deaths or physical signs in the F_0 females. Two animals (from 100 and 300/200 mg/kg/day groups) died as a result of intubation accidents during premating or gestation intervals. Two females (both in the high dose group) were sacrificed in the postpartum interval because they had no live pups remaining.

In the premating period of days 1 to 15 there was a significant treatment-related 84% decrease in mean body weight gain in the 300 mg/kg/day group when compared to control. Due to this excessive toxicity the dose of this group was lowered to 200 mg/kg/day prior to mating. There was a further significant treatment-related 7.4% decrease in mean body weight gain from days 0 to 20 of gestation (Table 3.4.2.1). In this same group average food consumption was significantly lower than control consumption for the entire premating period, day 19 of gestation and day 12 of lactation (Table 3.4.2.2). There were no significant effects either on mean body weight gain or on food consumption in other groups.

TABLE 3.4.2.1
AVERAGE MATERNAL BODY WEIGHT CHANGES (GRAMS) OF F₀ FEMALES. TT #90-708-0

TREATMENT GROUP:	CONTROL	25 MG/KG/DAY	100 MG/KG/DAY	300/200 MG/KG/DAY
<u>PREMATING PERIOD</u>				
DAY 1 TO 8	14 (40)	12 (40)	14 (39)	6 (40)
DAY 8 TO 15	10	8	9	-1
DAY 1 TO 15	25	20	23 ^{NS}	4 ^S
<u>GESTATIONAL PERIOD</u>				
DAY 0 TO 12	64 (32)	67 (34)	64 (32)	63 (32)
DAY 12 TO 16	24	30	26	23 (31)
DAY 16 TO 20	60 (31)	61	56	52
DAY 0 TO 20 ^a	148	158	145 ^{NS}	137 ^S
<u>LACTATIONAL PERIOD</u>				
DAY 0 TO 7	21 (15)	18 (18)	28 (18)	20 (18) ^{NS}
DAY 7 TO 14	17 (16)	19	17	27 (17) ^{NS}
DAY 14 TO 21	-20	-21	-15	-17 (16) ^{NS}
DAY 0 TO 21	18 (15)	16 ^{NS}	30 ^S	29 ^S

(N) = Group size and appears only if different from previous n. See individual table for exclusions.

NS = Trend not statistically significant through indicated dose ($p > 0.05$).

S = Trend statistically significant through indicated dose ($p \leq 0.05$).

a = Trend analysis was performed with an adjustment for day 0 weights.

TABLE 3.4.2.2
AVERAGE MATERNAL FOOD CONSUMPTION (GRAMS/DAY) OF F₀ FEMALES. TT #90-708-0

TREATMENT GROUP:	CONTROL	25 MG/KG/DAY	100 MG/KG/DAY	300/200 MG/KG/DAY
PREMATING PERIOD^a				
DAY 5	22 (40) ^a	22 (40)	21 (40) ^{ns}	19 (40) ^s
DAY 12	21	21	21 (39) ^{ns}	20 ^s
GESTATIONAL PERIOD^a				
DAY 5	26 (32)	27 (34)	26 (32)	27 (32) ^{ns}
DAY 12	28	30	29	29 (31) ^{ns}
DAY 19	29	31	29 ^{ns}	28 (30) ^s
LACTATIONAL PERIOD^a				
DAY 5	40 (16)	36 (16)	47 (18)	36 (16) ^{ns}
DAY 12	63	63 (17)	60 (17) ^{ns}	53 (17) ^s

a: Indicated day denotes end of 4 day interval.

n: Group size and appears only if different from previous n. See individual table for exclusions.

ns: Trend not statistically significant through indicated dose ($p > 0.05$).

s: Trend statistically significant through indicated dose ($p \leq 0.05$).

There were no treatment-related gross lesions found at necropsy in F₀ females sacrificed at the end of the study. Incidental findings included one mid and one high dose female with uterine distention with fluid, and one high dose female with pyometra.

There were no treatment-related effects on reproductive performance as assessed by mating index (mean of $1/(\text{time to mating})$) for mated females and zero for females that did not mate), incidence of mating (percent mated females/females cohabited), fecundity index (percent pregnant females/mated females), fertility index (percent pregnant females/females cohabited), percent females with live pups/pregnant females, and mean length of gestation. In the 300/200 mg/kg/day c-sectioned group, there were significantly ($P \leq 0.05$) fewer corpora lutea/female (-12.3%), implants/female (-17.6%) and live fetuses/female (-18%). In the 100 mg/kg/day group there was a slight but significant effect on number of corpora lutea/pregnant female (-11%) (Table 3.4.2.3). There was no effect on preimplantation loss in these groups. Postimplantation loss increased with dose (from 1.9 to 3.76 times control) but did not attain significance at any dose level.

Lower live female (5.5% below control, $P < 0.05$) and male fetal weights (4.2% below control, $P > 0.05$) observed in the high dose c-sectioned group were considered by the sponsor as treatment-related since the finding was consistent with the dose-related reduction in birth weights of pups of the natural delivered groups (see Table 3.4.2.4). External examination of fetuses showed one fetus in the low dose group with polydactyly, one fetus in the mid dose

TABLE 3.4.2.3
SUMMARY OF LAPAROTOMY DATA FROM F, FEMALES. TT #90-708-0

TREATMENT GROUP:	CONTROL	25 MG/KG/DAY	100 MG/KG/DAY	300/200MG/KG/DAY
FEMALES				
TOTAL FEMALES	20	19	19 ^c	20
LIVE PREGNANT	16	17	15	14
LIVE NOT PREGNANT	3	2	3	5
DEAD PREGNANT	0	0	0	1
NOT BRED	1	0	1	0
LENGTH OF GESTATION (DAYS)	22.3	22.1	22.3	22.4 ^{NS}
MATING INDEX ^d	0.87	0.93	0.89	0.92 ^{NS}
MATED FEMALES/FEMALES COHABITED, %	98	100	97	100 ^{NS}
FECUNDITY INDEX	82	90	87	85 ^{NS}
FERTILITY INDEX	80	90	85	85 ^{NS}
CORPORA LUTEA				
CORPORA LUTEA	288	289	240	221
CORPORA LUTEA/PREGNANT FEMALE	18.0	17.0 ^{NS}	16.0 ^S	15.8 ^S
% PREIMPLANTATION LOSS (LM)	10.9	6.8	10.9	14.0 ^{NS}
IMPLANTS				
IMPLANTS	264	270	223	191
IMPLANTS/PREGNANT FEMALE	16.5	15.9	14.9 ^{NS}	13.6 ^S
RESORPTIONS AND DEAD FETUSES				
RESORPTIONS	9	15	4	10
DEAD FETUSES	0	0	0	0
% (RESORP+DEAD FET)/IMP (LM)	2.9	5.6	8.5	10.9 ^{NS}
LIVE FETUSES				
LIVE FETUSES (M/F)	255 (120/135)	255 (127/128)	219 (98/121)	181 (92/89)
LIVE FETUSES/PREGNANT FEMALE	15.9	15.0	14.6 ^{NS}	12.9 ^S
LIVE FETAL WEIGHT (GM, LM), M/F ^b	3.60/3.48	3.60/3.43	3.60/3.41 ^{NS}	3.45 ^{NS} /3.29 ^S

% preimplantation loss = ((no. corpora lutea - no. implants) / no. corpora lutea) x 100.

LM = Litter mean. NS = Trend not statistically significant through indicated dose ($p > 0.05$). S = Trend statistically significant through indicated dose ($p \leq 0.05$). a = Trend analysis was performed with an adjustment for time of sacrifice. b = Trend analysis was performed with an adjustment for time of sacrifice and litter size. c = One additional female excluded which died prior to mating due to intubation accident. d = Mating index = Mean of $1/(\text{time to mating})$ for mated females and zero for females that did not mate.

TABLE 3.4.2.4
SUMMARY OF STATUS OF F₁ GENERATION PRIOR TO WEANING. TT #90-702-0

	CONTROL	25 MG/KG/DAY	100 MG/KG/DAY	300/200 MG/KG/DAY
PARENTAL FEMALES, F ₀ (A)	16	19	18	19
IMPLANTS PER FEMALE	14.8	14.8	15.3	14.9 ^{NS}
% POSTIMPLANTIN. SURVIVAL (L.M.)	96.5	89.9	94.5	85.8 ^{NS}
FEMALES WITH LIVE PUPS PND 0	16	18	18	18
FEMALES WITH LIVE PUPS PND 21	16	18	18	16
TOTAL PUPS (FEMALES/MALES)	232 (120/112)	275 (142/133)	270 (141/129)	266 (143/122)
LIVE PUPS ON POSTNATAL DAY 0	230 (118/112)	267 (136/131)	260 (134/126)	257 (138/119)
DEAD PUPS ON POSTNATAL DAY 0	2 (2/0)	8 (6/2)	10 (7/3)	9 (5/3)
LIVE PUPS/ LITTER, L.M. (% LIVE PUPS)	14.4 (99.0)	14.8 (97.4)	14.4 (96.1)	14.3 ^{NS} (96.7)
LIVE PUPS AFTER CULLING (PND 3)	128	144	144	143
PUP DEATHS (L.M.) ^a (% PUP DEATHS)				
POSTNATAL DAYS 0-3 ^b	2 (0.8)	4 (2.5)	7 (2.7) ^{NS}	17 (7.7) ^S
POSTNATAL DAYS 4-7	0 (0.0)	2 (1.4)	0 (0.0)	24 (17.2)
POSTNATAL DAYS 8-14	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.1)
POSTNATAL DAYS 15-21	0 (0.0)	0 (0.0)	0 (0.0)	6 (4.2)
POSTNATAL DAYS 4-21	0 (0.0)	2 (1.4)	0 (0.0) ^{NS}	33 (23.4) ^S
LIVE PUP WEIGHT (GM) (L.M.), M/F	M/F	M/F	M/F	M/F
POSTNATAL DAY 0 ^c	6.5/6.2	6.7 ^{NS} /6.2	6.3 ^S /6.0 ^{NS}	6.3 ^S /5.9 ^S
POSTNATAL DAY 7 ^d	18.8/18.0	17.9 ^{NS} /16.7 ^{NS}	17.6 ^S /16.4 ^S	16.3 ^S /15.1 ^S
POSTNATAL DAY 14 ^d (% CHANGE)	38.5/37.3	35.8 ^S (7.0)/34.4 ^S (7.8)	35.2 ^S (8.6)/33.5 ^S (10.2)	33.5 ^S (13.0)/30.4 ^S (18.5)
POSTNATAL DAY 21 (% CHANGE)	62.8/60.7	59.2 ^S (5.7)/56.5 ^S (6.9)	52.5 ^S (16.4)/49.5 ^S (18.5)	50.4 ^S (9.8)/46.0 ^S (24.3)

Total includes pups for which sex could not be determined. (A) = Excludes any females not surviving past day 20 of gestation. (L.M.) = Litter mean. M = Male. F = Female. PND = Postnatal day. NS = Trend not statistically significant through indicated dose ($p > 0.05$).

S = Trend statistically significant through indicated dose ($p \leq 0.05$).

a = Excludes pups born dead day 0.

b = Includes only deaths in day 0 pups which died after weighing.

c = Statistical analysis was performed with an adjustment for length of gestation and number of live pups per litter on postnatal day 0.

d = Statistical analysis was performed with an adjustment for length of gestation.

group with a perineal malformation and anasarca, microcardia, a reduced atrium, an enlarged ductus arteriosus and a displaced testes, and another fetus in the mid dose group with an azygos vein variation. Since these incidences are low in number, the sponsor considers them as spontaneous events unrelated to treatment. There was a slight increase in the percent of high dose fetuses with variations or sites of incomplete ossification (40.4% of high dose fetuses versus 31.7% of control fetuses). The increase in sites of incomplete ossification was the result of a non-dose related increase in incompletely ossified sternebra.

There were no effects of the test drug on % postimplantation survival or live pups/litter in the natural delivery groups. However, significant increases in pup mortality in the high dose group from postnatal days 0-3 (7.7%) and from days 4 to 21 (23.4%) were considered treatment-related (Table 3.4.2.4). The pup deaths were associated with decreased pup weights. There were significant treatment-related decreases in pup weights during lactation in all dose groups. In general, these decreases were dose and postnatal age-dependent with female pups being more severely affected than male pups. Similar percent decreases in weights of day 20 fetuses and day 0 pups in the high dose group suggests that these effects are due to late gestation and lactation exposure to losartan and it could be secondary to maternal toxicity. There was no evidence of treatment-related external malformations or variations in F_1 pups.

There was no effect of treatment on surface righting or testes descent in F_1 pups. In the female pups, there was a significant treatment-related delay in the estimated mean day of occurrence of the auditory startle reflex in the 100 and 300/200 mg/kg/day groups (0.44 and 0.47 days, respectively). There was also a delay of 1.2 days in the estimated mean day of vaginal canalization in the high dose group animals. According to the sponsor, these delays are considered to be related to the significantly decreased body weights in these groups and are secondary to generalized immaturity of the pups rather than a specific effect of losartan on developmental maturation. In the males from high dose group, the mean day of occurrence for preputial separation was significantly increased by 1.3 days compared to control. Treatment-related significant decreases in open field activity in male offspring in the mid and high dose groups (11 and 15.5%, respectively, compared to control) were observed. There was no effect of treatment on swim maze activity in F_1 rats.

From weaning (postnatal day 21) until postnatal day 25 there were pup deaths in the mid (4 of 143) and high dose (5 of 108) groups. These deaths were considered by the sponsor as unusual and were regarded as treatment-related. There were no physical signs of toxicity among weaned F_1 rats. The postweaning weight changes among males and females in all drug treated groups were different. In females, from postweaning weeks 1 to 9 there were slight but significant decreases in mean body weight gain of 4.3, 5.6 and 5.2% in the 25, 100 and 300/200 mg/kg/day groups, respectively, when compared to control. For the entire 14 week postweaning period the average weight gain of females in all treatment groups was within 2% of control.

Losartan had no adverse effects upon the reproductive capacity of the F_1 generation at any dose level tested (Table 3.4.2.5). There was no effect of treatment on mortality, weight or

TABLE 3.4.2.5

SUMMARY OF REPRODUCTIVE PERFORMANCE OF F₁ FEMALES AND STATUS OF F₂ GENERATION AT PARTURITION. TT #90-708-0

	CONTROL	25 MG/KG/DAY	100 MG/KG/DAY	300/200MG/KG/DAY
FEMALES COHABITED	16	18	17	15
MALES COHABITED	15	18	17	15
MATED FEMALES	16	15	15	14
PREGNANT FEMALES	15	15	14	12
DIED OR SACRIFICED PRIOR TO DAY 20	0	0	0	0
FEMALES WITH LIVE PUPS	15	15	14	12
TIME TO MATING (4-DAY PERIODS)	1.25	1.20	1.47	1.43 ^{NS}
MATED FEMALES/FEMALES COHABITED, %	100	83	88	93 ^{NS}
FECUNDITY INDEX (PREGNANT FEMALES/MATED FEMALES, %)	94	100	93	86 ^{NS}
FERTILITY INDEX (PREGNANT FEMALES/FEMALES COHABITED, %)	94	8	382	80 ^{NS}
FEMALES WITH LIVE PUPS/PREGNANT FEMALES, %	100	100	100	100
LENGTH OF GESTATION (DAYS)	22.2	22.6	22.3	22.5 ^{NS}
IMPLANTS PER FEMALE	17.8	16.7	16.6	16.8 ^{NS}
% POSTIMPLANTATION SURVIVAL (L.M.)	91.4	86.5	93.9	88.6
FEMALES WITH LIVE PUPS DAY 0 POSTPARTUM	15	15	14	12
TOTAL PUPS (FEMALES/MALES)	249 (130/119)	232 (125/105)	222 (118/104)	185 (92/93)
LIVE PUPS ON POSTNATAL DAY 0	244 (128/116)	217 (118/99)	218 (116/102)	179 (89/90)
DEAD PUPS ON POSTNATAL DAY 0	5 (2/3)	15 (7/6)	4 (2/2)	6 (3/3)
LIVE PUPS PER LITTER (%)	16.3 (98.1)	14.5 (93.8)	15.6 (98.2)	14.9 ^{NS} (96.7)
LIVE PUP WEIGHT (L.M.) ON DAY 0, M/F	6.7/6.3	7.0/6.6	6.6/6.3	6.9/6.4 ^{NS}

Total includes pups for which sex could not be determined

(L.M.) = Litter mean. NS = trend not statistically significant through indicated dose ($p > 0.05$).

a = Statistical analysis was performed with an adjustment for length of gestation and number of live pups per litter.

external morphology of the F₂ pups.

In conclusion, there was no evidence of teratogenicity in any dose group in the F₁ or F₂ generation. Developmental toxicity was observed in all dose groups based on decreased F₁ pup weight gain and mortality (in both lactation and postweaning periods and dose and time-dependent). Females had more severe weight gain reductions than males. In addition, developmental signs were adversely affected. The toxicity observed may be due to late gestation/lactation drug exposure. This study has failed to establish a no observed effect dose.

3.4.3. Oral Developmental Toxicity Study in Rats

Location of Data: Vol 19, Tab C-6

Testing Facility: Department of Safety Assessment, Merck Sharp & Dohme Research Laboratories, Merck & Co., Inc., West Point, PA

Study No.: T I #90-702-0

Study Dates: Initiated: April 9, 1990
Terminated: May 3, 1990

GLP Compliance: Studies were done in accordance with GLP regulations.

Animals: Female Sprague-Dawley (CrI:CD BR) rats from Charles River Laboratories were 11 weeks of age and weighed 223-346 gm at initiation of the study.

Mode of Administration/Dosage Levels: Doses of 50, 100, and 200 mg/kg/day were given orally, by gavage, to three groups of 25 mated females each on gestational days 6 through 17. An additional group of 25 mated females received the vehicle (water) at a dosing volume of 5 ml/kg and served as the control. The dosage levels were selected based on an oral range-finding study (#90-702-1) in pregnant rats in which treatment-related decreases ($P \leq 0.05$) in mean maternal body weight gain were observed in the 225 (18.1%) and 300 (23.2%) mg/kg/day groups from days 6 through 18 of gestation.

Observations/Measurements: All animals were observed for physical signs once daily on day 0 and on days 6 through 20 of gestation. Body weights were recorded on days 0, 6, 8, 10, 12, 14, 16, 18, and 20 of gestation. Food consumption was measured on every third day beginning on day 3 of gestation. Females were killed on day 20 of gestation, uterus was examined to determine reproductive status and the number of corpora lutea were counted. A gross examination of thoracic, pelvic, and abdominal viscera was done on all sacrificed females. All fetuses were weighed, sexed, and examined externally. One third of the fetuses in each litter and all externally malformed fetuses were examined for visceral alterations. All fetuses were examined for skeletal alterations.

Results: There were no treatment-related physical signs, deaths, abortions or gross lesions observed at necropsies. There was no effect on average maternal body weight gain in the 50 and 100 mg/kg/day groups. In the 200 mg/kg/day group there was a significant ($P \leq 0.05$) 21.4% treatment-related decrease in average maternal body weight gain from gestational day 6 to gestational day 18. In the postdosing interval of days 18 to 20 of gestation there was a significant ($P \leq 0.05$) increase (13.5%) in average maternal body weight gain. There was no evidence of developmental toxicity based on postimplantation survival, fetal weight, and external, visceral, or skeletal examination.

The no-observed-effect dose level in this study for maternal toxicity was 100 mg/kg/day, and for developmental toxicity was >200 mg/kg/day.

3.4.4. Oral Developmental Toxicity Study in Rats With Postweaning Evaluation

Location of Data: Vol 19, Tab C-7

Testing Facility: Department of Safety Assessment, Merck Sharp & Dohme Research Laboratories, Merck & Co., Inc., West Point, PA

Study No.: TT #91-727-0

Study Dates: Initiated: September 16, 1991
Terminated: January 7, 1992

GLP Compliance: Studies were done in accordance with GLP regulations.

Animals: Female Sprague-Dawley (CrI:CD BR) rats from Charles River Laboratories were 10 weeks of age and weighed 220-299 gm at initiation of the study.

Mode of Administration/Dosage Levels: Doses of 5, 20, and 100 mg/kg/day were given orally, by gavage, to three groups of 20 mated females each on gestational days 6 to 15. An additional group of 20 mated females received the vehicle (water) at a dosing volume of 5 ml/kg and served as the control.

Observations/Measurements: All animals were observed for physical signs once daily on gestation day 0, from gestation day 6 through end of gestation, and on days 0, 3, 7, 10, 14, and 17 of lactation. Body weights were recorded on days 0, 6, 8, 10, 12, 14, 16, 18, 20 and 22 of gestation and days 0, 3, 7, 10, 14, 17 and 21 of lactation. Food consumption was measured gestation days 3-5, 6-8, 9-11, 12-14, 15-17, 18-20, and lactation days 1-5, 8-12, 12-16 and 16-20. Females which delivered were killed between days 23 and 27 postpartum, uterine metrial glands were counted, and gross necropsies (limited to thoracic and abdominal viscera) performed.

All F₁ pups were counted, examined externally for malformations, weighed and sexed on

postnatal day 0. On postnatal day 3, litters were reduced to 4 males and 4 females. Selected pups from each litter (2 males and 2 females) were tested on postnatal days 2, 4, and 6 for surface righting reflex and on postnatal days 11, 12, and 13 for auditory startle reflex. Approximately on postnatal days 23 to 27, the same animals, when possible, were removed and housed separately for postweaning examinations. They were observed daily and body weights were recorded once a week from weaning until breeding or termination. Testicular descent was recorded on postnatal day 39 and preputial separation on postnatal days 39, 43, and 47. Vaginal canalization was recorded on postnatal days 31, 34, and 37. Behavioral tests (swimming maze on days 61 to 70 and open field motor activity on days 82 to 84) were performed on one male and one female animal from each litter. Of 1140 live F₁ pups examined externally, 238 pups were necropsied. One male and one female per litter from 10 litters in each group were necropsied on postnatal days 0 to 3 (9 litters were examined in 5 mg/kg/day group), 21 and 86 of life for gross and histological examination of the kidneys. Animals used in postweaning studies were sacrificed at 13 weeks of age.

Results: There were no treatment-related physical signs, deaths, abortions or gross lesions observed at necropsy of the F₀ females. There was no effect on average maternal body weight gain or food consumption during gestation or lactation. There were no treatment-related effects on reproductive performance as assessed by mean implants/female or live pups/litter. However, there was a very slight but statistically significant ($P \leq 0.05$) decrease (5.8%) in postimplantation survival in the high dose group (Table 3.4.4.1). The decrease is in part due to one female which had 7 pups and 12 metrial glands (a 58.3% postimplantation survival). This slight decrease, according to the sponsor, is not considered treatment-related because similar decreases were not observed in two previous studies in rats (see section # 3.4.2 and 3.4.3). There was no effect of treatment on F₁ pup survival, physical signs, body weights, or malformations based on external examinations. There was no treatment-related effect on developmental signs or behavioral tests. Also no drug-related gross or microscopic kidney pathology was observed in F₁ rats examined on days 0-3, 21 or 86 of life.

In conclusion, treatment of rats with up to 100 mg/kg/day of losartan from day 6 to day 15 of gestation had no adverse effects on the dams during gestation and lactation and no effect on the F₁ generation as assessed by mortality, physical signs, weight gain, external examinations, developmental signs, behavioral tests and gross or microscopic kidney morphology.

TABLE 3.4.4.1

REPRODUCTIVE PERFORMANCE OF F₀ FEMALES AND SUMMARY OF STATUS OF F₁ GENERATION PRIOR TO WEANING. TT #91-727-0

	CONTROL	5 MG/KG/DAY	20 MG/KG/DAY	100 MG/KG/DAY
PARENTAL FEMALES, F ₀	19	19	18	20
IMPLANTS PER FEMALE	16.4	15.6	17.7	15.6 ^{NS}
% POSTIMPLANTATION SURVIVAL (L.M.)	93.4	95.3	90.4 ^{NS}	88.0 ^S
FEMALES WITH LIVE PUPS DAY 0 POSTPARTUM	19	19	18	20
FEMALES WITH LIVE PUPS DAY 21 POSTPARTUM	19	19	18	20
TOTAL PUPS (FEMALES/MALES)	297 (146/150)	284 (144/140)	293 (158/135)	278 (133/145)
LIVE PUPS ON POSTNATAL DAY 0	292 (144/148)	283 (143/140)	289 (156/133)	276 (131/145)
DEAD PUPS ON POSTNATAL DAY 0	5 ^a (2/2)	1 (1/0)	4 (2/2)	2 (2/0)
LIVE PUPS PER LITTER (% LIVE, L.M.)	15.4 (98.1)	14.9 (99.7)	16.1 (98.5)	13.8 ^{NS} (99.3)
LIVE PUPS AFTER CULLING ON POSTNATAL DAY 3	152	152	144	160
PUP DEATHS (% PUP DEATHS) (L.M.)				
POSTNATAL DAYS 1-3	4 (1.2)	1 (0.4)	2 (0.7)	1 (0.3) ^{NS}
POSTNATAL DAYS 4-7	0 (0.0)	0 (0.0)	2 (1.4)	0 (0.0)
POSTNATAL DAYS 8-14	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
POSTNATAL DAYS 15-21	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
POSTNATAL DAYS 4-21	0 (0.0)	0 (0.0)	2 (1.4)	1 (0.6) ^{NS}
LIVE PUP WEIGHT (GM) (L.M.), M/F				
POSTNATAL DAY 0 ^b	6.4/6.1	6.8 ^{NS} /6.4	6.9 ^S /6.4 ^{NS}	7.1 ^S /6.6 ^S
POSTNATAL DAY 7 ^b	18.4/17.5	19.3/18.3	18.3/17.7	19.5 ^{NS} /18.2 ^{NS}
POSTNATAL DAY 14 ^c	37.4/36.2	39.1/37.3	37.7/36.2	38.3 ^{NS} /36.2 ^{NS}
POSTNATAL DAY 21 ^c	60.2/57.9	63.7/60.9	61.5/58.9	63.6 ^{NS} /59.6 ^{NS}

Total includes pups for which sex could not be determined

(L.M.) = Litter Mean

NS = Trend not statistically significant ($p > 0.05$) through indicated dose.S = Trend statistically significant ($p \leq 0.05$) through indicated dose.^a = Includes one pup that was dead before delivery was complete and was then missing on day 0 of lactation.^b = Statistical analysis was performed with an adjustment for length of gestation and number of the live pups per litter on postnatal day 0.^c = Statistical analysis was performed with an adjustment for length of gestation.

3.4.5. Oral Late Gestation and Lactation Study in Rats

Location of Data: Vol 21, Tab C-16

Testing Facility: Department of Safety Assessment, Merck Sharp & Dohme Research Laboratories, Merck & Co., Inc., West Point, PA

Study No.: TT #90-727-0

Study Dates: Initiaied: August 13, 1990
Terminated: January 5, 1991

GLP Compliance: Studies were done in accordance with GLP regulations. Animals: Female Sprague-Dawley (CrI:CD BR) rats from Charles River Laboratories were 10 weeks of age and weighed 218-313 gm at initiation of the study.

Mode of Administration/Dosage Levels: Dosage levels of 10, 25, and 100 mg/kg/day were given orally, by gavage, to three groups of 20 females each from gestation day 15 to lactation day 20. An additional group of 20 females received the vehicle (water, 5 ml/kg) and served as the control.

Observations/Measurements: All animals were observed for physical signs once daily on gestation days 0, 7 and 15 through sacrifice. Body weights were recorded on gestation days 0, 7, 15, 16, 18, 20 and 22; and lactation days 0, 3, 7, 10, 14, 17 and 21. Food consumption was measured on gestation days 8-12 and 15-19; and lactation days 1-5 and 8-12. Females which delivered were killed between lactation days 23 and 27, uterine metrial glands were counted, and gross necropsies (limited to thoracic and abdominal viscera) performed.

All F₁ pups were counted, examined externally for malformations, weighed and sexed on postnatal day 0. On postnatal day 3, litters were reduced to 4 males and 4 females. Two pups per sex from each litter were tested on postnatal days 2, 4 and 6 for surface righting reflex and on postnatal days 11, 12 and 13 for auditory startle reflex. The same animals, when possible, were used for postweaning examinations. They were observed daily for mortality and twice weekly for physical signs. Body weights were recorded once a week from weaning until breeding or termination. Testicular descent was recorded on postnatal day 39 and preputial separation on postnatal days 39, 43, and 47. Vaginal canalization was recorded on postnatal days 31, 34, and 37. Behavioral tests (swimming maze on days 61 to 69 and open field motor activity on days 75 to 79) were performed on one male and one female animal from each litter.

During postweaning week 9, one female and one male per litter were caged together for a maximum of 16 nights for mating. Non-selected pups were euthanized and discarded without further examination. All males used for mating were sacrificed after most females had completed delivery and the testes and epididymides were examined for gross changes and

weighed. Histomorphologic examination was performed on testes and epididymides from the control and high dose groups. All F₁ females which mated were weighed on gestation days 0, 7, 14, 20, and after natural delivery on lactation day 0. F₁ females which delivered were euthanized between lactation day 0 and 5 and the uterine metrial glands counted. The F₂ pups were counted, weighed, sexed, examined for external malformations, and mortality noted on postnatal day 0. All pups were killed within 5 days thereafter and discarded without further examination.

Results: There were no treatment-related physical signs, deaths, abortions or gross lesions observed at necropsy of the F₀ females. There was no effect of treatment on average maternal body weight gain from gestation day 15 to gestation day 20 or during lactation in the 10 and 25 mg/kg/day groups. However, in the 100 mg/kg/day group, average maternal body weight gain from gestation day 15 to gestation day 20 was 16.7% below control ($P \leq 0.05$) and weight gain during lactation was 20.6% below control ($P \geq 0.05$). Effects on food consumption were limited to the 100 mg/kg/day group, for which average food consumption on days 9 to 12 of lactation was 12.1% below control ($P \leq 0.05$). There were no treatment-related effects on reproductive performance of F₀ females (Table 3.4.5.1).

A significant treatment-related increase in pup mortality was observed in the 100 mg/kg/day group on postnatal days 1 to 3 (Table 3.4.5.1). There were statistically significant ($P \leq 0.05$) treatment-related decreases in pup weights during lactation in all dose groups which were, in general, time and dosage dependent and considered treatment-related. Table 3.4.5.1 gives both actual body weight and percent decrease in weights compared to controls. The magnitude of the difference from control in the 25 and 100 mg/kg/day groups is similar to that observed in a previous (female) fertility study (see section 3.4.2) at the same doses. No explanation was, however, advanced for the weight decrease being more severe in the 10 mg/kg/day group than in the 25 mg/kg/day group.

There were no treatment-related malformations or variations in F₁ pups. From weaning until postnatal day 27, there were four deaths of F₁ rats in the 100 mg/kg/day group. All of these rats had lower body weight than littermates at or near the time of death. This incidence of postweaning mortality (2.8%) is similar to that observed in a previously conducted fertility study in female rats (2.7%) at this dosage level (see section 3.4.2). The sponsor attributes these deaths to treatment. During the postweaning weeks 1-8, there were no treatment-related effects on average F₁ body weight gain in the 10 and 25 mg/kg/day groups. In the 100 mg/kg/day group, there was a treatment-related significant difference in body weight gain for both males and females. At postweaning week 1, both male and female F₁ rats had 17-18% lower average body weight than controls. During the next seven weeks, body weight of males but not females in the 100 mg/kg/day group caught up to body weight of controls. During postweaning weeks 9-13, there was no significant effect on average body weight gain in both males and females. There was no effect of treatment on physical and behavioral development. The reproductive performance of the F₁ generation was not significantly different from the control. There were no effects of treatment on F₂ mortality, weight, or external appearance.

TABLE 3.4.5.1
SUMMARY OF STATUS OF F₁ GENERATION PRIOR TO WEANING. TT #90-727-0

	CONTROL	10 MG/KG/DAY	25 MG/KG/DAY	100 MG/KG/DAY
PARENTAL FEMALES, F ₀	20	20	20	20
LENGTH OF GESTATION (DAYS)	22.1	21.9	22.2	22.2 ^{NS}
IMPLANTS PER FEMALE	16.5	15.6	16.1	14.8
% POSTIMPLANTATION SURVIVAL	93.6	97.3	94.0 ^{NS}	89.3 ^S
FEMALES WITH LIVE PUPS DAY 0 POSTPARTUM DAY 21 POSTPARTUM	20 20	20 19	20 20	20 19
TOTAL PUPS (FEMALES/MALES) LIVE PUPS ON PND 0 DEAD PUPS ON PND 0	315 (170/145) 310 (167/143) 5 (3/2)	305 (155/150) 302 (154/148) 3 (1/2)	309 (142/167) 303 (141/162) 6 (1/5)	274 (129/145) 265 (123/142) 9 (6/3)
LIVE PUPS PER LITTER, L.M. (% LIVE PUPS)	15.5 (98.5)	15.1 (99.1)	15.2 ^{NS} (98.1)	13.2 ^S (95.4)
LIVE PUPS AFTER CULLING ON PND 3	160	160	160	152
PUP DEATHS, L.M. (% PUP DEATHS) POSTNATAL DAYS 1-3 POSTNATAL DAYS 4-7 POSTNATAL DAYS 8-14 POSTNATAL DAYS 15-21 POSTNATAL DAYS 4-21	1 (0.3) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0)	4 (1.2) 9 (5.6) 8 (5.0) 0 (0.0) 17 (10.6)	4 (1.2) ^{NS} 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0)	6 (6.4) ^S 3 (2.0) 3 (2.0) 2 (1.3) 8 (5.3) ^{NS}
LIVE M/F PUP WEIGHT (GM), (L.M.), (%) ^c POSTNATAL DAY 0 ^a POSTNATAL DAY 7 ^a (%) ^f POSTNATAL DAY 14 ^b POSTNATAL DAY 21 ^b	6.5/6.2 18.1/17.4 37.0/35.7 59.6/57.5	6.5/6.2 16.5 ^S (8.9)/15.7 ^S (9.8) ^S 33.6 ^S (9.2)/32.3 ^S (9.6) ^S 53.9 ^S (9.6)/51.4 ^S (10.7) ^S	6.8 ^{NS} /6.5 ^{NS} 17.4 ^S (3.9)/16.7 ^S (4.1) 35.4 ^S (4.4)/34.1 ^S (4.5) 56.4 ^S (5.4)/54.5 ^S (5.3)	6.6 ^S (1.6) ^S /6.2 ^S (0) ^{NS,C} 16.2 ^S (10.5)/15.7 ^S (9.8) 32.2 ^S (13.0)/31.2 ^S (12.7) 47.9 ^S (19.7)/46.4 ^S (19.4)

(L.M.) = Litter Mean. M = Male. F = Female. PND = Postnatal day.

NS = Trend not statistically significant ($p > 0.05$) through indicated dose. S = Trend statistically significant ($p \leq 0.05$) through indicated dose.

a = Statistical analysis was performed with an adjustment for length of gestation and number of the pups/litter on postnatal day 0. b = Statistical analysis was performed with an adjustment for length of gestation. c = % Decrease in body weight compared to controls.

% Postimplantation survival = live pups on postnatal day 0/metrial glands x 100.

In conclusion, maternal toxicity was limited to the 100 mg/kg/day group and was expressed as decreased average body weight gain during gestation and lactation and decreased food consumption during lactation. Developmental toxicity was expressed in F₁ pups as decreased body weights in all dose groups from lactation day 7 to lactation day 21. There was also a slight but significant increase in pup deaths on postnatal days 1 to 3 in the high dose group and a treatment-related increase in deaths postweaning in this group. The body weight gain in the 100 mg/kg/day group during the postweaning period (weeks 1 to 8) was significantly less than control. The observations made in this study (i.e. decreased pup weights and increased pre and postweaning deaths in the high dose groups) are comparable to those observed earlier with the segment I study (see section 3.4.2). This indicates that the effects observed in the fertility study were due to exposure during late gestation and/or lactation.

3.4.6. Fostering/Cross-Fostering Study in Rats

Location of Data: Vol 21, Tab C-17

Testing Facility: Department of Safety Assessment, Merck Sharp & Dohme Research Laboratories, Merck & Co., Inc., West Point, PA

Study No.: TT #91-710-0

Study Dates: Initiated: March 10, 1991
Terminated: July 16, 1991

GLP Compliance: Studies were done in accordance with GLP regulations.

Animals: Female Sprague-Dawley (CrI:CD BR) rats from Charles River Laboratories were 12 weeks of age and weighed 228-353 gm at initiation of the study.

Mode of Administration/Dosage Levels: Since the previous study documented developmental toxicity, the present study was designed to further evaluate the association of treatment of F₀ females during late gestation and lactation or lactation only on growth, development, and behavior of the F₁ generation. Losartan was administered by oral gavage to a group of 50 mated females from day 15 of gestation to day 20 of lactation at a dose of 100 mg/kg/day. An additional group of 50 females received the vehicle (water), at a dosing volume of 5 ml/kg and served as the control. As soon after delivery as possible: 15 litters of control pups were fostered by control dams (CxC) and 15 litters were fostered by drug-treated dams (CxT); 15 litters of pups from drug-treated dams were fostered by control dams (TxC) and 15 litters were fostered by drug-treated dams (TxT).

Observations/Measurements: All animals were observed for physical signs once daily on gestation days 0 to 15 and twice daily during dosing from gestation day 15 to sacrifice. Body weights were recorded on gestation days 0, 7, 15, 16, 18, 20, 22 and 24, and lactation days 0, 3, 7, 10, 14, 17 and 21. Food consumption was not measured. Dams which delivered pups but

could not be used for cross fostering and dams that did not deliver were sacrificed on postnatal day 0 and gestation days 19 to 23, respectively. Females which were used to rear fostered litters were sacrificed between postnatal days 24 and 27 and numbers of metrial glands were recorded. All dams were given a gross examination of the thoracic and abdominal viscera. Excess litters were sacrificed and discarded on postnatal day 0 after litter weights were recorded.

The F₁ pups were counted, examined externally, weighed and sexed on postnatal day 0. On postnatal day 3, litters were sexed again and reduced to 4 males and 4 females. Body weights were recorded on postnatal days 7, 14 and 21. Two pups per sex from each litter were tested on postnatal days 2, 4 and 6 for surface righting reflex and on postnatal days 11, 12 and 13 for auditory startle reflex. On postnatal day 21, the same animals were removed and housed separately for postweaning examinations. Remaining pups were euthanized on the same day and one male and one female/litter from 10 litters per group were necropsied. Terminal body weights and heart weights were recorded for all pups. The study pups were observed daily for mortality and twice weekly for physical signs. Body weights were recorded once a week from weaning until termination. Testicular descent was recorded on postnatal day 39 and preputial separation on postnatal days 39, 43, and 47. Vaginal canalization was recorded on postnatal days 31, 34, and 37. Behavioral tests (swimming maze on days 56 to 64 and open field motor activity on days 70 and 71) were performed on one male and one female from each litter. F₁ adults were sacrificed at approximately 90 days of age. One male and one female per litter from 10 litters in each of the 4 treatment groups were necropsied. Body, brain and heart weights were recorded and kidneys were taken for histologic examination. Rest of the animals were discarded without further examination.

Results: There were no treatment-related physical signs, deaths or abortions in F₀ females. There was a significant treatment-related decrease (-9%) in average maternal body weight gain from gestation day 15 to gestation day 20 as compared to controls. However, there were no treatment-related effects on mean body weight gain during lactation. There were no treatment-related effects on reproductive performance of F₀ females, on pup survival, externally visible malformations or variations, or pup weights prior to cross-fostering on postnatal day 0.

A significant treatment-related increase in pup deaths was observed on postnatal days 1 to 3 in the groups treated with losartan (i.e., CxT and TxT) (Table 3.4.6.1). Treatment-related effects on survival were not observed between postnatal days 4 and 21. One male rat in the TxC group was found dead on postnatal day 39, and that death was considered related to treatment. On postnatal day 7 there was a statistically significant ($P \leq 0.05$) treatment-related decrease in pup body weights associated with postnatal treatment (i.e., CxT and TxT) for males (approximately 8.9%) and females (approximately 8.2%)(Table 3.4.6.1). There was a statistically significant, treatment-related effect of pre and postnatal administration of losartan to dams on the response of female pups in the surface righting test. Female pups of dams treated with losartan prenatally (TxC and TxT) had an earlier estimated day of occurrence (4.27 versus 4.9) than those from dams not treated during the prenatal period (CxC and CxT).

TABLE 3.4.6.1
SUMMARY OF STATUS OF F1 GENERATION PRIOR TO WEANING. TT #91-710-0

FOSTERING/CROSS-FOSTERING GROUPS⇒	CONTROL/ CONTROL ¹	CONTROL/ 100 MG/KG/DAY ²	100 MG/KG/DAY/ CONTROL ³	100 MG/KG/DAY/ 100 MG/KG/DAY ⁴
PARENTAL FEMALES	15	15	15	15
FEMALES WITH LIVE PUPS DAY 0 POSTPARTUM	15	15	15	15
FEMALES WITH LIVE PUPS DAY 21 POSTPARTUM	15	15	15	14
TOTAL PUPS (FEMALES/MALES)	150 (78/72)	150 (76/74)	147 (71/76)	147 (75/72)
LIVE PUPS ON POSTNATAL DAY 0	150 (78/72)	150 (76/74)	147 (71/76)	147 (75/72)
DEAD PUPS ON POSTNATAL DAY 0	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)
LIVE PUPS PER LITTER*	10.0	10.0	9.8	9.8
% LIVE PUPS (L.M.)	100.0	100.0	100.0	100.0
LIVE PUPS AFTER CULLING ON POSTNATAL DAY 3	120	120	119	119
PUP DEATHS, L.M. (% PUP DEATHS)				
POSTNATAL DAYS 1-3	2 (1.0) ^{NS}	3 (11) ^{S(b)}	0 (0.0) ^{NS}	6 (2.6) ^{S(b)}
POSTNATAL DAYS 4-7	2 (1.7)	8 (6.7)	7 (5.8)	13 (11.1)
POSTNATAL DAYS 8-14	1 (0.0)	0 (0.0)	2 (1.7)	4 (3.3)
POSTNATAL DAYS 15-21	1 (0.8)	0 (0.0)	1 (0.8)	0 (0.0)
POSTNATAL DAYS 4-21	3 (2.5) ^{NS}	8 (6.7) ^{NS}	10 (8.3) ^{NS}	17 (14.4) ^{NS}
LIVE PUP WEIGHT (GM, L.M.) (M/F)				
POSTNATAL DAY 7	17.1 ^{NS} /16.1 ^{NS}	15.8 ^{S(b)} /14.8 ^{S(b)}	16.8 ^{NS} /16.1 ^{NS}	15.1 ^{S(a)} /14.5 ^{S(b)}
POSTNATAL DAY 14	34.6 ^{NS} /33.2 ^{NS}	33.9 ^{NS} /32.1 ^{NS}	34.2 ^{NS} /32.4 ^{NS}	33.1 ^{NS} /31.6 ^{NS}
POSTNATAL DAY 21	57.5 ^{NS} /55.4 ^{NS}	56.2 ^{NS} /52.8 ^{NS}	51.1 ^{S(a)} /49.2 ^{S(a)}	51.9 ^{S(a)} /49.1 ^{S(b)}

1: control pups fostered by control dams; 2: control pups fostered by drug-treated dams; 3: pups from drug-treated dams fostered by control dams; 4: pups from drug-treated dams fostered by dams receiving drug. (L.M.) = litter mean

a = difference from the control group is not statistically significant ($p > 0.05$), based on the analysis defined in the text and appendix.

Ns = difference from the control group is not statistically significant ($p > 0.05$), based on the analysis defined in the text and appendix.

S^(a) = statistically significant ($p \leq 0.05$) Prenatal effect.

S^(b) = statistically significant ($p \leq 0.05$) Postnatal effect.

Females pups from dams treated with losartan during lactation (CxT and TxT) also had an earlier estimated day of occurrence (4.23 *versus* 4.93) than those from dams not treated during lactation (CxC and TxC). There was a statistically significant, treatment-related postnatal effect of losartan on the auditory startle response of the female pups. Female pups fostered to drug-treated dams (CxT and TxT) had a later estimated day of occurrence (13.31) than those with no postnatal treatment (CxC and TxC) (12.98). For the male pups there were no statistically significant treatment effects on surface righting or auditory startle response.

A significant ($P \leq 0.05$) interaction between prenatal and postnatal treatment in preputial separation was observed. Pups from dams which received losartan during gestation displayed preputial separation later (estimated day of occurrence 45.4) if fostered by drug treated dams during lactation (TxT) than if fostered by control females (TxC) (estimated day of occurrence 43.9). This observation was not made in earlier reproduction studies (see sections 3.4.2 and 3.4.5). There were no effects of treatment on vaginal canalization, testes descent, or open field activity. There was a statistically significant ($P \leq 0.05$) prenatal effect on the performance of males in the first swim maze trial. Pups from dams who received losartan during gestation required more trials to perform the first swim maze (7.07) than those whose natural mother received the control treatment (5.35). However, in the second swim maze, there was a statistically significant ($P \leq 0.05$) effect associated with postnatal administration of losartan in that male pups whose foster mothers received losartan during lactation required fewer trials to perform the second test than those fostered by control-treated dams. On the other hand, female pups from the CxT group took more trials to complete the second swim maze (not significant in the performance of the first swim maze) than female pups from the CxC group (see Table 3.4.6.2). The toxicologic significance of these sexually dimorphic effects on swim maze performance with high doses of losartan is not clear though effects on swim maze performance were observed in a previous late gestation and lactation study (section 3.4.5).

There was a decrease in group mean terminal body weights and cardiac weights in 21 day old male and female pups of dams which had been treated with losartan during gestation. The effect was greater when these pups were fostered by drug-treated dams (Table 3.4.6.3). These changes were not observed at 90 days of age.

At necropsy of the F_1 offspring (on postnatal day 21), 4/30 TxC pups (13.3%), and 1/26 TxT pups (3.8%) had unilateral or bilateral dilation of the renal pelvis suggesting that the effect observed here is related to *in utero* exposure rather than to neonatal exposure. Drug-induced medial hypertrophy of intracortical renal arterioles was observed in pups from the TxC (100%) and TxT (90%) groups but not from the CxT group. Electronmicroscopically, the hypertrophied myocytes contained structures compatible with renin granules in greater numbers than in controls. Further, there appeared to be hyperplasia of myocytes in vessels in the absence of an increase in granule content.

Considering the distribution of renin-producing cells in rats of this age, it would appear that the vascular changes noted were the result of drug-induced inhibition of angiotensin II

TABLE 3.4.6.2
SUMMARY OF SWIM MAZE TESTING OF F1 GENERATION. TT #91-710-0

FOSTERING/CROSS-FOSTERING GROUPS ¹ →	CONTROL/CONTROL		CONTROL/ 100 MG/KG/DAY		100 MG/KG/DAY/ C TROL		100 MG/KG/DAY/ 100 MG/KG/DAY	
	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
DAYS 56 TO 57 POSTNATAL								
NO. ANIMALS TESTED	15	15	15	15	15	15	14	14
MEAN TRIALS TO CRITERION - TEST 1	5.6 ^{NS}	6.2 ^{NS}	5.7 ^{NS}	5.9 ^{NS}	7.0 ^{S(a)}	5.9 ^{NS}	7.9 ^{S(a)}	6.4 ^{NS}
DAYS 63 TO 64 POSTNATAL								
NO. ANIMALS TESTED	15	15	15	15	15	15	14	14
MEAN TRIALS TO CRITERION - TEST 2	5.4 ^{NS}	5.8 ^{NS}	4.3 ^{S(b)}	9.1 ^{S(c)}	5.5 ^{NS}	7.1 ^{S(c)}	3.8 ^{S(b)}	5.9 ^{S(c)}

1: For explanation of groups see footnote in table 3.6.6.1

NS = Difference from the control group is not statistically significant ($p > 0.05$) based on the analysis defined in the text and appendix.

S^(a) = Statistically significant ($p \leq 0.05$) pre-natal effect.

S^(b) = Statistically significant ($p \leq 0.05$) post-natal effect.

S^(c) = Statistically significant ($p \leq 0.05$) for interaction between prenatal and postnatal in effect.

TABLE 3.4.6.3
AVERAGE ORGAN WEIGHTS OF F₁ WEANLINGS. TT #91-710-0

FOSTERING/CROSS-FOSTERING GROUPS ¹ ⇒	CONTROL/ CONTROL		CONTROL/ 100 MG/KG/DAY		100 MG/KG/DAY/ CONTROL		100 MG/KG/DAY/ 100 MG/KG/DAY	
	F	M	F	M	F	M	F	M
SEX								
N	28	29	28	24	24	26	22	24
BODY WEIGHT, GRAMS	56.0	56.9	52.8 ^{NS}	57.2 ^{NS}	50.4 ^S	53.4 ^S	48.8 ^S	52.0 ^S
HEART, GRAMS	0.32	0.32	0.30 ^{NS}	0.32 ^{NS}	0.26 ^S	0.28 ^S	0.26 ^S	0.26 ^S
% B.W.	0.57	0.57	0.58 ^{NS}	0.57 ^{NS}	0.53 ^S	0.53 ^S	0.54 ^S	0.51 ^S

1: For explanation of groups see footnote in table 3.4.6.1

B.W. = Body weight

NS = not statistically significantly different from control/control (p > 0.05)

S = statistically significantly different from control/control (p ≤ 0.05)

NDA 020386

FIRM:

MERCK

6 OF 10

TRADE NAME:

COZAAR (LOSARTAN POTASSIUM) 25/50 MG TAB

GENERIC NAME:

LOSARTAN POTASSIUM

resulting in hypertrophy and hyperplasia of renin-producing cells. There was no visible alteration in juxtaglomerular apparatus. Along with the arteriolar change, there were dilation of the renal pelvis (85% incidence of hydronephrosis in TxC and 65% incidence in TxT with a background incidence of about 10% in untreated controls) and edema of the renal papilla (75% incidence in TxC and 85% in TxT) (Table 3.4.6.4). While tubular dilation would be expected in association with the urodynamic alterations which caused hydronephrosis, another tubular degenerative change was also noted, characterized by "swelling" and tinctorial alteration in scattered tubular epithelia. This is a secondary effect related to hemo- and urodynamic effects on the kidney. The sponsor concludes that the vascular myohypertrophy and hyperplasia noted in these rats is related to the pharmacologic effect of losartan on renin-producing cells, but the pathophysiology of the papillary edema, tubular changes, and hydronephrosis remains unclear.

Cardiac and vascular effects disappeared with time in F₁ adults necropsied at 90 days. However, sequelae to intrauterine exposure were present: dilation of renal pelvis persisted in groups which had received prenatal treatment and was present at a much higher incidence than in controls (75-80%, similar to that seen at 21 days); edema of the renal papilla was still present in 50% of TxC and 55% of TxT; cortical tubular degeneration was seen in 5 to 35% of F₁ adults and was similar to that seen at 21 days; tubular mineralization (30% in TxC and 55% in TxT), and inflammation, apparently arising in the renal pelvis and extending centrifugally (Table 3.4.6.4). This nephritis was noted in about 38% of rats born to dams treated during gestation, but not in controls. The lesion progressed in one animal to produce severely damaged kidneys, similar to the diffuse chronic nephritis noted in aged rats.

In conclusion, average maternal body weight gain was significantly lower for treated than for control dams for the gestation day 15 to gestation day 20 period. In fostered/cross fostered F₁ pups there were a number of statistically significant treatment-related effects evident. Prenatal treatment of dams was associated with decreased pup weight on postnatal day 21 and effects on male performance in the first swim maze test. Treatment of dams during lactation increased pup deaths on postnatal days 1-3 and caused decreased pup weights on postnatal day 7. Additionally, decreased performance on the auditory startle test and second swim maze trial were observed in females. Intrauterine exposure to a high dose of losartan caused a decrease in cardiac weight which was slightly exacerbated by continued exposure during suckling. A pharmacologically-induced medial hypertrophy of small intracortical arterioles in the kidneys, as well as dilation of the renal pelvis and edema of the renal papilla, was also produced with *in utero* exposure. Further, while the cardiac and vascular effects disappeared with time, significant renal sequelae (nephritis, etc.) followed intrauterine exposure to losartan. Thus, the study indicates that losartan at a dose of 100 mg/kg/day is associated with adverse effects on pups when administered during late gestation and/or lactation.

TABLE 3.4.64
SUMMARY OF HISTOMORPHOLOGY F, RATS. TT #91-710-0

	GROUP 1		GROUP 2		GROUP 3		GROUP 4	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
R, WEANLINGS								
NO. NECROPSIED	28	29	28	23	24	26	22	24
KIDNEY								
NO. ANIMALS EXAMINED MICRO.	11	9	10	10	8	12	10	10
NUMBER NOT REMARKABLE	10	8	9	10	-	-	-	-
TUBULE, REGENERATION	-	-	-	-	5	6	6	9
PELVIS DILATATION	1	1	1	-	8	9	6	7
PAPILLA, EDEMA	-	-	-	-	6	9	9	8
ARTERIAL MEDIAL HYPERTROPHY	-	-	-	-	8	12	8	10
R, ADULTS								
NO. NECROPSIED	10	10	10	10	10	10	10	10
KIDNEY								
NO. ANIMALS EXAMINED MICRO.	10	10	10	10	10	10	10	10
NUMBER NOT REMARKABLE	9	6	9	8	-	-	-	-
TUBULE, DEGENERATION	-	-	-	-	1	2	4	3
PELVIS, DILATATION	1	4	1	2	7	2	6	10
PAPILLA, EDEMA	-	-	-	-	7	2	4	7
PAPILLA, INFLAMMATION	-	-	-	-	-	-	1	-
TUBULE, MINERALIZATION	-	-	-	-	3	3	7	4
CHRONIC NEPHRITIS	-	-	-	-	2	6	2	5

Group 1 = Control pups fostered by control dams (CxC)
 Group 2 = Control pups fostered by drug-treated dams (CxD)
 Group 3 = Pups from Drug-treated dams fostered by control dams (TxC)
 Group 4 = Pups from Drug-treated dams fostered by dams receiving drug (TxT)

3.4.7. Oral Late Gestation and Lactation Study in Rats with Renal Evaluation

Location of Data: Vol 22, Tab C-18

Testing Facility: Department of Safety Assessment, Merck Sharp & Dohme Research Laboratories, Merck & Co., Inc., West Point, PA

Study No.: TT #91-736-0

Study Dates: Initiated: December 29, 1991
Terminated: May 1, 1992

GLP Compliance: Studies were done in accordance with GLP regulations.

Animals: Female Sprague-Dawley (CrI:CD BR) rats from Charles River Laboratories were 10 weeks of age and weighed 226-315 gm at the initiation of the study.

Mode of Administration/Dosage Levels: This study is similar to previous oral late gestation and lactation study (#90-727-0, section 3.4.5) except for dosage of losartan, and observations made on selected urinary and clinical chemistry parameters, and kidney morphology of the F₁ generation. Dosage levels of 0.5, 1, 5, 20 or 100 mg/kg/day were given orally by gavage to five groups of 15 females each from gestation day 15 to lactation day 20. An additional group of 15 females received the vehicle (water) at a dosing volume of 5 ml/kg and served as the control.

Observations/Measurements: All animals were observed for physical signs once daily on gestation days 0, 7 and 15 through sacrifice. Body weights were recorded on gestation days 0, 7, 15, 16, 18, 20 and 22, and on lactation days 0, 3, 7, 10, 14, 17 and 21. Food consumption was not measured. Ten females per group which delivered were killed between lactation days 22 and 23. Females in excess of ten per group were sacrificed between lactation days 8 and 10. The uterus of each female was examined to count metrial glands, and a gross necropsy (limited to thoracic and abdominal viscera) was performed.

All F₁ pups were counted, examined externally for malformations and sexed on postnatal day 0. On postnatal day 3, litters were sexed again and reduced to 4 males and 4 females. Body weights were recorded on postnatal days 0, 7, 14 and 21. On postnatal day 21, one male and one female/litter from 10 litters per group were placed in metabolism cages at 3:30 p.m. for overnight urine collection. Next day at 7:30 a.m. the rats were removed. The volume of the urine samples and urinary creatinine, sodium and potassium were measured. The rats were sacrificed and bled for determination of serum urea nitrogen and creatinine. Kidneys were collected for histological analyses. On postnatal days 22 to 24 two males and two females per litter were removed from the dams and housed 2 per sex until postweaning week 5 when males were housed individually. Remaining non-selected pups were euthanized and discarded without further examination.

On postnatal day 91 (i.e. postweaning week 10), 1 male and 1 female rat/litter/group were placed in metabolism cages and had urine collected, and urinary creatinine, sodium, and potassium were measured. The rats were sacrificed on postnatal day 92 and bled for determination of serum urea nitrogen and creatinine. Kidneys were collected for histological analyses. During postweaning week 11, urine was collected from fasted rats (one/sex/litter/group) and analyzed for urine volume, pH, specific gravity, urobilinogen, creatinine, sodium, potassium, protein, glucose, bilirubin, occult blood, RBC, WBC, tubular and transitional epithelium and ketones.

Results: There were no treatment-related physical signs, deaths or abortions and no treatment-related gross lesions observed at necropsy of the F₀ females. There was no effect of treatment on average maternal body weight gain in the 0.5, 1.0, 5 or 20 mg/kg/day groups. In the 100 mg/kg/day group, average maternal body weight gain was 18.6% below control ($P \leq 0.05$) from gestation day 15 to gestation day 20. There were no changes in body weight gain during lactation in any dose group. There were no treatment-related effects on reproductive performance of F₀ females.

A significant ($P \leq 0.05$) treatment-related increase in pup deaths was observed in the 100 mg/kg/day group on postnatal days 1 to 3 (Table 3.4.7.1). Though the pup mortality in the high dose group was very low (2.8% *versus* 1.4% in controls), similar slight but significant increases in pup mortality were observed in two previous studies (see sections 3.4.5 and 3.4.6) at a dose of 100 mg/kg/day. At the end of the lactation period, pups of the 100 mg/kg/day group weighed significantly less ($P \leq 0.05$) than control pups (Table 3.4.7.1).

There were no treatment-related malformations or variations in F₁ pups. One female in the 100 mg/kg/day group was found dead during postweaning week 3 and that death was considered treatment-related. There were no effects on postweaning body weight gains in any group. There were no effects of treatment on urine or serum parameters in weanling pups (postnatal day 22) or in adult F₁ rats at 10 weeks postweaning at doses up to 20 mg/kg/day. In the 100 mg/kg/day group, there were treatment-related increases in urine volume and decreases in creatinine, sodium, and potassium values as compared to controls. These changes were consistent for weanling and week 10 postweaning rats (see Table 3.4.7.2). There was no effect on serum urea nitrogen or creatinine in any group with the exception of weanling males (determined on postweaning day 22) of the 100 mg/kg/day group in which mean serum urea nitrogen was increased 36% and one male had a high serum creatinine (1.3 mg/dl *versus* 0.4 to 0.7 for all other males). Also, F₁ rats in the 100 mg/kg/day group showed (determined in postweaning week 10) a slight increase in mean serum urea nitrogen (~15-20%; due to two males and three females with elevated levels) which may be treatment related.

TABLE 3.4.7.1
SUMMARY OF STATUS OF F1 GENERATION PRIOR TO WEANING. TT #91-736-0

	CONTROL	0.5 MG/KG/DAY	1.0 MG/KG/DAY	5.0 MG/KG/DAY	20.0 MG/KG/DAY	100 MG/KG/DAY
PARENTAL FEMALES (A)	13	15	14	15	15	15
IMPLANTS PER FEMALE	17.9	16.7	16.6	16.0	17.1	16.4
% POSTIMPLTN SURVIVAL (L.M.)	91.7	91.7	93.8	94.3	93.9	92.9 ^{NS}
FEMALES WITH LIVE PUPS DAY 0 POSTPARTUM DAY 21 POSTPARTUM	13 10	15 10	14 10	15 10	15 10	15 9
TOTAL PUPS (F/M) LIVE PUPS ON PN DAY 0 DEAD PUPS ON PN DAY 0	217(106/111) 214(103/111) 3(3/0)	239(122/117) 233(119/114) 6(3/3)	219(110/109) 219(110/109) 0(0/0)	227(123/104) 226(122/104) 1(1/0)	243(123/119) 241(123/118) 2(0/1)	231(123/108) 228(121/107) 3(2/1)
LIVE PUPS PER LITTER (L.M.), (%) LIVE PUPS AFTER CULLING ON PND 3	16.5 (98.7) 104	15.5 (97.9) 120	15.6 (100.0) 112	15.1 (99.6) 120	16.1 (99.1) 120	15.2 ^{NS} (98.8) 120
PUP DEATHS (L.M.), (% DEATHS) POSTNATAL DAYS 1-3 POSTNATAL DAYS 4-7 POSTNATAL DAYS 8-14 POSTNATAL DAYS 15-21 POSTNATAL DAYS 4-21	3(1.4) 0(0.0) 0(0.0) 0(0.0) 0(0.0)	2(0.8) 2(1.7) 0(0.0) 0(0.0) 2(1.7)	4(1.7) 0(0.0) 0(0.0) 0(0.0) 0(0.0)	2(0.8) ^a 0(0.0) 0(0.0) 2(0.0) 0(0.0)	4(1.7) ^{NS} 0(0.0) 0(0.0) 0(0.0) 0(0.0)	5(2.8) ^S 1(0.8) 1(0.8) 0(0.0) 2(1.7) ^{NS}
LIVE PUP WEIGHT (GM, L.M.) (M/F) POSTNATAL DAY 0 ^b POSTNATAL DAY 7 ^c POSTNATAL DAY 14 ^c POSTNATAL DAY 21 ^c	6.3/6.0 17.4/16.6 36.3/34.8 59.9/57.1	6.7/6.3 17.4/16.5 36.4/35.0 61.0/58.3	6.6/6.2 18.1/17.2 37.2/35.8 59.6/57.5	6.7/6.4 18.0/17.3 35.8/34.8 59.2/56.6	6.5 ^{NS} /6.0 ^{NS} 17.0/16.0 ^{NS} 35.2/33.2 57.7 ^{NS} /54.7 ^{NS}	6.3 ^S /6.0 ^S 17.0 ^{NS} /16.4 ^S 35.1 ^{NS} /34.4 ^{NS} 53.5 ^S /52.3 ^S

(A) = Excludes any females not surviving past day 20 of gestation. (L.M.) = Litter mean

NS = Trend not statistically significant ($p > 0.05$) through indicated dose. PND = Postnatal day. S = Trend statistically significant ($p \leq 0.05$) through indicated dose. ^aIncludes one pup that died after live weighting on day 0.

^bStatistical analysis was performed with an adjustment for length of gestation and number of live pups per litter on postnatal day 0.

^cStatistical analysis was performed with an adjustment for length of gestation.

TABLE 3.4.7.2
 AVERAGE CHANGES IN URINALYSIS VALUES FOR F₁ RATS EXPOSED TO 100 MG
 LOSARTAN/KG/DAY (PERCENT CHANGE FROM CONTROL). TT #91-736-0

Postweaning	Volume		Creatinine		Sodium		Potassium	
	F	M	F	M	F	M	F	M
Day 22	+34.5	+57.7	-48.3	-57.3	-44.4	-52.4	-46.5	-55.9
Week 10	+63.0	+62.1	-51.1	-48.6	-38.2	-60.8	-40.3	-53.4
Week 11*	+21.8	+53.1	-28.8	-43.4	-11.7	-49.0	-21.7	-36.6

*Fasted during collection period

There were no effects of treatment on morphology of the kidneys in 22- or 92-day old offspring dosed at 0.5, 1, 5, or 20 mg/kg/day. In weanlings receiving 100 mg/kg/day, edema of the renal papilla was noted in 5 of 18 animals (28%). In addition, medial hypertrophy of the renal cortical arterioles was seen in 16 of these same 18 animals (89%). Though occasional dilation of the renal pelvis is noted in this strain of rat, the animals of this group had an incidence of 83% (15 of 18) and the pelvic dilatation was thus attributed to treatment. In 92-day old rats, the pattern noted in weanlings was essentially repeated. Renal pelvic dilatation was seen in 78% (14 of 18) of animals (*versus* 15% in control) which had been exposed to 100 mg losartan/kg/day. Edema of the renal papilla was noted in 8 of 18 animals (44%). However, the arteriolar change was less prominent (seen in about one-quarter of the animals), and was replaced by chronic inflammation (44%, 8/18), characterized by cellular infiltration and irregular scarring of renal parenchyma (occasionally with mineralization) (Table 3.4.7.3). The inflammation is a sequela to disturbed renal blood- and urine flow.

As in the fostering and cross-fostering study (section 3.4.6), intrauterine exposure to a high dose of losartan caused a pharmacologically-induced medial hypertrophy of small intracortical arterioles in the kidneys, as well as dilation of the renal pelvis and edema of the renal papilla. The no observed effect dose level for these changes in this study was 20 mg/kg/day. Also, this dose was not associated with any maternal or developmental toxicity when administered during days 15 to 20 of gestation. However, in a previous late gestation/lactation study (section 3.4.5), losartan, at doses as low as 10 mg/kg/day, produced developmental toxicity. Thus all three studies (3.4.5 through 3.4.7) confirm that the critical period for adverse developmental effects, including renal toxicity, is after day 15 of gestation.

TABLE 3.4.7.3
SUMMARY OF HISTOMORPHOLOGY. TT #91-736-0

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5		GROUP 6	
	F	M	F	M	F	M	F	M	F	M	F	M
DAY 22 POSTNATAL												
NUMBER NECROPSIED	10	10	10	10	10	10	10	10	10	10	9	9
KIDNEY												
NO. ANIMALS EXAMINED MICRO.	10	10	10	10	10	10	10	10	10	10	9	9
NUMBER NOT REMARKABLE	9	10	10	10	9	8	9	9	9	9	2	-
PELVIS, DILATATION	1	-	-	-	1	2	1	1	1	1	7	8
PAPILLA, EDEMA	-	-	-	-	-	-	-	-	-	-	1	4
ARTERIOLE, MEDIAL HYPERTROPHY	-	-	-	-	-	-	-	-	-	-	7	9
DAY 92 POSTNATAL												
NUMBER NECROPSIED	10	10	10	10	10	10	10	10	10	10	9	9
KIDNEY												
NO. ANIMALS EXAMINED MICRO.	10	10	10	10	10	10	10	10	10	10	9	9
NUMBER NOT REMARKABLE	10	7	8	9	9	9	9	10	10	8	2	-
PELVIS, DILATATION	-	3	2	1	1	1	1	-	-	2	5	9
PAPILLA, EDEMA	-	-	-	-	-	-	-	-	-	-	3	5
ARTERIOLE, MEDIAL HYPERTROPHY	-	-	-	-	-	-	-	-	-	-	2	2
CHRONIC NEPHRITIS	-	-	-	-	-	-	-	-	-	-	3	5

GROUP 1 = CONTROL
 GROUP 2 = 0.5 MG/KG/DAY
 GROUP 3 = 1.0 MG/KG/DAY
 GROUP 4 = 5.0 MG/KG/DAY
 GROUP 5 = 20.0 MG/KG/DAY
 GROUP 6 = 100.0 MG/KG/DAY

3.4.8. Toxicokinetics Study in Pregnant Rats

Location of Data: Vol 37, Tab Q-7

Testing Facility: Department of Safety Assessment, Merck Sharp & Dohme Research Laboratories, Merck & Co., Inc., West Point, PA

Study No.: TT #91-718-0

Study Dates: Initiated: May 26, 1991
Terminated: June 12, 1991

GLP Compliance: Studies were done in accordance with GLP regulations.

Animals: Female Sprague-Dawley (CrI:CD BR) rats from Charles River Laboratories were 11 weeks of age and weighed 236-316 gm at initiation of the study.

Mode of Administration/Dosage Levels: Losartan was administered by oral gavage to a group of 20 mated females on days 6 to 15 of gestation at a dose of 135 mg/kg/day. An additional group of 4 mated females received the vehicle (water) at a dosing volume of 5 ml/kg and served as the control.

Observations/Measurements: All animals were observed for physical signs once daily on gestation day 0 and on day 6 through sacrifice. Body weights were recorded on gestation days 0, 6, 8, 10, 12, 14 and 15. Food consumption was not measured. On day 15 of gestation, females treated with losartan were subdivided into 5 groups for blood sample collection with 4 rats per group. The times (hours) and sites of sample collection were as follows:

Subgroup	Orbital Sinus Blood Sample (hr)	Inferior Vena Cava Blood Sample and Tissue Collection (hr)
1	0.5	5 (same animals)
2		1
3	2	7 (same animals)
4		3
5		24

Fetal and placental tissues, which were collected (at 1, 3, 5, 7 and 24 hours after treatment) from the same animals, were pooled separately by litter and the number and pooled weights of the fetuses and placentae were recorded. Control females were sampled (inferior vena cava blood, fetuses, placentae) as above on day 15.

Results: There were no physical signs, deaths, abortions or gross lesions observed in treated or control rats. There was a significant decrease (-18.9%) in average maternal body weight gain from gestation day 6 to gestation day 15 as compared to controls.

Plasma concentrations of losartan and its metabolites as a function of time are shown in Figure 3.4.8.1. The mean maternal rat plasma losartan C_{max} was 36.5 $\mu\text{g}/\text{ml}$ and occurred at one hour. By 24 hours postdose, losartan was not detectable in any maternal plasma sample. The plasma losartan AUC value was 88 $\mu\text{g}\cdot\text{hr}/\text{ml}$ and represented about 34% of the drug-related entities quantitated in the plasma. These findings suggest that losartan was rapidly absorbed in pregnant rats and was cleared relatively rapidly from the systemic circulation ($t_{1/2} \sim 3$ hours).

Pregnant rats metabolized losartan extensively and rapidly. The primary metabolite, E-3174, exhibited a C_{max} (28.9 $\mu\text{g}/\text{ml}$) at 2 hours after dosing and unlike parent compound was detectable at 24 hours postdose. The plasma E-3174 AUC value was 128.9 $\mu\text{g}\cdot\text{hr}/\text{ml}$ and represented about 50% of the drug-related materials quantitated in the plasma. Two other metabolites were also detected. The N-2-tetrazole glucuronide metabolite (L-158,783) was detected at all time periods except 24 hours. The plasma levels of this metabolite were below 1 $\mu\text{g}/\text{ml}$ and the AUC was 3.8 $\mu\text{g}\cdot\text{hr}/\text{ml}$. The third metabolite, a 'polar metabolite', appeared in some animals even at 24 hours (AUC 35 $\mu\text{g}\cdot\text{hr}/\text{ml}$) and accounted for about 14% of the drug-related materials quantitated in the plasma (Table 3.4.8.1).

Concentrations of losartan and its metabolites in rat placental and fetal tissues were substantially lower than the corresponding levels in maternal rat plasma. Generally, placental tissue to plasma (T/P) ratios were lower for both losartan and E-3174 in the early hours and increased at later time periods. Fetal concentrations of losartan and E-3174 were near the detection limit in a few instances where they were quantitated (see Table 3.4.8.2). The sponsor observes that although the N-2-tetrazole glucuronide metabolite was present in trace quantities in a few placental samples (levels not determined), it was not detectable in any fetal tissues.

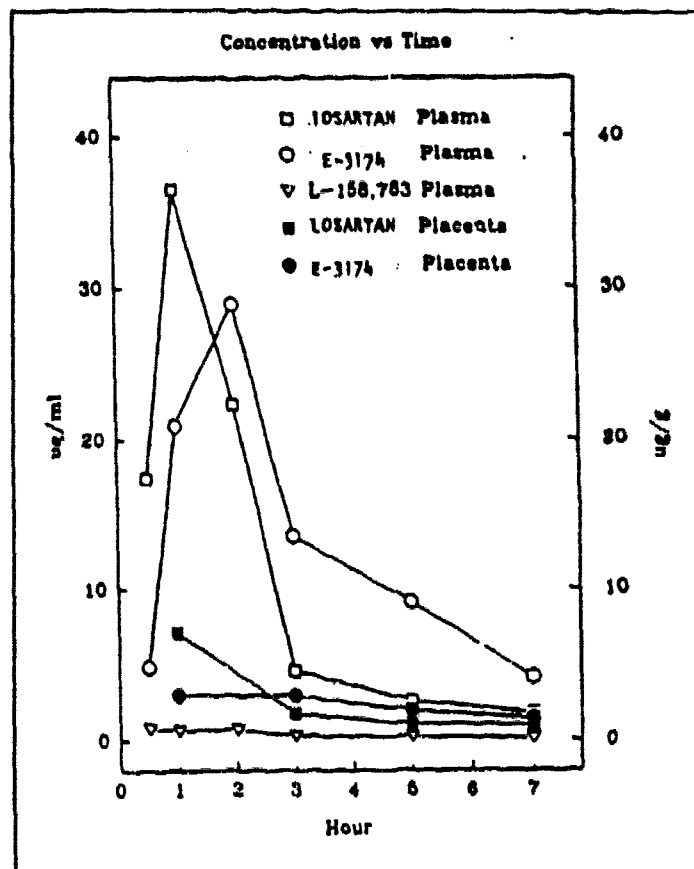


Fig. 3.4.8.1.: Mean losartan and its metabolites plasma and tissue concentrations as a function of time after dosing.

TABLE 3.4.8.1
MEAN PLASMA ($\mu\text{G}/\text{ML}$) LEVELS AND AUC OF LOSARTAN AND VARIOUS METABOLITES IN
PREGNANT RAT PLASMA. TT #91-718-0.

Hour	Losartan	E-3174	Polar metabolite	L-158,783
0.5 ^a	17.4 $\pm$ 6.25	4.82 $\pm$ 2.29	2.03 $\pm$ 0.53	0.76 $\pm$ 0.31
1	36.46 $\pm$ 10.09	20.90 $\pm$ 3.28	1.79 $\pm$ 0.61	0.66 $\pm$ 0.08
2	22.30 $\pm$ 8.80	28.93 $\pm$ 7.70	1.70 $\pm$ 0.15	0.72 $\pm$ 0.21
3	4.59 $\pm$ 0.82	13.63 $\pm$ 2.18	2.3 $\pm$ 0.36	0.29 $\pm$ 0.02
5 ^a	2.63 $\pm$ 0.49	9.14 $\pm$ 2.67	2.52 $\pm$ 0.64	0.22 $\pm$ 0.03
7	1.85 $\pm$ 0.44	4.18 $\pm$ 1.18	1.84 $\pm$ 0.37	0.13 $\pm$ 0.05
24	c	0.41 $\pm$ 0.02	0.52 $\pm$ 0.32 ^b	c
AUC ₀₋₂₄ $\mu\text{g}\cdot\text{hr}/\text{ml}$	88.0	128.9	35.0	3.8

a: Since one of the rats (n=4) was not pregnant, it was excluded from the calculation of the mean and AUC data. b: not detectable in two of the 4 animals. c: Value was below the detection limit of the method.

A comparison of the losartan AUC values for plasma and tissues indicates that placental drug content represents about 31% of the systemic drug exposure. Fetal exposure to losartan is estimated to be less than 0.3% of the drug in systemic circulation. The data suggest that very little amount of parental drug and its primary metabolite (E-3174) reach the fetus following oral dosing of losartan during day 6 to 15 of gestation.

TABLE 3.4.8.2
 LEVELS OF LOSARTAN AND E-3174 IN PLASMA, PLACENTAE AND EMBRYOS AFTER THE TENTH DOSE OF 135 MG/KG LOSARTAN.
 TT#91-718-0.

Hour	N=4	ug/ml Plasma		ug/g Placenta		T/P		ug/g Embryo		T/P	
		E-3174	Losartan	E-3174	Losartan	E-3174	Losartan	E-3174	Losartan	E-3174	Losartan
1		21.93	18.30	3.25	4.60	0.148	0.252	0.15	0.27	0.007	0.015
		11.51	19.87	1.75	4.04	0.152	0.203	*	*	**	**
		23.46	56.24	3.14	8.79	0.134	0.156	*	*	**	**
		26.70	51.45	3.88	10.87	0.145	0.211	*	0.14	**	0.003
	Mean	20.90	36.46	3.00	7.08	0.14	0.21	**	0.10	**	0.004
3		14.55	3.44	3.46	1.81	0.238	0.526	0.06	*	0.004	**
		17.01	7.02	3.89	2.52	0.229	0.359	*	*	**	**
		7.28	3.83	1.39	1.18	0.191	0.310	*	*	**	**
		15.70	4.07	3.13	1.64	0.199	0.404	0.05	*	0.003	**
	Mean	13.63	4.59	2.97	1.79	0.21	0.40	**	**	0.002	**
5		5.71	1.81	1.45	0.75	0.254	0.415	*	*	**	**
		14.38	2.58	2.88	0.97	0.200	0.374	*	*	**	**
		7.32	3.51	1.60	1.56	0.218	0.444	0.06	*	0.008	**
	Mean	9.14	2.63	1.98	1.09	0.22	0.41	**	**	**	**
	7		2.78	1.80	0.90	0.96	0.322	0.535	*	*	**
		7.68	3.12	2.45	1.17	0.319	0.374	*	*	**	**
		2.86	1.30	0.83	0.92	0.290	0.707	*	*	**	**
		3.38	1.17	1.63	1.03	0.483	0.880	0.07	*	0.020	**
Mean		4.18	1.85	1.45	1.02	0.35	0.62	**	**	**	**
24		0.42	*	0.47	0.35	1.104	**	*	*	**	**
		0.46	*	0.38	*	0.836	**	*	*	**	**
		0.43	*	0.39	0.44	0.902	**	*	*	**	**
		0.35	*	0.37	*	1.052	**	*	*	**	**
	Mean	0.41	**	0.40	0.20	0.97	**	**	**	**	**
AUC		128.9	88	31.6	27.7			**	**		

*Value was below the detection limit of the method. **Result was not calculated. T/P is the tissue-to-plasma ratio.

3.4.9. Toxicokinetics Study in Pregnant Rats

Location of Data: Vol 37, Tab Q-8

Testing Facility: Department of Safety Assessment, Merck Sharp & Dohme Research Laboratories, Merck & Co., Inc., West Point, PA

Study No.: TT #92-727-0

Study Dates: Initiated: November 2, 1992
Terminated: June 15, 1993

GLP Compliance: Studies were done in accordance with GLP regulations.

Animals: Female Sprague-Dawley (CrI:CD BR) rats from Charles River Laboratories were 11 weeks of age and weighed 221-315 gm at initiation of the study.

Mode of Administration/Dosage Levels: Losartan was administered by oral gavage to a group of 24 mated females on days 15 to 20 of gestation at a dose of 135 mg/kg/day. An additional group of 4 mated females received the vehicle (water) at a dosing volume of 5 ml/kg and served as the control.

Observations/Measurements: All animals were observed for physical signs once daily (1-5 hours dosing) on gestation days 0 and 7 and day 15 through sacrifice. Body weights were recorded on gestation days 0, 7, 15, 16, 18 and 20. Food consumption was not measured. On day 20 of gestation, blood samples (1 ml) from the inferior vena cava were collected at 1, 2, 3, 5, 7 and 24 hr postdose (n=3 rats/time point). Fetal blood samples (minimum of 0.5 ml/litter) were collected from the umbilical vessels. Fetal plasma samples were pooled by litter. The number of live fetuses per litter was recorded, and dams were discarded without further examination. Fetuses were sacrificed by exsanguination.

Results: There were no physical signs, deaths, abortions or gross lesions observed in treated or control rats. There was a treatment-related decrease (-11.3%) in average maternal body weight gain from gestation day 15 to gestation day 20 as compared to controls. Losartan had no apparent effect on fetal survival as indicated by the number of live fetuses per pregnant female (16.9 for treated group vs. 16.3 for control group).

The mean maternal plasma losartan C_{max} was 64.7 $\mu\text{g/ml}$ and occurred at approximately two hours postdose. Losartan was cleared from the maternal plasma compartment with a half-life of 5 hours and the mean concentration at 24 hour (0.48 $\mu\text{g/ml}$) was less than 1% of the mean C_{max} concentration. The mean peak fetal plasma losartan concentration of 4.07 $\mu\text{g/ml}$ also occurred at 2 hours postdose. Losartan was cleared from the fetal plasma compartment with a half-life value of about 8 hours (Fig. 3.4.9.1). Maternal and fetal plasma losartan concentrations were nearly equal at 24 hours postdose.

The losartan AUC values for maternal and fetal plasma were 194.8 and 50.7 $\mu\text{g}\cdot\text{hr}/\text{ml}$, respectively. The data indicate that the drug is readily available to the fetus and that the drug clearance from the fetal and maternal plasma compartments are comparable.

Pregnant rats metabolized losartan extensively and rapidly. The primary metabolite, E-3174, exhibited a mean maternal plasma C_{max} (38.97 $\mu\text{g}/\text{ml}$) at 3 hours after dosing (Fig. 3.4.9.2). The maternal plasma E-3174 half-life was estimated from the mean data to be about 4 hours. Though its concentration was lower than the parent drug losartan in the early hours of dosing, the AUC of E-3174 was approximately 1½ times higher than the mean maternal plasma AUC of parent drug (Table 3.4.9.1). Significant E-3174 levels were detected in the fetal plasma. The mean concentrations remained relatively constant (~ 6 $\mu\text{g}/\text{ml}$) for all the time points studied. This suggests a steady-state level of E-3174 was attained in the fetal compartment upon repeated dosing and that the fetus acts as a deep compartment for this metabolite. The relatively high concentration of E-3174 in the fetal compartment may explain, in part, the developmental toxicity observed during late gestation in pregnant rats.

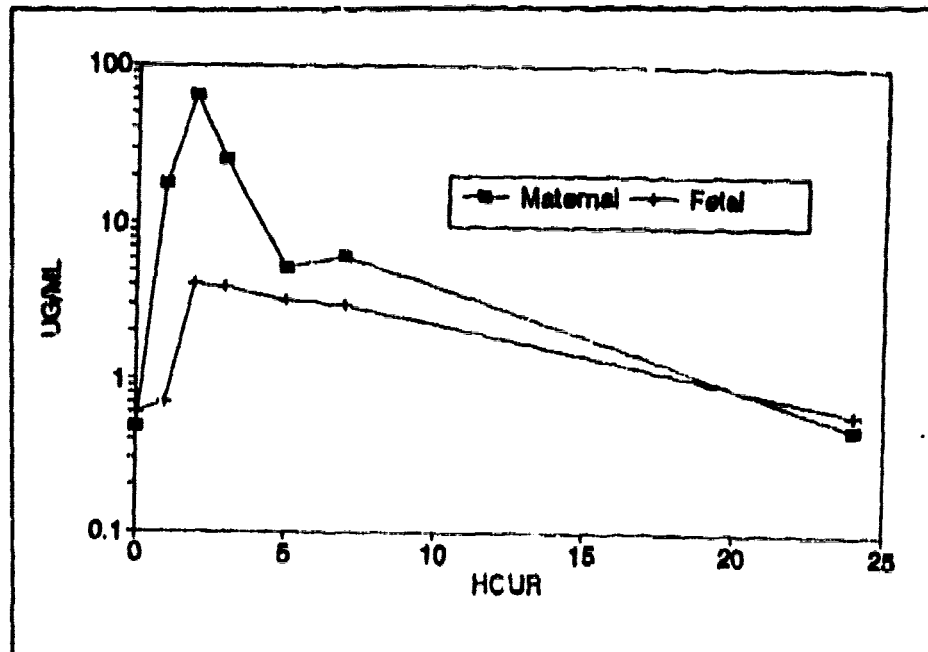


Fig. 3.4.9.1.: Mean losartan plasma levels in pregnant rats following oral dosing with losartan at 135 mg/kg/day during gestation days 15 through 20.

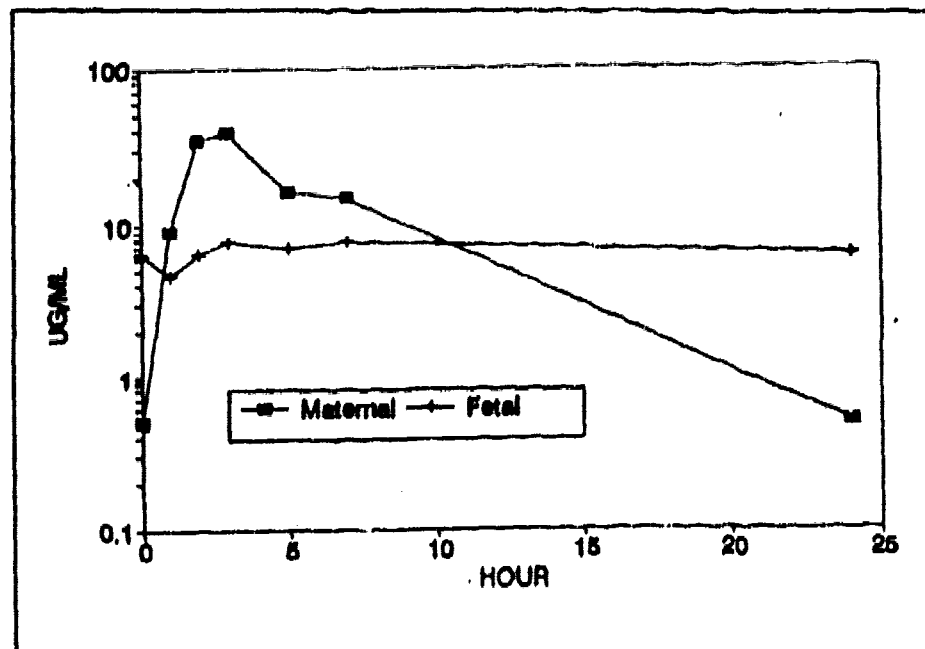


Fig. 3.4.9.2.: Mean E-3174 plasma levels in pregnant rats following oral dosing with losartan at 135 mg/kg during gestation days 15 through 20.

TABLE 3.4.9.1
MEAN LOSARTAN AND E-3174 PLASMA LEVELS (µg/ml) IN PREGNANT RATS FOLLOWING MULTIPLE ORAL DOSING WITH LOSARTAN. TT#92-727-0.

HOUR	LOSARTAN			E-3174		
	MATERNAL	FETAL	M/F	MATERNAL	FETAL	M/F
1	17.83	0.71	27.3	9.17	4.63	2.8
2	64.68	4.07	17.0	34.95	6.40	5.5
3	25.56	3.92	6.6	38.97	7.70	5.3
5	5.20	3.20	1.7	16.30	6.98	2.3
7	6.23	2.97	2.3	15.04	7.77	2.1
24	0.48	0.60	0.9	0.50	6.37	0.1
AUC	194.8	50.7		282.6	167.7	

M/F: Maternal divided by fetal plasma concentration
 AUC expressed as µg.hr/ml. 24 hour data were used for 0 hour.

The maternal systemic exposure (AUC) to losartan was much higher in rats that were dosed during late gestation (section 3.4.9) than in rats that were dosed during early gestation (section 3.4.8). An approximately 2-fold difference was noted upon comparison of the C_{max} values and AUC for both losartan and E-3174. This is illustrated in table 3.4.9.2. Data for this table is taken from Tables 3.4.8.2. and 3.4.9.1. This high losartan exposure in F₀ generation rats during late gestation may explain, in part, the toxicity seen in the postnatal F₁ generation.

TABLE 3.4.9.2
PLASMA LEVELS (µg/ml) AND MEAN AUC (µg.hr/ml) OF LOSARTAN AND E-3174 ON GESTATION DAYS 15 AND 20 FOLLOWING MULTIPLE ORAL DOSING WITH LOSARTAN AT 135 MG/KG

Hour	Dosed GD 6-15 (Values on GD 15)		Dosed GD 15-20 (Values on GD 20)	
	Losartan	E-3174	Losartan	E-3174
1	36.46	20.90	17.83	9.17
2	22.30	28.93	64.68	34.95
3	4.59	13.63	25.56	38.97
5	2.63	9.14	5.20	16.30
7	1.85	4.18	6.23	15.04
24	a	0.41	0.48	0.50
AUC	88	128.9	194.8	282.6

a: Value was below the detection limit of the method

3.4.10. Oral Range-Finding Study in Non-Pregnant Rabbits

Location of Data: Vol 20, Tab C-10

Testing Facility: Department of Safety Assessment, Merck Sharp & Dohme Research Laboratories, Merck & Co., Inc., West Point, PA

Study No.: TT #90-701-2

Study Dates: Initiated: January 2, 1990
Terminated: January 15, 1990

GLP Compliance: Studies were not done in accordance with GLP regulations.

Animals: Female New Zealand White rabbits from Hazleton Research Products Inc. were 45-46 weeks of age and weighed 3934-4596 gm at initiation of the study.

Mode of Administration/Dosage Levels: Losartan was administered orally at dosage levels of 3.125, 12.5, 50 or 200 mg/kg/day by gavage to four groups of 6 nonpregnant females. A control group of 6 females received the vehicle (tap water) at a dosing volume of 4 ml/kg. The 200 and 50 mg/kg/day groups were sacrificed on day 8 due to excessive toxicity and the remainder of the animals, including controls, were sacrificed on day 14. This study was conducted to aid in the selection of dosage levels for an oral range-finding study in pregnant rabbits.

Observations/Measurements: All animals were observed daily for physical signs of toxicity. Body weights were recorded on study days 1, 3, 5, 7, 9, 11, 13 and 14. Estimates of food consumption were made by daily visual inspection of food cups. Blood samples were taken on days 7 and 14 of the study for serum biochemical and hematological analyses.

Results: There were two treatment-related deaths and reduction or cessation of food intake in all females in the 200 mg/kg/day group and reduced food consumption in 2 and 3 females in the 50 and 12.5 mg/kg/day groups, respectively. Between days 1 and 7 of the study, there were treatment-related losses in mean body weight in the 200, 50, and 12.5 mg/kg/day groups of 143, 105, and 96 gm, respectively. Between days 1 and 14, there was a treatment-related and statistically significant loss of 165 gm in mean body weight at 12.5 mg/kg/day. A modest increase in body weight (+34 grams) was observed for control animals for this period.

On day 7 of the study, there were treatment-related decreases in erythron values in 2/6 rabbits in the 200 mg/kg/day group. On day 14, treatment-related decreases in erythron values were documented in 2/6 rabbits in the 3.125 mg/kg/day group and 4/6 rabbits in the 12.5 mg/kg/day group. In these affected rabbits, at least 2 out of 3 erythron parameters (RBC, hemoglobin and/or hematocrit) were depressed below the historical control range for non-pregnant rabbits. The mean platelet count in the 12.5 mg/kg/day group was lower ($P \leq 0.05$) than control on day 14 of the study. Losartan treatment elevated serum nitrogen and creatinine levels in all except low dose group. At 200 mg/kg/day, albumin, sodium, and chloride concentrations were slightly reduced while phosphorus and potassium levels were increased. Similarly, increases in serum phosphorus and potassium, and a decrease in serum chloride were observed in the 50 mg/kg/day treatment group. Increases in serum phosphorus

were also seen in the 12.5 mg/kg/day group. A no effect dose for alterations in erythron values was not achieved in the current study. The no-effect dose for elevations of serum urea nitrogen and creatinine and for mean body weight losses was 3.125 mg/kg/day.

3.4.11. Oral Developmental Toxicity Study in Rabbits

Location of Data: Vol 20, Tab C-13

Testing Facility: Department of Safety Assessment, Merck Sharp & Dohme Research Laboratories, Merck & Co., Inc., West Point, PA

Study No.: TT #90-701-0

Study Dates: Initiated: June 11, 1990
Terminated: July 12, 1990

GLP Compliance: Studies were done in accordance with GLP regulations

Animals: Female New Zealand White rabbits from Hazleton Research Products Inc. were 26-28 weeks of age and weighed 3383-4395 gm at initiation of the study.

Mode of Administration/Dosage Levels: Losartan was administered orally at dosage levels of 10, 20 or 40 mg/kg/day by gavage to three groups of 18 pregnant females each on gestation days 6 to 18. A control group of 18 females received the vehicle (tap water) at a dosing volume of 4 ml/kg. The dosage levels were selected based on an oral range-finding study (#90-701-4) in pregnant rabbits (8/dosage group) in which treatment-related decreases ($P \leq 0.05$) in mean maternal body weight gain were observed at 20 (35%), 40 (36%) and 60 (84%) mg/kg/day from days 6 through 18 of gestation. Also, there were three treatment-related deaths at 60 mg/kg/day after the administration of as few as seven doses of losartan. These animals stopped eating or had markedly reduced food intake 2 to 5 days prior to death. One rabbit in the 40 mg/kg/day group stopped eating on gestation day 12 and was sacrificed in poor condition on gestation day 20. There were slight treatment-related and dose-dependent decreases in mean numbers of erythrocytes, hemoglobin concentration, and hematocrit in all drug-treated groups (significant only in the high dose group). Dose-dependent increases in serum urea nitrogen in all dose groups and serum creatinine levels in the high dose group were attributed to losartan treatment.

Observations/Measurements: All animals were observed once daily for physical signs of toxicity. Body weights were recorded on gestation days 0, 6, 8, 10, 12, 14, 16, 18, 19, 22 and 28. Food consumption was measured on gestational days 0-1, 3-4, 6-7, 9-10, 12-13, 15-16, 18-19, 21-22, 24-25 and 27-28. All females were sacrificed on day 28 of gestation, uterine contents were examined and corpora lutea counted. The thoracic and abdominal viscera and contents of the stomach of all females were examined grossly.

All fetuses were counted, weighed, sexed, and given external, visceral, and skeletal examinations. The heads of one-half of the fetuses in each litter were processed so that freehand-cut coronal sections could be examined. All fetuses were fixed and cleared for skeletal examinations.

Results: There were three deaths (on gestation days 20, 21 and 23), and one abortion (on gestation day 23) in the high dose group. These four females stopped eating on gestational days 13-16 after receiving 7-10 doses of drug. In the middle dose group, there was one death on gestation day 17. Two of the dead females in the high dose group and the one in the middle dose group had large hair balls in the stomach, which are often associated with anorexia in the rabbit. One female in the low dose group aborted on gestation day 23. Since this female's daily food intake was normal through day 22 and had no physical signs, the abortion was considered by the sponsor as incidental and not related to treatment.

In the high dose group, there was a treatment-related reduction in mean maternal weight gain from gestation day 6 to gestation day 19 (1 vs. 115 gm in the control group). Despite the magnitude of this treatment-related difference, it was not statistically significant ($P > 0.05$). Mean daily food intake in the high dose group was lower than control on gestation days 16 - 22. This reduction in food intake ranged from 25% less than the mean control value (on day 16 of gestation) to 14% less (on day 22 of gestation) (Fig 3.4.11).

There were no treatment-related effects on reproductive status as measured by percent preimplantation loss, implants/female, resorptions and dead fetuses/implant, or live fetuses/female. In the high dose group there was a slight but not statistically significant reduction in mean live fetal weight (Table 3.4.11).

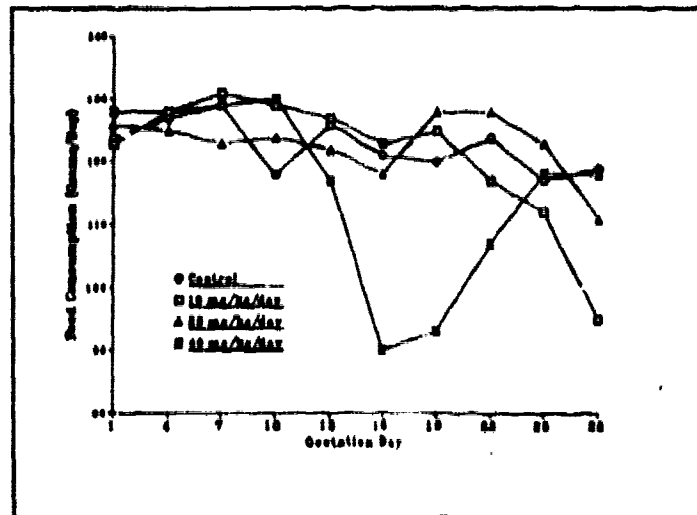


Fig: 3.4.9.1.: Average maternal food consumption

TABLE 3.4.11.1
ORAL DEVELOPMENTAL TOXICITY STUDY IN RABBITS. TT#90-701-0
SUMMARY OF LAPAROTOMY DATA

TREATMENT GROUP:	CONTROL	10 MG/KG/DAY	20 MG/KG/DAY	40 MG/KG/DAY
FEMALES				
TOTAL FEMALES	18	18	18	18
LIVE PREGNANT	17	13	16	10
LIVE NOT PREGNANT	1	4	1	4
DEAD PREGNANT	0	0	1	3
SACRIFICED PREGNANT	0	0	0	0
ABORTED	0	1	0	1
% PRE IMPLANTATION LOSS (LM)	24.3	15.9	32.2	23.9
IMPLANTS				
IMPLANTS	124	107	105	77
IMPLANTS/PREGNANT FEMALE	7.3	8.2	6.6	7.7 ^{NS}
RESORPTIONS AND DEAD FETUSES				
RESORPTIONS	14	18	12	2
DEAD FETUSES	0	1	0	0
%(RESORP+DEAD FET)/IMP (LM)	10.6	16.0	15.2	5.8 ^{NS}
LIVE FETUSES				
LIVE FETUSES	110	88	93	75
FEMALES	56	43	52	34
MALES	54	45	41	41
LIVE FETUSES/PREGNANT FEMALE	6.5	6.8	5.8	7.5 ^{NS}
LIVE FETAL WEIGHT (GM, LM)				
FEMALES ^a	37.8	37.3	38.9	35.8 ^{NS}
MALES ^a	38.9	37.7	39.8	36.1 ^{NS}

% preimplantation loss = ((no. Corpora lutea - no. Implants)/no. Corpora lutea) x 100. ns = trend not statistically significant through indicated dose (p>0.05). a = Trend analysis was performed with an adjustment for litter size. LM = Litter mean

External, visceral, and skeletal examination of fetuses did not reveal any treatment-related malformations. One fetus in the low dose group had a kidney displaced posteriorly, a fetus in the middle dose group had a ventricular septal defect, and one fetus in the high dose group had a retrocaudal ureter. These malformations, according to the sponsor, have been observed among controls of previous studies. There were treatment-related reductions in fetal ossification in the high dose group. The mean number of ossified sacrocaudal vertebrae in the high dose group (19.1) was significantly less than that of the control group (19.6). The number of fetuses with one or more incompletely ossified metacarpals (17) was significantly greater than the number of control fetuses with this alteration (2) (Table 3.4.11.2).

TABLE 3.4.11.2
ORAL DEVELOPMENTAL TOXICITY STUDY IN RABBITS. TT#90-701-0
SUMMARY OF FETAL OSSIFICATION DATA

TREATMENT GROUP:	CONTROL	10 MG/KG/DAY	20 MG/KG/DAY	40 MG/KG/DAY
FETUSES				
NUMBER EXAMINED	110	88	93	75
NUMBER WITH SITES OF INCOMPLETE OSSIFICATION	29	29	36	35 ^{NS}
NUMBER OF SITES OF INCOMPLETE OSSIFICATION	38	39	41	43
NUMBER OSSIFIED SACROCAUDAL VERTEBRAE (LITTER MEAN)	19.6	19.5	19.7 ^{NS}	19.1 ^{SIG}
LITTERS				
NUMBER EXAMINED	17	13	15	10
NUMBER WITH SITES OF INCOMPLETE OSSIFICATION	13	11	11	9
SITE OF INCOMPLETE OSSIFICATION				
INCOMP. OSS. STERNEBRA	6	6	5	6
INCOMP. OSS. METACARPAL	2	7	7 ^{NS}	17 ^{NS}
INCOMP. OSS. FOREFOOT PHALANX	23	17	27	17
INCOMP. OSS. PELVIC BONE	7	9	2	3

SIG = trend statistically significant through indicated dose ($p \leq 0.05$).

NS = trend not statistically significant through indicated dose ($p > 0.05$).

In conclusion, maternal deaths were observed in both 20 and 40 mg/kg/day dose groups. Further, decreases in maternal body weight gain and food consumption were observed in the 40 mg/kg/day group. The no effect dose for maternal toxicity in this study is 10 mg/kg/day. Developmental toxicity occurred in the form of decreased fetal body weight and delays in fetal ossification in the 40 mg/kg/day group, resulting in a no effect dose for developmental toxicity of 20 mg/kg/day.

3.4.12. Toxicokinetic Study in Pregnant Rabbits

Location of Data: Vol 37, Tab Q-11

Testing Facility: Department of Safety Assessment, Merck Sharp & Dohme Research Laboratories, Merck & Co., Inc., West Point, PA

Study No.: TT #91-719-0

Study Dates: Initiated: June 5, 1991
Terminated: June 21, 1991

GLP Compliance: Studies were done in accordance with GLP regulations.

Animals: Female New Zealand White rabbits from Hazleton Research Products Inc. were 30 weeks of age and weighed 3176-4388 gm at initiation of the study.

Mode of Administration/Dosage Levels: Sixteen pregnant rabbits received a single oral dose of 10 mg losartan/kg/day on days 6 through 15 of gestation. A control group of 4 females received the vehicle (tap water) at a dosing volume of 4 ml/kg/day. A dose of 10 mg/kg/day was selected based on a development toxicity study (#90-701-0, see section 3.4.9) in pregnant rabbits. In that study, 10 mg/kg/day was the no effect dose for maternal toxicity, and at higher dose levels treatment-related maternal deaths and abortions occurred.

Observations/Measurements: All animals were observed for physical signs one to five hours postdosing from gestation day 6 through sacrifice. Body weights were recorded on gestation days 0, 6, 8, 10, 12, 14 and 15. Food consumption was not measured. On day 15, twelve females treated with losartan were anesthetized and blood samples (2 ml) were collected from the inferior vena cava at 1, 3 or 7 hours (n=4/time point) postdosing. They were then sacrificed and the fetuses and placenta were collected and pooled within a litter, fetuses in one vial and placenta in another vial. The remaining 4 treated females, which were scheduled for the 24 hour sacrifice, were sequentially bled (1 ml from the ear artery/vein) at 0.5, 1, 2, 3, 5, 7 and 24 (from the vena cava) hours postdosing. All four were sacrificed to pool fetuses and placenta. Losartan and its metabolite E-3174 were estimated from blood, fetus and placenta collected from all drug treated females.

Results: There were no deaths, abortions or treatment-related physical signs during the study. The average body weight gains between dosing days 6 and 15 were 60% lower in the losartan treated group than in the control animals.

Following the dosing of losartan (10 mg/kg/day), the mean peak maternal plasma losartan concentration (C_{max}) occurred at approximately one hour with a value of 0.49 $\mu\text{g/ml}$, indicating that the drug is rapidly absorbed. The mean plasma drug concentrations did not change appreciably during the 0.5 to 7 hr period postdose, suggesting prolonged drug absorption. These results were comparable to the data generated with rabbits that provided plasma specimens at one time period (Table 3.4.11.1). By 24 hours postdose, however, no drug was detected in the majority of specimens.

The drug was rapidly metabolized to the acid metabolite, E-3174. By 1 hour postdose, the E-3174 plasma concentrations reached a mean of 0.46 $\mu\text{g/ml}$ (also C_{max} value). The magnitude of plasma concentrations of E-3174 at all time points were slightly higher than those obtained with losartan (Table 3.4.11.1). Similarly, the AUC values for the metabolite were greater than for the parent compound. There were no detectable levels of drug or acid metabolite in any rabbit placental or fetal tissues regardless of the time period postdose. In this reviewer's opinion, the sponsor should have estimated the drug concentrations in the fetal plasma (where it is readily detected even at low concentrations) rather than in the fetal tissue during late

gestation period. Thus the present study does not answer the question of whether or not the drug readily reaches the fetal compartment in rabbits.

TABLE 3.4.11.1
PLASMA PROFILES OF LOSARTAN AND E-3174 IN PREGNANT RABBITS AFTER ORAL DOSING WITH 10 MG/KG/DAY OF LOSARTAN ON DAY 15 OF GESTATION (TT #91-719-0)

Hour	Plasma level data (mean $\pm$ s.e.) generated with rabbits that were bled			
	Same 4 animals sequentially bled		4 different animals/time point	
	Losartan	E-3174	Losartan	E-3174
0.5 ^a	0.40 $\pm$ 0.11	0.28 $\pm$ 0.05		
1	0.44 $\pm$ 0.11	0.46 $\pm$ 0.03	0.383 $\pm$ 0.07	0.332 $\pm$ 0.02
2	0.36 $\pm$ 0.06	0.45 $\pm$ 0.04		
3	0.32 $\pm$ 0.05	0.46 $\pm$ 0.05	0.322 $\pm$ 0.08	0.398 $\pm$ 0.05
5	0.32 $\pm$ 0.03	0.48 $\pm$ 0.06		
7	0.25 $\pm$ 0.04 ^b	0.36 $\pm$ 0.09	0.250 $\pm$ 0.03 ^d	0.270 $\pm$ 0.05
24	0.013 $\pm$ 0.01 ^c	0.146 $\pm$ 0.03		
AUC (μ g.hr/ml)	4.50 $\pm$ 0.46	7.75 $\pm$ 1.23		

a: No samples were obtained at 0 hr, the 24 hr values were used to calculate the AUC for 0-24 hr; b: n=3; c: in three animals it was below the detection limit of the method (for losartan and E-3174 the detection limits were -0.05μ g/ml plasma, 0.125μ g/g of fetus, and -0.25 and 0.125μ g/g of placenta, respectively); d: two rabbits were inadvertently bled and sacrificed at 6 hours.

4. OVERALL SUMMARY AND EVALUATION

Pharmacodynamics

Losartan potassium (losartan) is the first of a new class of nonpeptide angiotensin II receptor antagonists which affect the renin angiotensin aldosterone system. Losartan is a competitive, potent, orally-effective, specific antagonist active at the AT₁ angiotensin II receptor. It was developed by DuPont Merck Pharmaceutical Company for the treatment of hypertension.

In rat, rabbit and man, losartan is converted to a pharmacologically active carboxylic acid metabolite, E-3174 (L-158,641). E-3174 shares the specificity of losartan for the AT₁ angiotensin II receptor. Since the pharmacological profiles of losartan and its metabolite are similar, the extent of angiotensin II receptor blockade induced by losartan in the rat, rabbit and man, represents the net effect of losartan and E-3174.

The receptor specific effects of losartan were demonstrated both *in vitro* and *in vivo*. Losartan exhibited a high affinity for the AT₁ receptor in binding to rat aortic smooth muscle and adrenal cortical microsomes, that are rich in the AT₁ receptor. Similar binding results have been reported with losartan in adrenal cortex in rabbits and monkeys, glomerular, cortical tubular and outer medullary membranes from the rat kidney, and human platelets. In isolated rabbit aortic strips, losartan behaved as a potent competitive angiotensin II receptor antagonist, whereas E-3174 behaved as a noncompetitive antagonist of angiotensin II and was more potent. Similar results were obtained with losartan or E-3174 following i.v. or oral administration in antagonizing the angiotensin II-induced pressor response in pithed rats. The pressor responses to norepinephrine or vasopressin were not reduced by either of the compounds. Losartan *per se* had no effect on the blood pressure of normotensive rats (no partial agonistic effect). The tolerance to the inhibitory effects of losartan on the blood pressure response to angiotensin II was evaluated in normotensive conscious rats. In this study, losartan (10 to 100 mg/kg p.o.) caused a dose-dependent inhibitory effect both acutely and after 11 days of treatment. In conscious normotensive rhesus monkeys and anesthetized normotensive chimpanzees, the hypotensive effect of oral or i.v. administration of losartan is shorter lived than in rats.

Functional studies conducted to explore the biochemical mechanism for the blockade of the vasoconstrictor response to angiotensin II have shown that losartan inhibits angiotensin II-induced formation of inositol 1,4,5 triphosphate, and both influx of extracellular Ca²⁺ and release of intracellular Ca²⁺ in vascular smooth muscle cells. By contrast, PD123177, a selective AT₂ receptor antagonist, did not affect these responses to angiotensin II.

Angiotensin II acts in the brain to stimulate drinking, to increase sodium appetite, to increase blood pressure, and to release pituitary hormones. It controls sodium balance by regulating the synthesis and excretion of aldosterone. Some of these responses are mediated by both AT₁ and AT₂ receptors. In conscious normotensive rats, 10 mg/kg losartan i.v., given 15 minutes before an i.v. infusion of angiotensin II, effectively blocked the release of aldosterone by angiotensin II. Similarly, angiotensin II-induced drinking response was blocked dose-dependently by losartan at 3 and 10 mg/kg s.c.

Daily treatment with losartan at 10 mg/kg p.o. for 2 weeks produced a significant reduction in systolic blood pressure in SHR after the first week of treatment, and a further decline in

blood pressure was observed after two weeks of treatment. This suggests a relatively slow onset of antihypertensive action and no tolerance. The antihypertensive effect was not associated with a significant increase in heart rate. Compared with the control, the plasma renin activity (PRA) and plasma levels of angiotensin I and angiotensin II were markedly elevated in losartan-treated animals. The increase in these parameters tended to be greater in the SHR than in the WKY rat. In contrast, losartan treatment significantly lowered aldosterone in both the SHR and WKY rat. In salt-depleted conscious dogs, infusion of losartan (30 µg/kg/min) produced a persistent inhibition of the mean blood pressure response to angiotensin II infusion (54 ng/kg/min). The short duration of action of losartan on MAP (30% recovery in 2 hr) and rise in heart rate could be due to a limited conversion of losartan to its primary metabolite E-3174. Circulating plasma angiotensin II and renin concentrations were elevated in the control in keeping with the sodium-deplete status of the animals. Infusion of losartan caused highly significant increases in plasma levels of angiotensin II and renin resulting from blockade of the inhibitory effect of angiotensin II on renin release, a calcium-mediated process at the renal juxtaglomerular cell.

Losartan (and its metabolite E-3174) was found to be an efficacious antihypertensive agent when evaluated in a number of renal hypertension models in rat, monkey and dog. Hypertension in these models is due to the activation of the RAS.

Similar antihypertensive effects of losartan were observed in furosemide pretreated SHR. Furosemide-treated SHR displayed significantly elevated levels of PRA, resulting in the formation of circulating angiotensin II in addition to tissue angiotensin II. Thus, furosemide pretreatment enhanced the blood pressure lowering effect of losartan. In genetically (Penn) hypertensive dogs, losartan (1 to 30 mg/kg i.v.) caused a dose-related slight but significant reduction in blood pressure. This effect was relatively small when compared to the antihypertensive effects described for rat models of hypertension. Losartan at 10 mg/kg i.v. had no significant effect on blood pressure in two low renin models, bilateral nephrectomized SHR and DOCA-salt treated rats. This indicates that normal levels of PRA are necessary to demonstrate the antihypertensive action of losartan.

Pharmacokinetics

Bioavailability of oral losartan varied among species and averaged approximately 9% in monkeys, 25% in dogs, 33% in rats and 39% in chimpanzees and humans.

Following intravenous (3 mg/kg) or oral (10 mg/kg) administration of radiolabelled losartan to rats, the highest level of radioactivity (approx. 20X that of plasma) was found in the liver and accounted for 40% to 60% of the administered dose within one hour after dosing. Plasma, gastrointestinal tract and kidney also contained high levels of radioactivity. Radioactivity declined with time after IV and oral losartan and was undetectable in most tissues 24 hours following IV dosing and minimally detectable 24 hours after oral dosing. The volume of distribution of losartan following IV administration of non-labelled losartan to rats (1 mg/kg), monkeys (40 mg) and humans (30 mg) was small (< 0.8 L/kg), indicating that diffusion of losartan in tissues may be limited by plasma protein binding. Both losartan and its pharmacologically active metabolite (E-3174, L-158,641) displayed extensive, concentration-independent binding to plasma proteins. The unbound fractions of losartan were 0.7%-1.0% in rat, 1.2%-1.4% in man and 2.7%-3.1% in dog. Binding of the metabolite E-3174 to plasma proteins was stronger (approx. 99.8% bound in man) than that of losartan.

Radioactivity was detected in fetal tissue following oral administration of 10 mg/kg of ^{14}C -losartan to 18-day pregnant rats. The distribution of radioactivity into fetal tissue and its elimination from the fetus was slow relative to maternal distribution and removal. Radioactivity in fetal tissue remained essentially constant from 8 to 24 hours, whereas only trace levels of radioactivity were detected in maternal tissues at 24 hours postdose.

Radioactivity was detected in the milk of lactating rats as early as 30 min after a single 10 mg/kg oral dose. The peak concentration of radioactivity in milk occurred 8 hours after dosing with ^{14}C -losartan and comprised about 1/4 of the peak (at 1 hr) maternal concentration. The radioactivity in the milk declined from 8 to 48 hours in parallel to that in plasma.

The metabolism of losartan varied among species. In the rat, the primary route of metabolism was oxidative, yielding monohydroxylated or carboxylic acid (E-3174) metabolites. In monkeys, glucuronidation of the tetrazole moiety predominated. The metabolism of losartan by human liver slices *in vitro* was not dominated by a single pathway, but was characterized by an approximately equal distribution of both oxidized and conjugated metabolites. All metabolites, except E-3174, were pharmacologically weaker than the parent drug. In rats, more N-glucuronide metabolite was produced from oral (10 mg/kg) versus intravenous (3 mg/kg) losartan, suggestive of first-pass metabolism following oral dosing. The parent drug detected in feces accounted for only 7.8% to 12.8% of the dose after IV administration of losartan to rats; the hydroxylated and carboxylic acid metabolites constituted a large percentage (23%-31%) of the drug-related products.

Excretion of losartan-related material (parent drug and metabolites) in rats was predominately via the feces. Following an IV dose (3 mg/kg) of ^{14}C -losartan to rats, 90% of the dose was excreted in the feces and 4.2% in the urine in 48 hours. In bile-duct cannulated rats, 95.5% of the radioactive oral losartan dose (10 mg/kg) was excreted in the bile in 48 hours, while 4.2% was found in urine and less than 1% was detected in the feces. This indicates that in rats (1) absorption of losartan was almost complete, (2) metabolism of losartan was extensive and (3) biliary excretion constituted the major route of elimination. When ^{14}C -losartan was given intravenously (2 mg/kg) to dogs, 72% of the radioactive dose was excreted in the urine in 168 hours. Following IV administration of ^{14}C -losartan (30 mg) to healthy volunteers, 43.3% and 49.5% of total radioactivity was recovered in urine and feces, respectively. Renal clearance of losartan in healthy volunteers was about 12% of total clearance of IV ^{14}C -losartan; in chimpanzees, renal clearance accounted for 14% of total drug clearance. Thus, renal excretion of parent compound represents a minor portion of losartan-related elimination products in chimps and humans.

A summary of comparative pharmacokinetic parameters of oral losartan in animals and man is given in Table 4.1.

TABLE 4.1
Comparative Pharmacokinetic Parameters for Losartan and Active Metabolite (E-3174)

Study #	Species	Losartan		Losartan			E-3174		
		Dose mg/kg/day	Time	C _{max} ug/ml	AUC ₀₋₂₄ ug.hr/ml	AUC ₀₋₂₄ AUC _{human}	C _{max} ug/ml	AUC ₀₋₂₄ ug.hr/ml	AUC ₀₋₂₄ AUC _{human}
90-2755	Mouse-M	250	8 days	40.7	28.4	34.4	30.3	69.8	8.4
90-2702	Mouse-F	500	8 days	74.2	90.3	75.6	57.6	200.1	56.2
		250	7 days	77.0	94.0	113.8	ND	ND	-
		500	7 days	171.1	234.7	284.1	ND	ND	-
92-055-0	Rat	135	18 wks	37.3	67.1	81.2	37.5	263.4	74.0
135 ^a		18 wks	53.7	113.6	137.6	53.9	268.3	75.4	
90-2715	Pregnant Rat	270	7 days	43.1	134.7	111.3	38.3	325.6	91.5
91-718-0		135	GD 6-15	36.5	88.0	106.5 ^b	28.9	128.9	36.2
92-727-0		135	GD 15-20	64.7	194.8	235.8 ^b	39.0	282.6	79.4
90-701-3	Pregnant Rabbit	25	GD 14	0.74	213.0	258.9 ^b	0.74	120.1	33.7
92-054-0	Dog	125	15 wks	35.6	82.4	99.8	1.58	3.42	0.96
		125 ^b	15 wks	36.0	85.7	103.8	1.52	3.36	0.94
90-149-0	Monkey	300	13 wks	5.0	28.1	34.0	0.62	3.76	1.06
015 & 022	Man	100 ^c	1 day	0.49 - 0.57 ^d	0.722 - 0.826 ^{d,e}	-	0.50 - 0.58 ^d	3.10 - 3.56 ^{d,f}	-

^a Losartan/HCTZ combination (135/33.75 mg/kg/day)

^b Losartan/HCTZ combination (125/31.25 mg/kg/day)

^c Tablet and capsule dosage forms

^d Range of mean values for dosage forms from both studies

^e AUC value of 0.826 ug.hr/ml used in deriving animal-to-human AUC ratio

^f AUC value of 3.56 ug.hr/ml used in deriving animal-to-human AUC ratio

^g AUC ratio derived from pregnant animals and normal humans; ratio may be lower due to possibly higher AUC values in pregnant humans.

Acute Toxicity

The acute intraperitoneal and oral single-dose toxicity of losartan was determined in mice and rats. Deaths were observed with 400 mg/kg IP or 1000 mg/kg PO in mice and 200 mg/kg IP or 2000 mg/kg PO in rats. Following intraperitoneal administration, the no-observable-adverse-effect dose was 160 mg/kg in mice and 100 mg/kg in rats. Clinical signs of toxicity observed with higher doses include decreased locomotor activity, ataxia, tremors, ptosis, labored respiration and perianal/urogenital staining. Following oral administration, the no-observable-adverse-effect level was approximately 500 mg/kg in mice and 1000 mg/kg in rats. At higher doses, observed clinical signs of toxicity included decreased locomotor activity, prostration, facial and perianal staining.

Subchronic Toxicity, Chronic Toxicity and Carcinogenicity

The long-term toxic potential of losartan was evaluated in a series of repeated dose oral toxicity studies of up to 3 months duration in monkeys, 12 months duration in dogs, 21 months duration in mice and 24 months duration in rats.

No deaths or clinical signs of toxicity were noted in monkeys treated with oral losartan doses of 20, 100 or 300 mg/kg/day for 14 weeks. The only treatment-related effects were noted in treatment Weeks 8 and 11 and consisted of slightly lower (approx. 5%) than control erythrocyte counts, hematocrit and hemoglobin concentration in male and female monkeys receiving 300 mg/kg/day. Parent drug and metabolite were barely detectable in monkey plasma after oral dosing with 20 mg/kg/day. Following 100 and 300 mg/kg/day, systemic exposure (AUC) and C_{max} of the parent and active carboxylic acid metabolite increased in near dose-proportional manner.

The most prominent findings observed in oral administration studies of 1 and 3 months duration in dogs were adverse gastrointestinal effects as evidenced by emesis, increased salivation and fecal occult blood. The frequency and severity of these observations were dose-dependent (45 or more mg/kg/day) and considered to be dose-limiting in the high dose group (135 mg/kg/day). These clinical observations occurred sporadically and were relatively mild in nature at lower doses (15 to 25 mg/kg/day). Histopathological findings did not indicate that losartan was irritating to the mucosal wall. In the one year toxicity study gastrointestinal effects were mild and transient in dogs receiving 125 mg/kg/day and thus not considered significant. Moderate and recurrent increases in serum ALT were observed in one of sixteen mid (25 mg/kg/day) and three of sixteen high dose (125 mg/kg/day) dogs during the one year study; however, the magnitude of the increase was not dose- or time-dependent and there was no histomorphological evidence of hepatic injury in these animals. The lack of correlation of findings among these three toxicity studies in dogs may be related to (a) the different testing facilities (the two subchronic studies were conducted by the DuPont Laboratory whereas the chronic study was conducted by the Merck Research Laboratory), and (b) differences in the mode of administration of test drug (by gastric intubation in one month and 1 year studies, and via liquid-filled gelatin capsules in the 3-month study).

Additionally, the sponsor has conducted a 17-day intravenous toxicity study with losartan (study #TT 90-609-0) and a 15-day i.v. toxicity study with L-158,641, the primary pharmacologically active metabolite of losartan (study #TT 90-098-0) in male and female dogs. In both studies, no treatment-related effects were observed at doses up to 10 mg/kg/day.

In a 53-week oral toxicity study in rats, losartan, administered by oral gavage at dose levels of 15, 45 and 135 mg/kg/day, caused no increased mortality. The high dose was associated with decreases in erythroid parameters and heart weights in both males and females, with increased BUN (more marked in males) and with focal erosions of the glandular mucosa of the stomach (noted at both 6 month and terminal sacrifices, primarily among high dose males). The low heart weights, relative to concurrent control heart weights, are attributed to the pharmacodynamic properties of losartan as it is a common response to other antihypertensive agents. JG cell hyperplasia was seen in all losartan treated groups (dose-related) and is a known response to agents that block the renin-angiotensin system. Although body weight gains for both males and females appeared to be adversely affected at both the intermediate and high dose levels of losartan, the magnitude of effect (about 10% for males and 15% for females) did not differ for the two dose levels (45 and 135 mg/kg/day).

Carcinogenic potential was assessed in a 105-week study in rats and in a 92-week study in mice. Losartan was administered orally by gavage in both studies.

Dose selection for the rat carcinogenicity study was based on results of a 14-week oral dose-rangefinding study in which 4 dose levels (50, 150, 250 and 450 mg/kg/day) were evaluated. Doses of 150, 250 and 450 mg/kg/day caused dose-related reductions from control body weights (-10%, -13%, and -14%, respectively) and body weight gains (-15%, -18% and -21%, respectively). Treatment with 450 mg/kg/day also altered serum biochemistry (increased serum urea nitrogen and phosphorus) and was lethal to 5/30 rats. Doses of 250 and 450 mg/kg suppressed erythroid parameters and produced gastric lesions (hemorrhage, hyperemia and epithelial erosion). In view of the fact that a dose of 450 mg/kg/day was clearly toxic and lethal to some animals and that doses of 150 and 250 mg/kg/day caused significant reductions in body weight and produced GI toxicity, a dose of 135 mg/kg/day was selected by the sponsor as the high dose for the carcinogenicity study in rats. When interim (6 mo.) results from a 1-year chronic rat study revealed only slight body weight reduction from a dose of 135 mg/kg/day and no adverse effect on survival, the sponsor, at week 6 of the carcinogenicity study, increased the high dose to 270 mg/kg/day. This elevation of the high dose resulted in decrements in rat body weights and increased GI-related toxicity. Based on these findings, it appears that a maximally tolerated oral dose was achieved with 270 mg/kg/day, particularly since the next highest dose tested (450 mg/kg/day) in the range-finding study was lethal to some rats. Despite the fact that a dose of 135 mg/kg/day was administered for the first 5 weeks, the study's value was not compromised since the animals were exposed to the higher dose for the remaining 100 weeks, i.e., 95% of the study's duration. The sponsor's statistical analysis of the results of the carcinogenicity study showed no increase in mortality with increasing oral doses of losartan to rats over the course of the study. There was also no increased trend in the incidence of any neoplasm for either sex of rat. However, statistical analysis of the tumor data by FDA's Division of Biometrics revealed a significant trend (P value=0.0084) in the incidence (0%, 0%, 0%, 4% for Control, LD, MD and HD, respectively) of pancreatic acinar adenoma in female rats. The pairwise comparison of the high dose group with control was also considered to be statistically significant (P value=0.043). No statistically significant trend was detected for the incidence of pancreatic acinar adenoma (3%, 3%, 0%, 7% for Control, LD, MD and HD, respectively) in male rats.

Non-neoplastic, drug-related pathology in rats included dose-dependent increases in the incidences of JG cell hyperplasia and focal tubular hypertrophy in the kidneys of both sexes

and non-dose-dependent increases in gastric lesions in losartan-treated males (all doses). The losartan-related increase in JG cell hyperplasia is regarded as an adaptive response of the renin-angiotensin system in response to blockade of angiotensin II activity; such a response is similarly seen with ACE inhibitors.

Dose selection for the mouse carcinogenicity study was based on a 14-week oral (gavage) dose rangefinding study in which 3 dose levels (50, 250 and 500 mg/kg/day) of losartan were evaluated. Doses of 250 and 500 mg/kg/day caused significant reductions from control body weight (-12%, -9.4%, respectively) and body weight gains (-31%, -35%, respectively) in males. A dose of 500 mg/kg/day caused significant reductions from control body weight (-5%) and body weight gain (-25%) in females. Doses of 250 and 500 mg/kg/day caused dose-dependent increases in serum urea nitrogen in females and dose-dependent increases in renal JG cell hyperplasia and tubular focal basophilia in males and females. Mean erythrocyte, hemoglobin and hematocrit were decreased by 4% to 10% in high dose males and females. Based on the finding that body weights were significantly lower in males treated with 250 or 500 mg/kg/day, the sponsor selected a dose of 300 mg/kg/day as an appropriate high dose for males in the carcinogenicity study. Because female weights were affected to a lesser degree, the sponsor selected a dose of 500 mg/kg/day as an appropriate high dose for females. After initiation of the carcinogenicity study, treatment-related decreases in body weight gain and a higher incidence of early deaths prompted the sponsor to decrease the high dose in females from 500 to 300 mg/kg/day in Drug Week 28 and lower the 300 mg/kg/day dose in both males and females to 200 mg/kg/day in Drug Week 43. The increased incidences of early deaths/early sacrifices at 300 mg/kg/day is strong evidence that the 200 mg/kg/day dose administered for the final 49 weeks of the study is at-or-near the maximally tolerated level for this agent by this route in this species.

The sponsor's and the FDA's analyses of the results of the carcinogenicity study revealed a statistically significant increased trend for mortality in female mice. Much of this difference was associated with a higher incidence of treatment-related early deaths with the high dose group. The two analyses also showed a statistically significant increased trend in the incidence of lung adenocarcinoma in males. The incidences of lung adenocarcinoma in female mice were not significantly different from control. No increase in lung adenoma was observed for either sex. A pairwise comparison of the high dose and control groups of male mice showed no statistically significant difference in the incidence of lung adenocarcinoma. In addition, historical control incidence data for this tumor type from sponsor's 18 most recent control groups of mice showed that the 16% incidence rate seen in high dose males is within the sponsor's historical control range (0%-24%). Because of (1) the absence of a significant pairwise difference (high dose vs. control) in lung adenocarcinoma incidence, (2) the lack of increased incidence for combined lung adenocarcinoma and lung adenoma and (3) the fact that the high dose male incidence is within the sponsor's historical control range, it is reasonable to conclude that this finding represents a false positive and is unlikely to be treatment-related. The same conclusion was reached by the Carcinogenicity Assessment Committee-Executive Committee which reviewed the findings of the rodent carcinogenicity studies for losartan on November 15, 1994. There was no statistically significant increased trend in the incidence of neoplasms in any other organ in this study.

Non-neoplastic drug-related pathologies in mice included dose-dependent increases in the incidences of JG cell hyperplasia and gastric and intestinal lesions, primarily in high dose males and females and in mid dose males. The losartan-related increase in JG cell

hyperplasia is regarded as an adaptive response of the renin-angiotensin system in response to blockade of angiotensin II activity; such a response is similarly seen with ACE inhibitors.

Thus, the administration of high doses of losartan were associated with signs of gastrointestinal toxicity in rats and mice (GI lesions), dogs (emesis, fecal occult blood), and monkeys (reddened gastric mucosal foci). Decreased erythroid parameters were observed with losartan administration in rats, dogs and monkeys; these decreases are known effects associated with agents that inhibit the renin-angiotensin system. Losartan-induced increases in serum urea nitrogen were noted in rats, mice, monkeys and rabbits; these increases were not associated with histological evidence of renal injury. Increased incidences of JG cell hyperplasia, a known response to agents that inhibit the formation (ACE inhibitors) and/or function (Ang. II inhibitors) of angiotensin, were noted in rats and mice.

Genotoxicity

The genotoxic potential of losartan was determined *in vitro* in microbial mutagenesis assays (*S. typhimurium* and *E. coli* tester strains), in the Chinese hamster lung mutagenesis assay, an alkaline elution/rat hepatocyte assay, in a chromosomal aberration assay in Chinese hamster ovary and in one *in vivo* assay for chromosomal aberration in mouse bone marrow.

Losartan was not genotoxic in this battery. The concentrations/doses of losartan which were judged to be negative are summarized in Table 4.2.

TABLE 4.2.

Genotoxicity Assay	Concentration/Dose*
Ames Test (<i>S. typhimurium</i>) (<i>E. coli</i>)	50 - 5000 ug/plate 100 - 10000 ug/plate
Chinese hamster lung	0.05 - 2.0 mM
Alkaline elution/rat hepatocyte	0.6 - 2.4 mM
Chinese hamster ovary	0.125 - 2.5 mM
Mouse bone marrow	150 - 1500 mg/kg

* Concentrations/doses that did not produce unacceptable levels of cytotoxicity

Also, the pharmacologically active metabolite of losartan (E-3174) was negative in the bacterial mutagen assays at concentrations of 100 - 10000 ug/plate, in the alkaline elution/rat hepatocyte assay at concentrations of 1.6 - 9.0 mM and in the CHO assay at concentrations of 0.125 - 1.0 mM. E-3174 was not tested in Chinese hamster lung or mouse bone marrow.

Reprotoxicity

In a male rat fertility study (see section 3.4.1), administration of losartan (up to 150 mg/kg/day) prior to mating and throughout mating had no effects on mating or fertility indices or on reproductive performance of pregnant F₀ females, or on the prenatal development of the F₁ generation.

Table 4.3. summarizes losartan dosage thresholds for adverse effects for all rat reprotoxicity studies other than the male fertility study. Administration of losartan to pregnant rats up to a dose of 200 mg/kg/day during organogenesis (gestation days 6 to 17, segment II) had no adverse effects on the dams except for a significant decrease in body weight gain during gestational days 6-18. There was no effect on the F₁ generation as assessed by mortality, physical signs, weight gain, external, skeletal and visceral examinations, developmental signs, behavioral tests and gross or microscopic changes in the kidney. In contrast to this, studies in which treatment with losartan included the third trimester and/or lactation period (segment I or III), fetal and neonatal effects were observed.

In both segment I and segment II studies, losartan administration at doses of 100 or more mg/kg/day resulted in significant decreases in maternal body weight gain and food consumption (during gestation and lactation periods). An apparent effect on ovulation was observed in the segment I study in F₀ females dosed at 100 or more mg/kg/day (treatment begun 15 days prior to mating) as reflected by significant decreases in the number of corpora lutea/pregnant female. Significant decreases in implants/female and live fetuses/female were also observed at these doses. A significant increase in pup mortality in groups receiving 100 or more mg losartan/kg/day was observed throughout lactation with the major effect occurring between lactation days 0 and 7. During the postweaning period (postnatal days 21 to 25), additional pups from these groups died. The pup deaths were associated with decreased pup weights which were seen during lactation at maternal doses as low as 10 mg/kg/day (both male and female pups) and from postweaning weeks 1 to 9 in female pups born to females receiving 25 and both male and female pups born to females receiving 100 mg/kg/day.

Attributed to the effect on pup body weight and relative immaturity of affected animals was a delay in the mean day of occurrence of auditory startle, and estimated day of occurrence of vaginal canalization and preputial separation in the 100 and 300/200 mg/kg/day treatment groups. Since the findings from segment I and segment III studies suggested that exposure during late gestation, and possibly lactation, was required to induce fetal and/or neonatal toxicity, a fostering/cross fostering study was conducted to further investigate the association of treatment of F₀ females during late gestation and lactation, late gestation only or lactation only on fetal and neonatal parameters. In fostered/cross fostered F₁ pups there were a number of statistically significant treatment-related effects evident. Prenatal treatment of dams was associated with decreased pup weight on postnatal day 21 and decreased male pup performance in the swim maze test. Treatment of dams during lactation was associated with increased pup deaths on postnatal days 1-3, decreased pup weights on postnatal day 7, delayed preputial separation, and decreased performance on the auditory startle test and swim maze trials in females.

TABLE 4.3.
DOSAGE THRESHOLDS FOR ADVERSE EFFECTS OF LOSARTAN IN RAT (SPRAGUE-DAWLEY) REPRODUCTION STUDIES

Study #/section#	90-708-0/3.4.2	90-702-0/3.4.3	91-727-0/3.4.4	90-727-0; 3.4.5	91-710-0/3.4.6	91-736-0/3.4.7
Dose (mg/kg/day by gavage)	25, 100, 300/200 ^a	50,100,200	5, 20, 100	10, 25, 100	100 ^k	0.5, 1, 5, 20, 100
Days of drug administration	see below ^b	GD 6-17	GD 6-15	GD 15-LD 20	GD 15- LD 20	GD 15- LD 20
Day of necropsy	GD 20; LD 25	GD 20	LD 23-27	LD 23-27	LD 24-27	LD 22-23
Maternal Toxicity 1. ↓ weight gain 2. ↓ food intake 3. ↓ corpora lutea + ↓implants	100-200 100-200 25-100 ^c	100-200 >200 NA	>100 >100 NA	25-100 25-100 NA	<100 Not recorded NA	20-100 Not recorded >100
Embryo/Fetal toxicity 1. ↓ fetal/pup birth weight 2. Bone variant	100-200 100-200 ^d	>200 >200	>100 NA	>100 NA	>100 NA	>100 NA
Neonatal Toxicity 1. ↓ survival 2. ↓ body weight gain 3. Postnatal development Auditory startle reflex (♀) ^f Vaginal canalization (♀) ^f Preputial separation (♂) ^f Swim maze test (♂ and ♀) ^g ↓ open field activity (♂) 4. ↓ heart weight 5. Renal Morphology: Ptv dil/papilla edema/cort arterial hypertrophy ^h Cort t/b degen/mineraliz ⁱ Chronic nephritis 6. Renal Clin Pathology ^j	25-100 <25 ^e 25-100 25-100 25-100 >200 25-100 ND ND ND ND ND ND ND ND ND ND	Not applicable	>100 >100 >100 >100 >100 >100 ND >100 >100 >100 ND	25-100 <10 >100 >100 >100 >100 ND ND ND ND ND ND ND ND ND	<100 ^l <100 ^m <100 ^l >100 <100 ^l <100 ^m >100 <100 ^m ND ND ND ND ND ND ND ND ND	20-100 20-100 ND ND 20-100 >100 20-100 20-100

When two doses are given, the first is the highest dose at which an effect was not seen and the second is the lowest dose at which an effect was seen.
a: The initial dose of 300 mg/kg was lowered to 200 mg/kg/day at the start of mating due to excessive toxicity. b: 15 days prior to mating, during mating, and through days 0 to 19 of gestation (c-sectioned animals) or through day 20 of lactation. c: This resulted in ↓ live fetuses/female. d: Incompletely ossified sternbra. e: Throughout lactation and in postweaning weeks 1 to 9 for females receiving 25 or more mg/kg, and in week 14 for high dose females. f: Delay in time to occurrence. g: Decreased swim maze performance. h: Renal pelvic dilation, edema of renal papilla, medial hypertrophy of cortical renal arteries. i: Cortical tubular degeneration and mineralization. j: Increased urine volume, decreased urine creatinine, Na⁺ and K⁺; and increased serum urea nitrogen and creatinine. k: Soon after delivery pups in the control and treated groups were divided into: control pups fostered by control or treated dams, and pups from drug-treated dams fostered by dams receiving the vehicle or drug. l: Postnatal effect. m: Prenatal effect. NA: Not applicable in this study. ND: Not determined/studied.

Intrauterine exposure to losartan at a dose of 100 mg/kg/day caused a decrease in cardiac weight which was slightly exacerbated by continued exposure during suckling. Renal findings observed at 100 mg/kg/day included pelvic dilation, papillary edema, medial hypertrophy of the renal cortical arterioles with increased urine volume and decreased urine creatinine, sodium and potassium; and increased serum urea nitrogen and creatinine. The disturbed renal blood and urine flow resulted in chronic nephritis, characterized by cellular infiltration and irregular scarring of renal parenchyma (occasionally with mineralization). The no observed effect dose level for losartan to produce effects on renal morphology was 20 mg/kg/day. However, losartan doses as low as 10 mg/kg/day produced developmental toxicity (reduced pup weight gain). Two segment III studies confirm that the critical period for adverse developmental effects (including renal toxicity) in the rat is late gestation (after day 15 of gestation) and/or lactation.

Pregnancy altered the pharmacokinetic profile of losartan in rats. The following data (Table 4.4.) indicates that losartan AUCs were ~62% and ~258% higher for pregnant females dosed on gestation days 6 to 15 and on gestation days 15 to 20, respectively, than for nonpregnant females receiving 135 mg losartan/kg/day for 7 consecutive days.

TABLE 4.4.

Parameters	Nonpregnant rat, dosed 7 days (TT #90-2715)		Pregnant rat, dosed GD 6-15 (TT # 91-718-0)		Pregnant rat, dosed GD 15 -20 (TT # 92-727-0)	
	Losartan	E-3174	Losartan	E-3174	Losartan	E-3174
C _{max} (µg/ml)	20.84 ^a	21.58 ^b	36.46 ^a	28.93 ^c	64.68 ^c	38.97 ^d
AUC ₀₋₂₄ (µg.hr/ml)	54.47	92.84	88	128.9	194.8	282.6

In all three studies the dose of losartan was 135 mg/kg/day. a: at 1 hr. b: at 0.5 hr. c: at 2 hr. d: at 3 hr. Concentrations of losartan and its metabolite were determined on final treatment day.

Similarly, AUCs for E-3174 were ~39% and ~205% higher for pregnant females than for nonpregnant females on gestation days 15 and 20, respectively.

Concentrations of losartan and its metabolite, E-3174, determined on gestation day 15 in pregnant rats that were dosed from gestation day 6 to gestation day 15 were substantially lower in placenta than in maternal rat plasma. A comparison of the losartan AUC values for plasma and tissues indicates that placental drug content represents about 31% of the systemic drug exposure. Fetal exposure to losartan is estimated to be less than 0.3% of maternal exposure. In contrast, significant losartan and E-3174 levels were detected in fetal plasma even at 24 hr postdosing with maternal administration of losartan from gestation day 15 through 20. The relatively high concentration of E-3174 in the fetal compartment suggests that the fetus acts as a deep compartment for this metabolite. This may explain, in part, the developmental toxicity observed in the postnatal F₁ generation. The association between the critical period of exposure beyond the second trimester, the onset of development of the RAS in the rat fetus on approximately gestation day 17, the increase in maternal and fetal exposure in late gestation, and the demonstrable exposure to losartan and E-3174 during lactation would suggest that the observed adverse fetal and neonatal effects are pharmacologically-

mediated. Similar observations have been made with angiotensin converting enzyme inhibitors.

In pregnant rabbits, maternal toxicity was evidenced by mortality at doses of 20 or more mg/kg/day and decreased body weight gain and elevated serum nitrogen and creatinine levels at doses of 12.5 or more mg/kg/day. Though there were no treatment-related effects on reproductive status, losartan administration resulted in reductions in mean live fetal weight and delayed metacarpal and sacrocaudal vertebral ossification in the 40 mg/kg/day group. No detectable levels of losartan or its primary metabolite (E-3174) were observed in placental or fetal tissues (does had been dosed on gestation days 6 through 15). Fetal plasma concentrations of losartan or its metabolites were not determined.

5. LABELING

Those sections in the proposed labeling that refer to preclinical studies were reviewed and considered acceptable with the following exceptions:

Under PRECAUTIONS: *Carcinogenesis, Mutagenesis, Impairment of Fertility*

The sponsor presents values for the animal-to-human exposure multiples for losartan and metabolite based on a human daily dose of 50 mg. However, the multiples of human exposure should be based on the maximum recommended human daily dose of 100 mg. Also, the increased incidence of pancreatic acinar adenoma in female rats needs to be included in this section based on FDA's analysis of the tumor data. The following statement incorporates the recommended changes:

"Losartan potassium was not carcinogenic when administered at maximally tolerated dosage levels to rats and mice for 105 and 92 weeks, respectively. Female rats given the highest dose level (270 mg/kg/day) had a slightly higher incidence of pancreatic acinar adenoma. These maximally tolerated dosage levels (270 mg/kg/day in rats, 200 mg/kg/day in mice) provided respective margins of systemic exposure for losartan and its pharmacologically active metabolite over that achieved in humans treated with 100 mg of losartan of approximately 111- and 91-fold in rats and 30- and 7-fold in mice"

In the *Mutagenesis* statement, the sponsor gives a dose multiple for the chromosomal aberration assay in mice based on body weight only. This dose multiple should also be given based on body surface area. The sentence should now read:

"Similarly, there was no induction of chromosomal aberrations in bone marrow cells of male or female mice after the administration of toxic oral doses of up to 1500 mg/kg (750 times** the maximum recommended daily human dose on a body weight basis and 68 times** the maximum recommended daily human dose on a body surface area basis)."

In the *Impairment of fertility* statement, the sponsor notes: Fertility and reproductive performance were not affected in studies with male and female rats given oral doses of losartan potassium up to approximately 150 and 300 mg/kg/day, respectively. The sponsor further presents values for the animal-to-human exposure multiples for losartan and metabolite based on a human daily dose of 50 mg. The statements made here are incorrect. Doses of 300/200 mg/kg/day in females resulted in significantly ($P \leq 0.05$) fewer corpora lutea/female, implants/female and live fetuses/female. In the 100 mg/kg/day group there was a slight but significant effect on corpora lutea/female. The correct no observed effect dose level in female rats is 25 mg/kg/day. The following statement incorporates the recommended changes:

"Fertility and reproductive performance were not affected in studies with male rats given oral doses of losartan potassium up to approximately 150 mg/kg/day. Doses of 300/200 mg/kg/day in females resulted in significantly ($P \leq 0.05$) fewer corpora lutea/female, implants/female and live fetuses/female. In the 100 mg/kg/day group there was a slight but significant effect on the number of corpora lutea/female. In nonpregnant rats dosed at 135 mg/kg/day for 7 days, systemic exposure (AUCs) for losartan and E-3174 were approximately 66 and 26 times the exposure achieved in man at the maximum recommended human daily dosage (100 mg)."

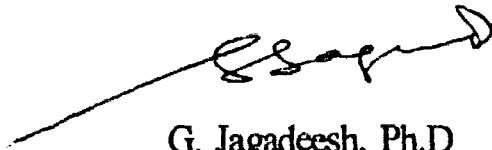
Under WARNINGS: *Fetal/Neonatal Morbidity and Mortality.*

Losartan has been shown to affect physical and behavioral development in addition to causing decreased body weight, mortality and renal toxicity. In addition, significant levels of losartan and its active metabolite were present in maternal and fetal plasma. Thus the 8th para should read:

" Losartan potassium has been shown to produce adverse effects in rat fetuses and neonates. These effects include decreased body weight, delayed physical and behavioral development, mortality and renal toxicity. In addition, significant levels of losartan and its active metabolite were shown to be present in fetal plasma and rat milk. Based..."

6. RECOMMENDATION

Based on preclinical safety considerations, this new drug application for losartan potassium is approvable.



G. Jagadeesh, Ph.D



A. Proakis, Ph.D.

cc:

Original NDA 20,386

HFD-110

HFD-110/CSO

HFD-110/G. Jagadeesh

HFD-110/T. Proakis

HFD-502/A. Taylor

HFD-345/G. James

Initialed by: LAR 12/2/94

gj/12/6/94 /NDA20386.PKZ (data compressed)

CAC Executive Committee Final Report

Application: NDA 20-836
Division: HFD-110
Date: November 15, 1994
Reviewer: Proakis
Chairperson: Taylor *u.s. 11/16/94*
Members: Contrera, Resnick, Defelice

Dr. Proakis presented results of mouse and rat dose rangefinding studies and carcinogenicity studies of losartan (Merck & Co. NDA# 20,836) before the Carcinogenicity Assessment Committee-Executive Committee (CAC-EC) on Nov. 15, 1994 to obtain decisions on the adequacy of high-dose selections, on the adequacy of the studies and on conclusions of tumor findings. CAC-EC members present were Drs. Alan Taylor, Joseph Contrera and Albert DeFelice.

DISCUSSION AND DECISIONS

Each CAC-EC member was provided a summary of the dose rangefinding studies, carcinogenicity studies and copies of FDA statistician's analysis of the tumor data. The CAC-EC members agreed that, based on study results, maximally tolerated doses were achieved in both the mouse and rat carcinogenicity studies; both studies were deemed adequate based on acceptable numbers of surviving animals at study-termination.

It was the committee's conclusion that the slightly increased incidence of lung adenocarcinoma in male mice was unlikely drug-related and should be disregarded based on (1) the absence of a significant pairwise difference between high dose and control, (2) the absence of significant increased trend for combined incidence of lung adenocarcinoma and lung adenoma and (3) the observed increased incidence of lung adenocarcinoma was within the sponsor's historical control range for this tumor in this mouse strain.

In the case of the increased incidence of pancreatic acinar adenoma in female rats, the committee recommended that this increased incidence should be addressed in the product labeling.

Anthony Proakis
Anthony Proakis, Ph.D
11/16/94

CC:
NDA 20-836
HFD-110/div file
/Resnick
Proakis
HFD-502/cac file

Printed: 02-28-95
By: Proakis, Anthony
Priority: Normal
Topic: RE>Losartan Labeling-
Sent: 02-28-95
From: Lipicky, Raymond; Proakis, Anthony
To: Proakis, Anthony

Reply to: RE>Losartan Labeling

I know that estimate of potency depends upon the assay. Everywhere that the figure appears it should say about 10 to 40 times.

I added the 20 to 40. receptor-binding assays are the most precise (best point estimate). I think it is important to labelling because it is the metabolite that is really doing the job, not losartan, under any circumstance (with or without other diseases or malfunctions).

Date: 2/28/95 1:56 PM
To: Raymond Lipicky
From: Anthony Proakis
Dr. Lipicky;

In Dr. Temple's comments regarding Losartan labeling, he requested some consensus (consistency) in reference to potency values between losartan and its metabolite, E-3174. Under Clinical Pharmacology it is stated that the metabolite is 20 to 40 times more potent, whereas in the Pharmacokinetics section it states that E-3174 potency is 5 to 10 times that of losartan. I was asked to help in sorting this out.

The sponsor's original version of the labeling makes no reference to potency of the metabolite relative to parent. I understand that the Biopharm folks added the 5-10X value; I'm not sure who added the 20-40X value. In reality, all of these values are correct depending on assay used.

Keep in mind that the parent drug behaves as a competitive antagonist and that the metabolite behaves as a non-competitive antagonist. In functional assays (inhibition of tissue contraction, pressor responses) it typically is inappropriate to use potency comparisons when the nature of inhibition is different, especially when maximal responses are lowered in non-competitive inhibitory conditions. I don't feel as confident in assigning potency values from results of receptor-binding assays.

At best, one may say that the metabolite appears more potent than the parent. I'm not sure what that adds to the product information since the metabolite is not being given....except that under impaired elimination a more potent (and longer acting) metabolite may give rise to exaggerated effects.

If you need more information, please let me know.

Tony

=====

CAC Executive Committee Final Report

Application: NDA 20,386
Division: HFD-110
Date: January 24, 1995
Chairperson: A. Taylor
Members: J. Contrera, G. Fitzgerald

J.D. Taylor For A. Taylor, 2/06/95
J. Contrera 997 1/31/95

Dr. Proakis presented results from two rat studies conducted by Merck Research Labs to investigate and/or confirm findings reported to the sponsor by a group of independent investigators (Remuzzi et al) who detected possible renal tumor promoting properties of losartan. CAC-EC members present were Drs. Alan Taylor, Joseph Contrera and Glenna Fitzgerald.

DISCUSSION AND DECISIONS

Each CAC-EC member was provided with the reviewer's (Dr. Proakis) summary of the 2 Merck studies which employed a larger number of animals than the study conducted by Remuzzi et al and explored additional doses of losartan. Briefly, the results from the Merck studies are as follows:

In both studies, a high percentage (35% and 42%) of rats treated with a single 60 mg/kg IV dose of the diabetogenic agent, streptozotocin (STZ), developed renal tumors which were grossly evident one year after STZ. The oral administration of 5, 30 or 90 (reduced to 60 in Study Week 19) mg losartan/kg/day to STZ-treated rats caused no significant increase in the incidence of grossly evident renal tumors. A significant increase in the incidence of histologically-detected renal tumors (primarily attributed to an increase in benign tubular adenomas) was noted in high dose losartan-treated diabetic rats in which losartan administration was initiated 5 days after STZ. Rats given the same high dose (90-60 mg losartan/kg/day) for one year beginning 29 days after STZ showed no significant increase in the incidence of histologically-detected renal tumors.

Whereas an oral dose of 30 mg losartan/kg/day for one year (the dose and duration employed by the independent investigators) to STZ-diabetic rats did not increase the incidence of grossly evident or histologically detected renal tumors compared to STZ-diabetic controls, the co-administration of lisinopril with this dose of losartan was associated with an increased incidence of grossly evident and histologically-detected renal tumors, primarily benign adenomas.

It was the conclusion of the reviewer, Dr. Proakis, that the increased renal tumor incidence in one of the two losartan high-dose (90-60 mg/kg/day) groups and in the losartan/lisinopril group were spurious findings unrelated to a tumor promotion effect of losartan because these treatments were associated with an increased incidence of

nephrotoxicity and death. The more expansive studies of Merck failed to reproduce the original findings of Remuzzi et al.

The CAC-EC members agreed that no tumor promotion effect by losartan was detected.



Anthony G. Proakis, Ph.D.
1/30/95

cc:
NDA 20,386
HFD-110/div. file
HFD-110/AProakis
HFD-110/CResnick
HFD-502/cac file

JAN 30 1995

NDA # 20,386

REVIEW AND EVALUATION OF SPECIAL CARCINOGENICITY STUDIES

Anthony Proakis, Ph.D.

SPONSOR: Merck & Co., Inc.
West Point, PA 19486
(610) 397-2310

AMENDMENT DATED: 10/5/94
CENTER RECEIPT DATE: 10/7/94
REVIEWER RECEIPT DATE: 10/10/94

DRUG: COZAAR (Losartan potassium)

RELATED NDA: #20,387 HYZAAR (losartan potassium/HCTZ)

BACKGROUND: Losartan is an angiotensin II receptor antagonist developed for the treatment of hypertension. Special animal studies were conducted by the sponsor to investigate and/or confirm findings reported to the sponsor by a group of independent investigators (Drs. Remuzzi et. al.) who, while in the course of examining the potential beneficial effects of losartan against experimentally-induced diabetic nephropathy, detected possible renal tumor enhancing properties of losartan. In the Remuzzi study, diabetes was experimentally-induced in male rats with a single IV dose (60 mg/kg) of streptozotocin (STZ). Losartan was administered in the drinking water at a dose of 30 mg/kg/day to a group of 16 rats beginning 5 days after STZ. A separate group of STZ-treated rats and another group of 16 untreated animals served as respective diabetic and non-diabetic controls. An interim renal function evaluation was conducted on 8 rats/group after 4 weeks of losartan treatment; the remaining 8 rats/group were treated for approximately 1 year at which time the animals were killed and kidneys examined for gross and microscopic pathology. The study design was not intended for a systematic evaluation for the presence of renal pre-neoplastic or neoplastic lesions; however, the investigators detected grossly evident, unilateral renal masses in 5/8 diabetic rats treated with losartan but no similar findings in the STZ-diabetic control group. These tumor findings were not included in the published study titled "Short and Long-Term Effects of Angiotensin II Receptor Blockade in Rats with Experimental Diabetes" by Remuzzi et al (J. Am. Soc. Nephrol. 4: 40-49, 1993). A summary of the gross and histomorphologic findings conveyed by these investigators to the sponsor are summarized as follow:

Renal Tumor Incidence

Untreated Control	0/8	-
STZ (60)	0/8	-
STZ/Losartan (60/30)	5/8	3 renal epithelial tumors (identified as renal cell carcinomas), 1 renal mesenchymal tumor (identified as sarcomatous carcinoma), 1 epithelial tumor not evaluated histologically.

In view of these tumor findings, two studies were conducted by the sponsor at two separate Merck research laboratory sites (MSD-West Point, PA and MSD-Chibret, France) to determine whether losartan, or losartan-induced increases in circulating angiotensin II, were associated with the enhancement of STZ-induced renal tumorigenesis. Prior to the initiation of these 1-year renal tumorigenicity studies, preliminary experiments were conducted by the sponsor to examine the genotoxic and cytotoxic interaction of losartan with STZ in rats. Review of the preliminary genotoxicity/cytotoxicity study was conducted using the sponsor's study summaries (from Background Package for FDA-MRL Meeting, August 3, 1994).

28-Day Genotoxicity/Cytotoxicity Study in Streptozotocin-Treated Rats

Study Facility: Merck Research Labs., West Point, PA

Study No: TT# 93-047-0

Study Dates: 4/13/93 -8/30/93

GLP Compliance: Sponsor indicates that this study was conducted in compliance with GLP regulations.

Animals: Male Crl: CD(SD)BR rats (57 days old, 181-338gm)

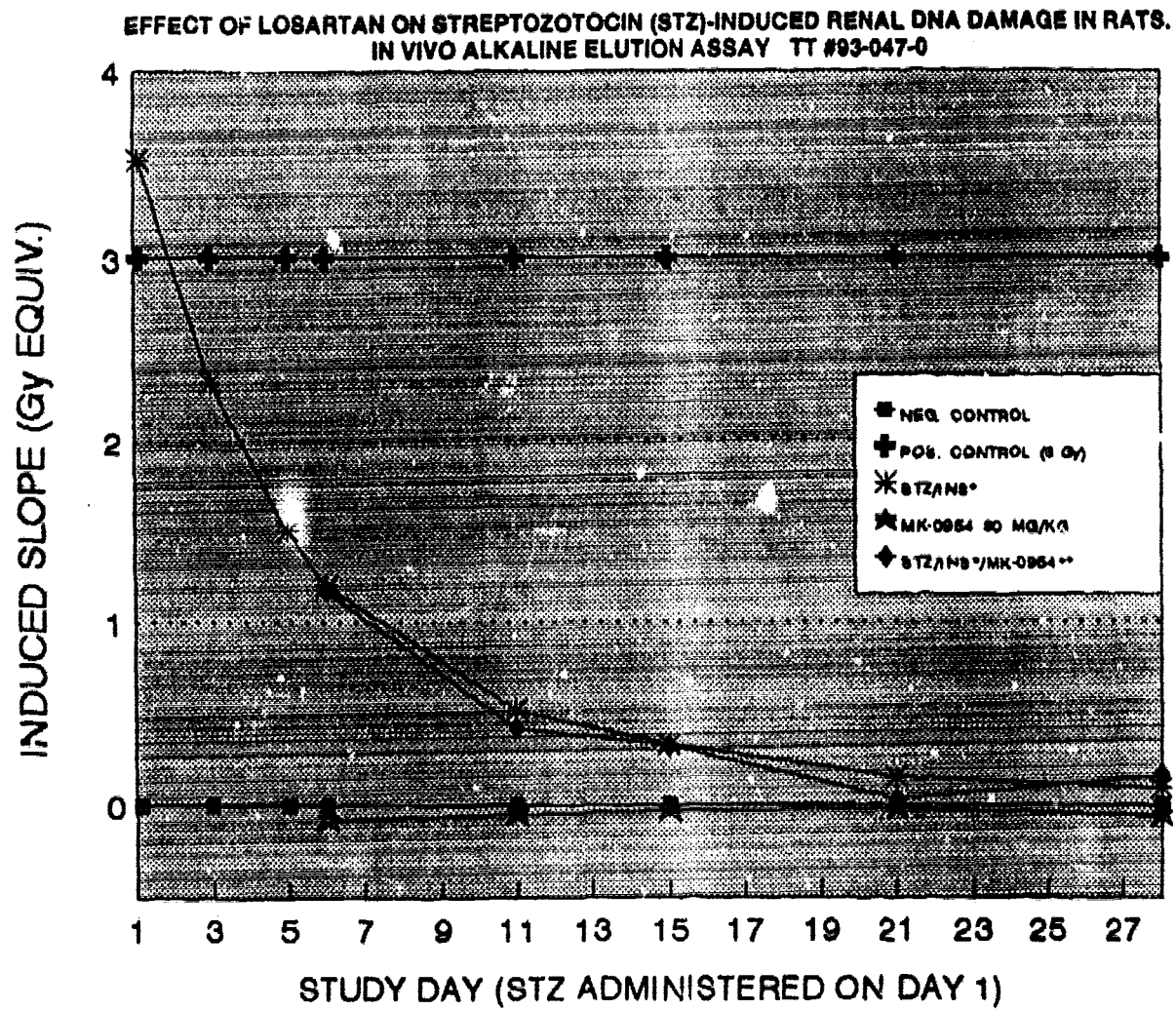
Procedure: This study was conducted to define the extent and time course of repair of STZ-induced DNA damage in the presence and absence of losartan. Rats were allocated to the following treatment groups:

Control (water)	47
STZ (60 mg/kg IV)	47
Losartan (30 mg/kg PO)	30
STZ/Losartan (60/30)	30

On Day 1, all STZ-treated animals received a single IV injection of STZ (60 mg/kg) in a citrate buffer. Losartan treatment (30 mg/kg/day in the drinking water) was initiated in losartan-designated groups on Day 5. Control animals received tap water only. Beginning on Day 3 through study termination, all STZ-treated rats received daily subcutaneous injections of insulin (4-9 units) to achieve a targeted non-fasted serum glucose range of 200-400 mg/dl. Necropsies for genotoxicity evaluation were performed on selected groups of four animals on Days 1 (3 hours post STZ administration), 3, 5, 6, 11, 15, 21 and 28. For the alkaline elution assay, one kidney was removed from each rat and a 1-2 mm thick section of kidney forced through a 100-mesh screen into ice cold buffer to yield a suspension of cells/nuclei. Approximately 1.25×10^6 cells/nuclei were loaded per elution column. An alkaline solution (pH 12) was used to elute the DNA from the column. The assay sensitively detects small changes in molecular weight by measuring the rate at which single alkali-denatured strands of DNA elute through the column filters. Elution rates are higher following drug-induced breaks in DNA strands. The criteria for determining a positive genotoxic effect in the *in vivo* alkaline elution/rat kidney DNA damage assay is a dose-related increase in the induced slope (treatment slope-control slope) of at least 0.042 at one or more dose levels that is not associated with compound-induced renal cell necrosis. At each necropsy, a portion of the cell/nuclei from control animals was irradiated in a gamma irradiator prior to alkaline elution to serve as a positive control. For the analysis of nuclear labeling, osmotic pumps containing bromodeoxyuridine (BrdU) were implanted subcutaneously in 4-5 rats per group in (1) control and STZ groups on Day -1 (with necropsy on Day 5), (2) all dosage groups on Day 5 (with necropsy on Day 10) and (3) all dosage groups on Day 23 (with necropsy on Day 28). The kidneys were prepared for light microscopic examination and for immunohistochemical detection of BrdU-labeled nuclei in renal epithelial cells in the cortex and outer stripe and cortical interstitial cells.

Results: The results (illustrated in Figure 1) of the *in vivo* alkaline elution/rat kidney DNA damage assay of STZ showed that STZ-induced DNA damage was severe at 3 hours after a single 60 mg/kg IV dose and declined with time to background levels by 20 days after STZ treatment. There were no statistically significant effects of losartan (30 mg/kg/day) on the level of STZ-induced damage at any time point measured. Also, losartan alone showed no evidence of a genotoxic effect in rat kidney.

An increase in cell turnover (BrdU Labeling Index %) occurred in rats treated with STZ on Day 5 in all three compartments of the kidney (cortex, outer stripe and interstitial cells). The Labeling Indices returned to control levels by Day 28. No effects on cell turnover were observed in animals treated with losartan in the absence of STZ. There were no significant gross or microscopic differences in kidneys among the groups.



53/57-Week Oral Tumorigenicity Study in STZ-Treated RatsStudy Facility: Merck Research Labs, West Point, PAStudy No.: TT# 93-048-0Study Dates: 4/12/93 -5/13/94GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.Animals: Male Crl:CD(SD)BR rats (59 days old, 214-367 gm)Drug Administration: Losartan (Lot# 005H042, 005H01 and 005H059) was dissolved in filtered tap water and administered in the drinking water.Procedure: Animals were allocated to the following treatment groups:

Placebo	0	38	37	75
STZ	60	38	37	75
STZ/Losartan	60/5	50	0	50
STZ/Losartan	60/30	50	0	50
STZ/Losartan	60/90(60) ^b	50	0	50
STZ/Losartan	60/90(60) ^b	0	50	50

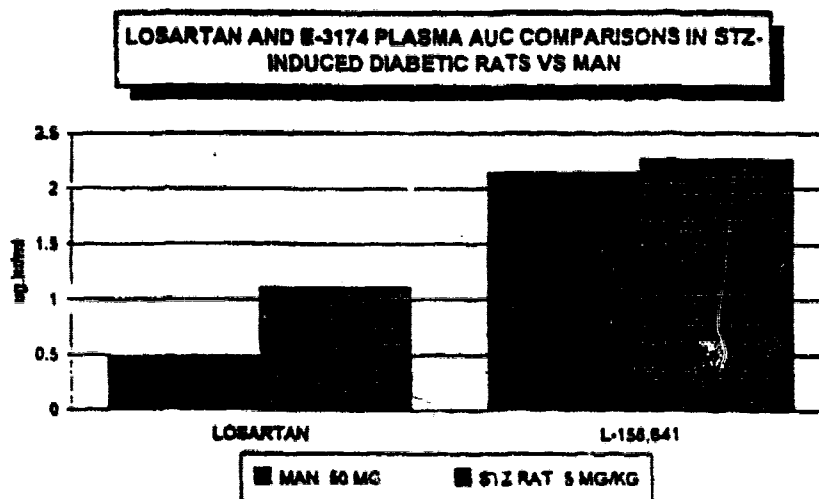
^a STZ administered as a single IV dose; losartan administered in the drinking water as a daily dose.

^b Daily dose of losartan lowered from 90 to 60 mg/kg/day in Study Week 19 due to drug-related toxicity.

On Day 1 of study all STZ-designated rats received a single IV injection of 60 mg/kg STZ as a citrate buffered (pH 4.5) solution. Beginning on Day 3, all STZ-treated animals received daily SC injections of Ultralente Insulin (4-9 u; adjusted weekly) to maintain serum glucose concentrations between 200 and 400 mg/dl. Losartan (5, 30 or 90 mg/kg/day) was administered in the drinking water beginning on Day 5 of study. Rats were observed daily for mortality and clinical signs of toxicity. Body weights were recorded at pretest, once in Week 1, twice weekly through Week 13 and then once weekly thereafter. Food consumption was measured weekly. Venous blood samples were obtained (via tail vein) from 4 to 5 rats per dose group (except the high dose group started on Day 29) at 1, 6 and 12 months at 7:30-9:30 AM and 1:00-3:00 PM for determination of plasma angiotensin II levels. Serum urea nitrogen and creatinine were measured from vena caval samples collected from all surviving rats immediately prior

to scheduled necropsies. All surviving losartan-treated rats and an appropriate complement of STZ-treated and untreated controls were sacrificed in Study Week 53. An additional group of diabetic rats was treated with 90 mg/kg/day of losartan beginning on Day 29 to assess any difference in the effect of treatment when administered subsequent to the resolution of detectable genotoxicity and cytotoxicity. These rats and concurrent diabetic and untreated controls were sacrificed in Study Week 57.

*Dose Selection Rationale: The 5 mg/kg/day losartan dose was based on pharmacokinetic data in STZ-diabetic rats which showed equal or greater plasma exposures of losartan and active metabolite (E-3174, L-158,641) than those achieved in man at the recommended therapeutic dose of 50 mg. The 30 mg/kg/day losartan dose was selected to assess the validity of those findings of the Remuzzi *et al* diabetic nephropathy study. The high dose was selected to assess, in conjunction with the low and mid dose, any potential dose-response relationship for enhanced STZ-induced renal tumorigenicity.*



Kidney weights were recorded post-mortem and grossly evident renal lesions were noted prior to and after post-fixation sectioning. Light microscopic evaluation of 5 standardly selected sections per kidney (10 sections per rat) was conducted for the presence of renal lesions. Two primary response variables, the number of kidney tumors (any type) per rat and the number of malignant tumors (any type) per rat, were analyzed statistically. The statistical analyses were adjusted for survival differences among groups.

Results:

Mortality

The high dose of 90 mg/kg/day of losartan appeared to exceed the maximum tolerated dose in STZ-induced diabetic rats as evidenced by the higher than expected early deaths. The percent early deaths through Study Week 12 were 0% for untreated controls, 4% for STZ controls and 6% and 8% for the two high dose losartan groups. By Study Week 19, the percent early deaths were 0% for untreated controls, 5% for STZ controls and 16%

and 18% for the two high dose losartan groups (high dose lowered from 90 to 60 mg/kg/day during Study Week 19). Animal survival at scheduled sacrifice was decreased for STZ-controls compared with untreated (placebo) controls (P=0.007). Pairwise comparison of STZ-losartan treated groups with STZ-controls showed decreased survival in high dose STZ-losartan groups (P=0.062 for the Day 5 group and P=0.003 for the Day 29 group).

Animal Survival

Group	Day	Survived/Total	Survived/Total	Survived/Total (%)
Placebo	0	34/38	34/37	68/75 (91)
STZ	60	31/38	26/37	57/75 (76)
STZ/Losartan	60/5	40/50	-	40/50 (80)
STZ/Losartan	60/30	42/50	-	42/50 (84)
STZ/Losartan	60/90(60)	31/50	-	31/50 (62)
STZ/Losartan	60/90(60)	-	25/50	25/50 (50)

Body Weight

Mean body weights in high dose STZ-losartan groups were slightly lower than mean body weight in STZ controls at Week 18 but were not appreciably different at Week 52 or Week 56 following the downward adjustment of the losartan high dose in Study Week 19. Mean body weights of mid and low dose STZ-losartan groups were comparable to those of STZ controls.

Treatment Group	Mean Body Weight (gm) (% Difference from STZ)			
	Baseline	Week 18	Week 52	Week 56
Placebo	289	646	827	872
STZ (60)	294	624	774	809
STZ/Losartan (60/5)	287	620 (-0.6%)	761 (-0.4%)	-
STZ/Losartan (60/30)	295	619 (-0.8%)	821 (+7%)	-
STZ/Losartan(60/90-60) ^a	292	585 (-6%)	769 (-0.6%)	-
STZ/Losartan(60/90-60) ^b	291	600 (-4%)	-	800 (-1%)

^a Sacrificed at Study Week 53

^b Sacrificed at Study Week 57

Serum Chemistry

Serum urea nitrogen and creatinine levels were comparable in all treatment groups.

Plasma Angiotensin II Levels

Plasma angiotensin II levels were comparable in placebo and STZ diabetic control groups throughout the study, whereas, sustained increases in angiotensin II levels were noted in all losartan-treated groups. At one month, losartan produced dose-related increases in mean angiotensin II concentrations, ranging from 2-3 fold in the low dose group to 9-17 fold in the high dose group relative to combined mean control values. At 6 and 12 months, mean angiotensin II levels in the losartan 30 and 90/60 mg/kg/day (Week 53 sacrifice) groups were not remarkably different from 1-month values.

Plasma Angiotensin II (pg/ml) Levels

Treatment Group	1 Month		6 Months		12 Month	
	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.
Placebo	36	62	49	58	54	28
STZ	17	54	33	50	38	26
STZ/Losartan-5	75	112	249	186	262	236
STZ/Losartan-30	341	283	452	236	323	232
STZ/Losartan 90-60 (Week 53)	448	526	270	435	290	249

a.m.= Samples obtained between 7:30 and 9:30 a.m.

p.m.= Samples obtained between 1:00 and 3:00 p.m.

Renal Tumors

The renal tumor incidences were tabulated as the number of tumor bearing rats and as the number of renal tumors per rat.

Grossly evident renal tumors were not seen in any of the untreated controls, but were often seen in STZ-diabetic control rats (significantly different; $p < 0.001$). There were no statistically significant differences in the mean number of grossly evident renal tumors comparing STZ-controls with STZ/losartan groups (either as grossly evident tumor-bearing animals or grossly evident tumors per animal). Additional analyses conducted by the sponsor on age-adjusted number of gross renal tumors per rat detected no statistical differences among STZ/losartan groups and STZ-controls. Grossly evident tumor findings are summarized as follows:

Number of Rats with Renal Tumors

Treatment Group (mg/kg)	No. Rats with Grossly Evident Renal Tumors	
	Number of Total No. of Rats (%)	Number of Rats Sacrificed at Study Week (%)
Placebo	0/75 (0%)	0/73 (0%)
STZ (60)	26/75 (35%)	26/70 (37%)
STZ/Losartan (60/5)	19/50 (38%)	19/48 (40%)
STZ/Losartan (60/30)	18/50 (36%)	18/46 (39%)
STZ/Losartan(60/90-60) ^a	15/50 (30%)	14/37 (38%)
STZ/Losartan(60/90-60) ^b	13/50 (26%)	13/34 (38%)

^a Sacrificed at Study Week 53

^b Sacrificed at Study Week 57

Number of Renal Tumors per Rat

Treatment Group (mg/kg)	Mean Number of Grossly Evident Tumors	
	Unadjusted	Age-Adjusted
Placebo	0.00	-
STZ (60)	0.57	0.47 [0.60] ^c
STZ/Losartan (60/5)	0.54	0.54
STZ/Losartan (60/30)	0.46	0.46
STZ/Losartan(60/90-60) ^a	0.42	0.49
STZ/Losartan(60/90-60) ^b	0.42	[0.57]

^a Animals sacrificed at Study Week 53

^b Animals sacrificed at Study Week 57

^c Value for those rats sacrificed in Study Week 57

The numbers and percent of STZ/losartan tumor-bearing rats with histologically detected renal tumors were not significantly different from the number of STZ-treated tumor-bearing rats.

Incidence of Histologically Detected Renal Tumors

Treatment Group (mg/kg)	Renal Tumor-Bearing Rats	
	Rats with tumors / Total Rats	Percent of rats with tumors
Placebo	0/75	0%
STZ (60)	51/75	68%
STZ/Losartan (60/5)	36/50	72%
STZ/Losartan (60/30)	38/50	76%
STZ/Losartan (60/90-60) ^a	37/50	74%
STZ/Losartan (60/90-60) ^b	31/50	62%

^a Animals sacrificed at Study Week 53

^b Animals sacrificed at Study Week 57

In the STZ/losartan 60/90-60mg/kg/day (losartan initiated Study Day 5) group, there was a slight, but statistically significant, increase (P<0.05) in the incidence of renal tumors (any type). The increased incidence in this group was due solely to an increase in the incidence of benign tumors (tubular adenomas) since there was no significant increase in the incidence of malignant renal tumors. There was no similar increased tumor incidence (any type or malignant) associated with the administration of the same dosage level of losartan beginning on Study Day 29.

Age-Adjusted Incidence of Histologically Detected Renal Tumors/Rat

Treatment Group (mg/kg)	No. Rats	Renal Tumors/Rat at Week 53		No. Rats	Renal Tumors/Rat at Week 57	
		Malignant or Benign	Malignant		Malignant or Benign	Malignant
Placebo	30	0.00	0.00	34	0.00	0.00
STZ (60)	31	1.22	0.22	26	1.21	0.28
STZ/Losartan (60/5)	40	1.28	0.26			
STZ/Losartan (60/30)	42	1.63	0.14			
STZ/Losartan (60/90-60)	31	2.27*	0.28			
STZ/Losartan (60/90-60)				25	1.21	0.18

*Significantly different from STZ-control (p<0.012; adjusted for multiple tests)

52-Week Oral Losartan and Losartan/Lisinopril Tumorigenicity Study in STZ-Treated RatsStudy Facility: Laboratories Merck Sharp and Dohme-Chibret, Rion, FranceStudy No.: TT#93-617-0Study Dates: 4/14/93 - 4/13/94GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.Animals: Male Crl:CD(SD)BR rats (8 weeks old, 244-375 gm)Drug Administration: Losartan (Lot# 005H029) and lisinopril (Lot# 000T100) were dissolved in tap water and administered orally in the drinking water.Procedure: Animals were allocated to the following treatment groups:

Treatment Group	STZ Dose (mg/kg)	No. of Rats
Placebo	-	50
STZ	60	50
STZ/Losartan	60/30	50
STZ/Losartan/ Lisinopril	60/30/3.5 ^b	50

^a STZ administered as a single IV dose; losartan and losartan/lisinopril administered in the drinking water as daily doses.

^b Lisinopril daily dosage level lowered from 6.25 mg/kg/day in Study Week 13.

Dose Selection Rationale: The 30 mg/kg/day losartan dose was selected to assess the validity of those findings of the Remuzzi et.al. diabetic nephropathy study. Lisinopril (initial dose of 6.25mg/kg/day) was coadministered with losartan (30 mg/kg/day) in order to inhibit losartan induced increases in angiotensin II levels.

On Study Day 1, all STZ-designated rats received a single IV injection of 60 mg/kg of STZ as a citrate buffered (pH 4.5) solution. Beginning on Day 3, all STZ-treated animals received daily SC injections of Ultralente Insulin (6 units; dosage adjusted weekly) to maintain serum glucose concentrations between 200 and 400 mg/dl. Losartan 30 mg/kg/day and losartan/lisinopril 30/6.35 (subsequently lowered to 3.5) mg/kg/day were administered in the drinking water beginning on Study Day 5. Rats were observed daily for mortality and clinical signs of toxicity. Body weights were recorded at pretest and twice weekly for all STZ-treated animals. Placebo control rats were weighed twice

weekly until Study Week 13 and then once weekly thereafter. Food consumption was measured weekly. Venous blood was obtained via a tail vein from 5 rats/group at 6:30-8:30 AM and 1:00-3:00PM in Study Weeks 4, 27 and 52 for determination of plasma drug levels and plasma angiotensin II levels. Venous blood was also obtained from the vena cava of all surviving rats and from all rats sacrificed during the study prior to final necropsy for measurement of serum urea nitrogen and creatinine. Urine samples were collected from 15 rats/group in Study Week 52 for urinalysis. Kidneys from rats found dead, sacrificed or killed at the scheduled necropsy (Week 52) were weighed, examined for grossly evident tumors and fixed on slides for microscopic examination.

Results:

Mortality

A statistically significant ($P < 0.05$) increased mortality was seen in STZ/losartan/lisinopril treated rats compared to STZ-controls or STZ/losartan treated rats. Of the 17 rats found dead or sacrificed in this group, 7 rats died prior to lowering the dose of lisinopril from 6.25 to 3.5 mg/kg/day in Study Week 13; 3 of these animals (found dead in Study Week 12) had slight necrosis of the proximal convoluted tubules. Clinical signs of toxicity noted prior to death or sacrifice included decreased motor activity, pallor, piloerection, hypothermia, dyspnea staining of the muzzle and urinary areas. As necropsy was limited to the kidneys, the sponsor was unable to determine the exact cause of death.

Animal Survival/Mortality

Treatment Group	Rats Surviving / Rats Tested (%)	Sacrificed	Deaths
Placebo	45/50 (90%)	2	3
STZ (60)	43/50 (86%)	3	4
STZ/Losartan (60/30)	46/50 (92%)	2	2
STZ/Losartan/Lisinopril (60/30/6.25-3.5)	33/50 (66%)	4	13

Body Weight

Compared to placebo or to STZ controls, the mean body weight and body weight gain decrements were more pronounced in rats treated with the losartan/lisinopril combination than in rats treated with losartan alone.

Body Weight and Body Weight Gain

Treatment Group	Mean Body Wt (g)	% Change in Body Wt	% Change in Body Wt	% Change in Body Wt
	Placebo	STZ	STZ/Losartan	STZ/Losartan/Lisinopril
Placebo	312	833	-	-
STZ	311	733	-	-19%
STZ/Losartan	313	727	-7.6%	-20%
STZ/Losartan/Lisinopril	314	671	-8.5%	-31%

Food Consumption

Food consumption in STZ/losartan and STZ/losartan/lisinopril treated rats was similar to that of STZ controls.

Serum Chemistry

Serum urea nitrogen in STZ/losartan and STZ/losartan/lisinopril treated rats was elevated above placebo and STZ controls.

Serum Urea Nitrogen

Treatment Group	% Change Compared to Placebo
STZ	+6.0
STZ/Losartan	+21.8
STZ/Losartan/Lisinopril	+74.4

Kidney Weight

STZ-diabetic rats had increased absolute and relative (% of body weight) kidney weights compared to placebo controls. The increase in absolute and relative kidney weights in STZ/losartan-treated rats did not differ from STZ controls; however, higher increases in absolute and relative kidney weights were noted in rats treated with STZ/losartan/lisinopril.

Absolute and Relative Kidney Weights

Treatment Groups	No. Rats	% Difference in Absolute Kidney Weights		% Difference in Relative Kidney Weights	
		vs. Placebo	vs. STZ	vs. Placebo	vs. STZ
STZ	43	+22%	-	+44%	-
STZ/Losartan	46	+23%	+1%	+42%	-1%
STZ/Losartan/ Lisinopril	33	+34%	+10%	+72%	+19%

Renal Tumors

Grossly evident renal tumors were not seen in any of the placebo controls, but were often seen in STZ-diabetic control rats. There was a statistically significant ($P < 0.001$) increase in the incidence of grossly evident renal tumors (age-adjusted) in the STZ/losartan/lisinopril treated rats compared to STZ controls and STZ/losartan treated rats.

Incidence of Grossly Evident Renal Tumors

Treatment Groups	No. Rats Necropsied	% of Rats with Renal Tumors	Mean Renal Tumors/Rat
Placebo	45	0%	0.00
STZ	43	42%	1.51
STZ/Losartan	46	39%	1.11
STZ/Losartan/Lisinopril	33	70%	3.35*

* Age-adjusted values

* $P < 0.001$ compared to STZ-control and STZ/losartan groups.

There was a statistically significant ($P < 0.001$) increase in the incidence of histologically detected renal tumors (any type) in STZ/losartan/lisinopril rats compared to STZ controls. The incidence of histologically detected renal tumors or percent of tumor-bearing rats treated with STZ/losartan did not significantly differ from STZ controls.

Incidence of Histologically Detected Renal Tumors^a

	Placebo	STZ	STZ/Losartan	STZ/Losartan/Lisinopril
Percent of Rats with Renal Tumors	0%	52%	50%	74%
Mean Renal Tumors/Rat ^b	0	0.76	0.54	2.59*
Percent of Rats with Malignant Tumors	0%	14%	8%	18%

^a Renal histologic examination conducted on 50 rats/group

^b Age-adjusted values

* P<0.001 compared to STZ control

The increase in the number of histologically detected renal tumors in STZ/losartan/lisinopril treated rats was not associated with an increase in malignant tumors but was due to an increase in benign renal tumors (tubular adenomas).

Plasma Angiotensin II Levels

Morning plasma sampling resulted in angiotensin II levels that were 7.8-15.5 fold greater for the STZ/losartan-treated group than for the STZ control group. Afternoon plasma sampling resulted in angiotensin II levels that were 6.2-8.3 fold greater for the STZ/losartan-treated group than for the STZ control group. Co-administration of lisinopril inhibited the angiotensin II increase induced by losartan. Angiotensin II levels for the STZ/losartan/lisinopril group were similar to placebo control values.

Mean Plasma Angiotensin II (pg/ml) Levels

Week	Time	Placebo	STZ Control	STZ/Losartan	STZ/Losartan/Lisinopril
4	a.m.	30.7	46.8	367.1	57.7
	p.m.	83.1	48.7	494.8	56.8
14	p.m.	-	53.8	701.5	81.3
18	p.m.	-	95.0	605.0	68.6
	a.m.	33.5	38.9	602.9	44.5
27	p.m.	58.0	59.9	498.5	51.5
	a.m.	-	21.2	222.8	34.9
52	p.m.	67.1	46.8	290.6	35.4

a.m.= Samples obtained between 6:30 and 8:30 a.m.

p.m.= Samples obtained between 1:00 and 3:00 p.m.

OVERALL SUMMARY AND EVALUATION

Two one-year rat tumorigenicity studies were conducted by the sponsor to address the previous preclinical observation by Remuzzi *et al* of renal neoplasia in streptozotocin (STZ)-induced diabetic rats treated for 1 year with 30 mg/kg/day of losartan. STZ is a known carcinogen and is reported to induce renal adenomas and carcinomas in rats and mice (refs. 1-14). In both studies, the sponsor used the same dose of STZ (60 mg/kg IV), and tested the same dose (30 mg/kg/day) of losartan that was used in the Remuzzi *et al* study. In one study (T1# 93-048-0), two additional doses of losartan (low dose=5 mg/kg/day; high dose=90 mg/kg/day for 18 weeks and then reduced to 60 mg/kg/day) were evaluated; in the other study (TT# 93-617-0) losartan (30 mg/kg/day) was also co-administered with the ACE inhibitor, lisinopril, to determine if renal tumorigenesis was associated losartan-induced increases in plasma angiotensin II levels.

In both studies, daily administration of 30 mg losartan/kg/day for one year caused no significant increases in the incidences of grossly evident or histologically detected renal tumors compared to STZ-diabetic controls. The statistical analysis compared the number of renal tumor-bearing rats and also the number of tumors per rat. Similarly, no significant increases in the incidences of grossly evident or histologically detected renal tumors were observed with 5 mg losartan/kg/day and for one of the two high dose (90-60 mg losartan/kg/day) groups compared to STZ-diabetic controls. In the second high dose group (90-60 mg/kg/day; losartan initiated on Study Day 5) losartan caused no significant increase in the incidence of grossly evident or histologically detected renal tumor-bearing rats; however, a statistically significant increase in the age-adjusted incidence of histologically detected renal tumors/rat (any type) was detected. The increased incidence in this group was due solely to an increase in the incidence of benign tubular adenomas. There was no significant increase in the incidence of malignant renal tumors. The biological relevance of this increased incidence in one of the two high dose groups is questionable, particularly since the other high dose group (90-60 mg/kg/day; losartan initiated on Study Day 29) showed no statistically significant increase in age-adjusted histologically detected renal tumors. Given the fact that the dose of losartan administered for the initial 18 weeks of the study exceeded a maximally tolerated dose (associated with increased mortality and body weight decrements), it is reasonable to suspect that this singular positive benign tumor finding could be attributed to pathophysiologic factors (stress, hormones) accompanying the severe toxicity and not from interaction with losartan. Administration of the initial high losartan dose (90 mg/kg/day, which exceeded the maximally tolerated dose) that was initiated on Study Day 5 coincided with the period of continuing STZ-induced DNA renal damage as determined by the Alkaline Elution genotoxicity assay. Losartan did not alter the level of renal DNA damage induced by STZ in the genotoxicity assay.

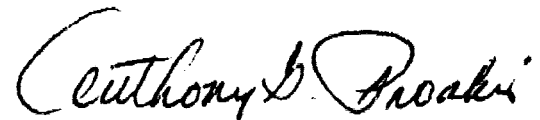
Although losartan treatment did not significantly increase the incidences of grossly evident or histologically detected renal tumors in STZ-diabetic rats in the second study

co-administration of lisinopril (6.25-3.5 mg/kg/day) with losartan (30 mg/kg/day) caused statistically significant increases in the incidence of grossly evident renal tumors per rat and in histologically detected renal tumors. The increase in the number of histologically detected renal tumors in STZ/losartan/lisinopril treated rats was not associated with an increase in malignant tumors but was due to an increase in benign renal tubular adenomas. The addition of lisinopril to the STZ/losartan treatment (which was done to determine whether anticipated losartan-associated increases in the incidence of STZ-induced renal tumors could be prevented by preventing the losartan-induced increases in angiotensin II levels) was associated with severe toxicity (decreased motor activity, hypothermia, dyspnea) and increased mortality. This toxicity prompted the sponsor to make a downward adjustment of the lisinopril dose from 6.25 to 3.5 mg/kg/day in Study Week 13. Despite the lisinopril dose adjustment, decrements in mean body weight and mean body weight gain at the end of the one-year study were more pronounced in STZ-diabetic rats treated with the losartan/lisinopril combination than STZ-diabetic rats treated with losartan alone. Losartan/lisinopril treatment was also associated with absolute and relative kidney weights above those of STZ-diabetic controls. The sponsor attributes the increased incidence of benign renal tumors and renal hyperplasia in STZ-diabetic rats which received the losartan/lisinopril combination to nephrotoxicity. Chronic renal injury has been shown to enhance the renal tumorigenic potential of several nitrosamines (including STZ).

The increased incidence of benign renal tumors in STZ-diabetic rats treated with the losartan/lisinopril combination, but not with the same dose of losartan alone, fails to implicate losartan as a tumor promoter. The initial dose of lisinopril, when co-administered with losartan, was both lethal and nephrotoxic in these diabetic rats. Defense mechanisms against effects that injure DNA may not be optimal in sick animals. It is generally accepted that high doses of non-genotoxic substances that produce toxicity, cell death and cell replacement create conditions favorable for the growth of tumors. It should be further emphasized that losartan was not genotoxic when evaluated in a battery of genotoxicity assays and showed no evidence of renal tumorigenic activity in the two-year mouse and rat bioassays.

A major difference exists between the Remuzzi et al and Merck studies on the incidences of renal tumors in STZ-diabetic control rats. In the Remuzzi et al study, no grossly evident renal tumors were observed in a group of 8 STZ-treated rats, whereas, in the Merck studies (using larger groups of rats) the percentages of STZ-treated rats with grossly evident renal tumors were 35% and 42%. The renal tumor incidence rates observed in the Merck studies are more consistent with the incidence rates cited in published reports on STZ-induced renal tumors in various strains of rats (refs. 2-14). For Sprague-Dawley rats, three independent studies (Refs. 7, 10, 14) using single STZ doses of 35-65 mg/kg IV revealed 36%-56% of rats with renal tumors within one year following STZ treatment. It appears, therefore, that the zero incidence noted by Remuzzi et al is inconsistent with the results of the Merck studies as well as the relevant literature.

In summary, the results of two studies conducted by the sponsor do not support the losartan-associated renal tumor findings of Remuzzi et al. No evidence of a renal tumor promotion effect by losartan at non-lethal doses was detected.



Anthony G. Proakis, Ph.D.
1/30/95

cc: Orig.

HFD-110

HFD-110/CSO

HFD-110/AProakis

Accepted by CAA on 1/30/95

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CAC Executive Committee Final Report

Application: NDA 20-836
Division: HFD-110
Date: November 15, 1994
Reviewer: Proakis
Chairperson: Taylor *u.s.* 11/16/94
Members: Contrera, Resnick, Defelice

Dr. Proakis presented results of mouse and rat dose rangefinding studies and carcinogenicity studies of losartan (Merck & Co. NDA# 20,836) before the Carcinogenicity Assessment Committee-Executive Committee (CAC-EC) on Nov. 15, 1994 to obtain decisions on the adequacy of high-dose selections, on the adequacy of the studies and on conclusions of tumor findings. CAC-EC members present were Drs. Alan Taylor, Joseph Contrera and Albert DeFelice.

DISCUSSION AND DECISIONS

Each CAC-EC member was provided a summary of the dose rangefinding studies, carcinogenicity studies and copies of FDA statistician's analysis of the tumor data. The CAC-EC members agreed that, based on study results, maximally tolerated doses were achieved in both the mouse and rat carcinogenicity studies; both studies were deemed adequate based on acceptable numbers of surviving animals at study termination.

It was the committee's conclusion that the slightly increased incidence of lung adenocarcinoma in male mice was unlikely drug-related and should be disregarded based on (1) the absence of a significant pairwise difference between high dose and control, (2) the absence of significant increased trend for combined incidence of lung adenocarcinoma and lung adenoma and (3) the observed increased incidence of lung adenocarcinoma was within the sponsor's historical control range for this tumor in this mouse strain.

In the case of the increased incidence of pancreatic acinar adenoma in female rats, the committee recommended that this increased incidence should be addressed in the product labeling.

Anthony Proakis
Anthony Proakis, Ph.D
11/16/94

cc:
NDA 20-836
HFD-110/div file
/Resnick
Proakis
HFD-502/cac file

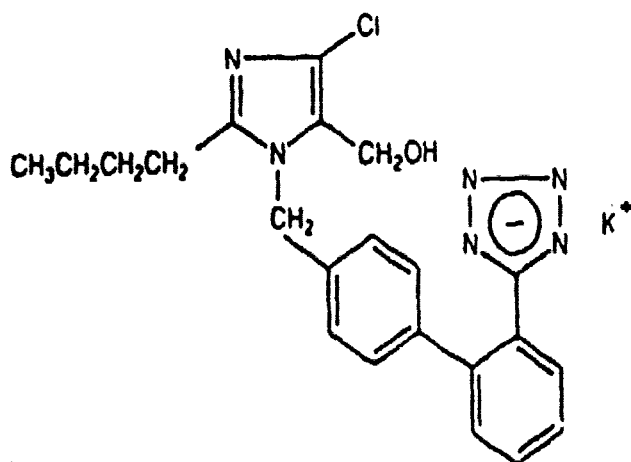
CAC-EC CONSIDERATION OF CARCINOGENICITY STUDIES

Anthony G. Proakis, Ph.D
11/15/94

NDA # 20,386 (Submission dated 12/03/93)

SPONSOR: Merck & Co., Inc.
West Point, PA 19486

DRUG: (COZAAP[®], Losartan)



BACKGROUND: Losartan is an angiotensin II receptor antagonist developed for the treatment of hypertension. For evaluation of carcinogenicity potential, the sponsor conducted a 105-week oral (gavage) carcinogenicity study in rats and a 92-week oral (gavage) carcinogenicity study in mice. Dose selection for each study was based initially on 14-week oral dose-rangefinding studies in the respective species; subsequent dose adjustments were made based on toxicity considerations occurring in the long-term studies.

14-Week Oral Range Finding Toxicity Study in Rats**Study Facility:** MSD Research Laboratories, West Point, PA**Study No:** TT #90-013-0**Study Dates:** 1/25/90- 1/27/90**GLP Compliance:** Statement indicates that this study was conducted in compliance with GLP regulations.**Animals:** Male and female Crl:CD(SD) BR rats (39 days old at initiation of study).**Drug Administration:** Losartan (Lot # 005H004 and 005H010) was dissolved in deionized water and administered orally by gavage.**Dose Levels:** 0 (vehicle), 50, 150, 250 and 450 mg/kg/day (15/sex/dose group)

Observations/Measurements: Rats were observed daily for mortality and clinical signs of toxicity. Food consumption was measured weekly and body weights were measured prior to treatment, during week 1 and twice weekly, thereafter. Ophthalmoscopic examinations were conducted on all surviving control and high dose rats during weeks 3 and 11 of treatment. Blood samples were obtained from the orbital sinus or tail vein during weeks 5, 8 and 13 for hematologic and serum chemistry measurements. Urine was collected from 10 rats/sex/group during treatment weeks 8 and 13 for urinalysis. Rats that survived to scheduled necropsy were weighed, sacrificed and examined for gross pathology. Major organs were removed and weighed. Sections of major organs and tissues from the control and high dose animals were fixed on slides, stained and examined for microscopic pathology.

Results: A total of 5 high dose rats died during the study (3F, 1M during week 5 and 1M during week 8 of treatment).

Mortality

Dose (mg/kg/day)	# Died/# Treated	
	Males	Females
0	0/15	0/15
50	0/15	0/15
150	0/15	0/15
250	0/15	0/15
450	2/15	3/15

Clinical Signs

Some rats in the 150-450 mg/kg/day dose groups had occasional dyspnea which was associated with excessive salivation following dosing. Most high dose rats had excessive salivation following dosing that was gone within 1 hour.

Other Treatment-Related Effects

Measurement		% Difference from Control			
		50	150	250	450
Body Weight**	M	-2	-10	-13	-14
	F	-2	-5	-8	-8
Body Wt. Gain	M	-4	-15*	-18*	-21*
	F	-4	-8*	-13*	-16*
<u>Hematology</u>					
RBC Count	M	-1	-4	-9	-12
	F	+1	-4	-4	-12
Hct	M	-1	-2	-4	-8
	F	0	-4	-5	-10
Hb	M	0	-2	-4	-7
	F	0	-2	-4	-12
<u>Serum Chemistry</u>					
Urea Nitrogen	M	+25	+84	+99*	+229*
	F	+19	+50	+83*	+132*
ALT	M	+12	0	-6	+50
	F	+6	-6	-3	+10
Potassium	M	+4	+2	+4	+13*
	F	+8*	+10*	+10*	+10*
<u>Organ Weight</u>					
<u>Heart</u>					
Absolute Wt	M	-16.4*	-24.0*	-26.9*	-23.4*
	F	-3.7	-12.0*	-13.8*	-15.7*
Relative Wt	M	-12.5*	-15.6*	-15.6*	-6.2*
	F	-2.8	-8.3*	-5.6*	-8.3*

*Significantly difference from control (P<0.05)

** No statistical evaluation conducted

Histopathology

Macroscopic examination revealed the presence of dark, red-brown foci in the glandular mucosa of the stomach. Most of these foci were confirmed microscopically as focal erosions of the glandular epithelium with adjacent hyperemia, hemorrhage and mild inflammation.

Histopathology

Observation		Incidence				
		Control	50	150	250	450
Stomach Mucosa						
Focal Erosions	M	0/15	1/15	0/15	7/15	6/15
	F	0/15	0/15	0/15	3/15	4/15
Kidney						
JG Cell	M	0/15	0/15	3/15	5/15	8/15
Hyperplasia	F	0/15	0/15	1/15	1/15	3/15

One Hundred-Five-Week Oral Carcinogenicity Study in Rats**Study Facility:** MSD Research Laboratories, West Point, PA**Study No:** TT #90-099-0**Study Dates:** 7/11/90 - 7/13/92**GLP Compliance:** Statement indicates that this study was conducted in compliance with GLP regulations.**Animals:** Male and female Sprague-Dawley Crl:CD (SD) BR rats (115-175 gm females, 119-194 gm males, 38 days old, housed individually).**Drug Administration:** Losartan (Batch # 9, 10, 19 and 29) was dissolved in deionized water and administered orally by gavage once daily.**Dose Levels:** 0 (Vehicle; 130/sex), 15, 45 and 135/270 mg/kg/day * (75/sex/group)

** Note: High dose raised from 135 to 270 mg/kg/day in week 6 of treatment because previous dose did not appear (from 1-year chronic rat study) to be the maximally tolerated dose (MTD).*

Observations/Measurements: Animals were observed daily for mortality and observed weekly for clinical sign of toxicity. Rats were palpated for the presence of masses every 4th week beginning Drug Week 26. Body weights were recorded prior to study initiation, twice per week through Drug Week 13 and once weekly thereafter. Ophthalmologic examinations were conducted in Drug Weeks 52 and 102. A complete necropsy was performed on all animals. Sections of major tissues and organs were fixed on slides and examined microscopically. Treatment-related increases in tumor incidence were assessed by use of a trend test (Mantel-Haenszel procedure).

Results:

Mortality and Survival: Two high dose rats (1M,1F) died and one high dose female was sacrificed between Drug Weeks 18 and 34 due to marked weight loss associated with cecal erosive inflammation. Two additional high dose rats were sacrificed (1F & 1M in Drug Weeks 49 and 70, respectively) due to marked weight loss with associated intestinal lesions. In addition, moderate to marked edema of the lungs, presumably due to hypotension, was the cause of death or sacrifice of a high dose female and 7 high dose males between Drug Weeks 25 and 92. Although these deaths were related to drug treatment, they did not significantly affect the overall incidence of mortality at termination of the study. In fact, there was a statistically significant decrease in mortality (increase in survival) in males with increasing dose.

Animal Survival at Study Termination

Parameter		Dose Group (mg/kg/day)			
		0	15	45	135/270
# Alive/Total	M	21/130	19/75	26/75	26/75
	F	37/130	20/75	20/75	19/75
% Survival	M	16.2	25.3	34.7	34.7
	F	28.5	26.7	26.7	25.3

Physical Signs: Excessive salivation immediately after dosing and lasting up to approximately 45 min was seen occasionally throughout the study in high dose rats. Tarry stools occurred in 3 high dose rats (1M, 2F) between Drug Weeks 18 and 34.

Body Weight: Male and female rats given 135 mg/kg/day for the first 5 weeks had body weights slightly below control values at the end of those 5 weeks (mean decrement less than 10%). After increasing the high dose to 270 mg/kg/day, body weight in this group was further reduced compared to controls.

Effect on Mean Body Weight

Dose Group (mg/kg/day)	Percent Difference From Control Weight									
	5 Wks		26 Wks		52 Wks		78 Wks		104 Wks	
	F	M	F	M	F	M	F	M	F	M
15	-1	-2	-3	-1	-1	+1	+3	+3	-4	+7
45	-4	-5	-6	-5	-6	-2	0	+5	-7	+10
135/270	-2	-5	-10	-11	-14	-11	-13	-8	-13	+4

Mean Pretest Weight: Control=147gm, Low Dose=145gm, Mid Dose=143gm, High Dose=147gm

Body Weight Gain of Survivors at Study Termination

Dose Group (mg/kg/day)	% Difference from Control Body Wt. Gain	
	Females	Males
15	-8.2	+9.5
45	-8.0	+14.5
135/270	-18.5	+4.9

Ophthalmologic Effects: No treatment-related ocular effects were observed.

Gross Pathology: No evidence of treatment-related pathology on gross examination.

Microscopic Pathology:

Neoplastic Lesions: The sponsor's analysis revealed no evidence of a statistically significant increased trend in the incidence of any neoplasm in either sex of rat (Appendix I for tumor type and site). Summary of tumor incidence is as follows:

Summary of Neoplasms in Male Rats

	Number (% Incidence)			
	Control	Low Dose	Mid Dose	High Dose
# Rats with Neoplasms				
Malignant	28 (22)	24 (32)	23 (31)	20 (27)
Benign	91 (70)	59 (79)	63 (84)	49 (65)
Malignant or Benign	98 (75)	68 (91)	67 (89)	54 (72)
Total # of Neoplasms				
Malignant	30 (23)	25 (33)	24 (32)	21 (28)
Benign	170 (131)	105 (140)	116 (155)	95 (127)
Malignant or Benign	200 (154)	130 (173)	140 (187)	116 (155)

Control= 130 rats, Other Groups=75 rats

Summary of Neoplasms in Female Rats

	Number (% Incidence)			
	Control	Low Dose	Mid Dose	High Dose
# Rats with Neoplasms				
Malignant	42 (32)	26 (35)	29 (39)	13 (17)
Benign	126 (97)	68 (91)	70 (93)	65 (87)
Malignant or Benign	128 (98)	70 (93)	74 (99)	68 (91)
Total # of Neoplasms				
Malignant	45 (35)	30 (40)	31 (41)	14 (19)
Benign	261 (201)	144 (192)	135 (180)	129 (172)
Malignant or Benign	306 (235)	174 (232)	166 (221)	143 (191)

Control=130 rats, Other Groups=75 rats

Positive Tumor Findings: Whereas the sponsor's analysis showed no significant increase in tumor incidence, analysis of the tumor data by FDA statisticians Section (Statistical Review and Evaluation attached) revealed a statistically significant trend in pancreatic acinar adenomas in female rats. A pairwise comparison (high dose vs. control) also showed a statistically significant difference.

Pancreatic Acinar Adenomas in Female Rats

Dose Group (mg/kg/day)	Tumor Incidence	Trend Test	Pairwise Test
Control	0/130		
15	0/75		
45	0/75		
135/270	3/75	P=.0084*	P=.043*

*Statistically significant

Non-Neoplastic Lesions: There was a treatment-related, dose-dependent increase in the incidence of juxtaglomerular (JG) cell hyperplasia in the kidneys of both sexes. This effect was characterized by an increase in the size and number of the JG cells comprising the wall of the afferent arteriole of the glomerulus. Increased incidences of renal focal tubular hypertrophy were seen in male rats in the mid and high dose groups compared to controls.

Renal Effects

Renal Effect		% Incidence			
		Control	Low Dose	Mid Dose	High Dose
JG Cell Hyperplasia	F	0	4.0	12	43
	M	0	11	43	71
Renal Tubular Hypertrophy	F	1.5	4.0	2.7	5
	M	2.3	1.3	7.1	15

A slight increase in the incidence of losartan-related cecal erosive inflammation was noted in high dose males (5%) and females (7%) compared to controls (1% and 0% for males and females, respectively). Also, an increased incidence of gastric lesions was noted in losartan-treated males.

Gastrointestinal Effects

Gastric Lesion	% Incidence in Male Rats			
	Control	Low Dose	Mid Dose	High Dose
Fundus, Erosion/Ulcer	11	23	17	20
Pylorus, Erosion/Ulcer	8	15	5.3	15
Nonglandular Mucosa, Focal Hyperplasia	2.3	1.3	1.3	12

A non-dose-dependent increase in the incidence of focal vacuolation of the adrenal cortex was seen in rats in all losartan-treated groups. The incidence of this change was 22%, 45%, 44% and 51% for the control, low, mid and high dose groups, respectively. The change was characterized by the presence of one or more focal regions of cytoplasmic lipid-like vacuolation in the cortex, primarily in the zona fasciculata.

Dose Selection and MTD Considerations

Dose selection for the rat carcinogenicity study was based on results of a 14-week oral dose-rangefinding study in which 4 dose levels (50, 150, 250 and 450 mg/kg/day) were evaluated. Doses of 150, 250 and 450 mg/kg/day caused dose-related reductions from control body weights (-10%, -13%, and -14%, respectively in males and -5%, -8% and -8%, respectively in females) and body weight gains (-15%, -18% and -21%, respectively in males and -8%, -13% and -16%, respectively in females). Treatment with 450 mg/kg/day also altered serum biochemistry (increased serum urea nitrogen and phosphorus) and was lethal to 5/30 rats. Doses of 250 and 450 mg/kg suppressed erythroid parameters and produced gastric lesions (hemorrhage, hyperemia and epithelial erosion). In view of the fact that a dose of 450 mg/kg/day was clearly toxic and lethal to some animals, the 250 mg/kg/day dose produced GI toxicity and doses of 150 and 250 mg/kg/day caused significant reductions in body weight, a dose of 135 mg/kg/day was selected by the sponsor as the high dose for the carcinogenicity study in rats. When interim (6 mo.) results from a 1-year chronic rat study revealed only slight body weight reduction from a dose of 135 mg/kg/day and no adverse effect on survival, the sponsor, at week 6 of the carcinogenicity study, increased the high dose to 270 mg/kg/day. This elevation of the high dose resulted in further decrements in rat body weights and increased GI-related toxicity. Based on these findings, it appears that a maximally tolerated oral dose was achieved with 270 mg/kg/day, particularly since the next highest dose tested (450 mg/kg/day) in the range-finding study was lethal to some rats. Despite the fact that a dose of 135 mg/kg/day was administered for the first 5 weeks, the study's value was not compromised since the animals were exposed to the higher dose for the remaining 100 weeks., i.e., 95% of the study's duration.

The sponsor's analysis of the results of the carcinogenicity study showed no evidence of a statistically significant increase in mortality with increasing oral doses of losartan to rats over the course of the study.

MTD Conclusions

- Male Rat MTD: Yes
Basis: GI toxicity, renal histopathology in 2-yr study.
Body weight and weight gain decrements, serum urea nitrogen elevation in 14-week study. Next highest dose (450 mg/kg/day) associated with mortality.
- Female Rat MTD: Yes
Basis: Body weight and weight gain decrements, renal histopathology in 2-yr study. Body weight and weight gain decrements, serum urea nitrogen and serum potassium elevations in 14-week study. Next highest dose (450 mg/kg/day) associated with mortality

Tumor and Other Histopathologic Findings

Sponsor found no evidence of a statistically significant ($p < 0.05$) increased trend in the incidence of any neoplasm in either sex of rat. However, statistical analysis of the tumor data by FDA's Division of Biometrics revealed a statistically significant trend in the incidence (0, 0, 0, 3 for Control, LD, MD and HD, respectively) of pancreatic acinar adenoma in female rats. The pairwise comparison (P value=0.043) of the high dose group with control was considered statistically significant. The significance level ($P < 0.05$) employed in this analysis, based on concurrent control data, assumes a spontaneous rate for this tumor type of no more than 1% (i.e., sponsor's overall historical control incidence in SD rats=0.4% and historical control range=0% to 2%). No statistically significant trend was detected for the incidence of pancreatic acinar adenoma (4, 2, 0, 5 for Control, LD, MD and HD, respectively) in male rats.

Non-neoplastic, drug-related pathology in rats included dose-dependent increases in the incidences of JG cell hyperplasia and focal tubular hypertrophy in the kidneys of both sexes and non-dose-dependent increases in gastric lesions in losartan-treated (all doses) males. The losartan-related increase in JG cell hyperplasia is regarded as an adaptive response of the renin-angiotensin system in response to blockade of angiotensin II activity, such a response is similarly seen with ACE inhibitors.

Appendix I- Primary Neoplasms in Rats

L-158,086: 105-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT 890-099-0
SUMMARY OF PRIMARY NEOPLASMS

NUMBER NECROPSIED	GROUP 1		GROUP 2		GROUP 3		GROUP 4	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
	130	130	75	75	75	75	75	75
STOMACH								
LEIOMYOMA	-	-	-	-	-	-	1	-
LEIOMYOSARCOMA	-	1	-	-	-	-	-	-
NONGLANDULAR MUCOSA, PAPILLOMA	-	1	-	-	-	-	1	-
NONGLANDULAR MUCOSA, SQUAMOUS CELL CARCINOMA	-	-	-	-	-	1	-	-
SMALL INTESTINE								
ADENOCARCINOMA	-	-	-	1	-	-	-	-
LEIOMYOMA	1	-	-	-	-	-	-	1
POLYP	1	-	-	-	-	-	-	-
LARGE INTESTINE								
FIBROMA	1	-	-	-	-	-	-	-
POLYP	-	1	-	-	-	-	-	1
LIVER								
BILE DUCT, CARCINOMA	-	-	-	-	-	1	-	-
HEPATOCELLULAR ADENOMA	4	4	1	2	3	2	3	4
HEPATOCELLULAR CARCINOMA	-	4	-	4	1	3	1	5
PANCREAS								
ACINUS, ADENOMA	-	4	-	2	-	-	3	5
ISLET, ADENOMA	10	20	10	10	9	14	3	6
ISLET, CARCINOMA	1	4	3	3	-	1	1	3
PERITONEUM								
LEIOMYOSARCOMA	1	-	-	-	-	-	-	-
BENIGN MESOTHELIOMA	-	-	-	-	1	-	-	-
MALIGNANT MESOTHELIOMA	1	-	-	-	-	-	-	-
OSTEOSARCOMA	-	1	-	-	-	-	-	-
ADRENAL								
CORTEX, ADENOMA	4	1	2	1	2	-	2	2
CORTEX, CARCINOMA	1	-	2	1	1	2	1	-
BENIGN PHEOCHROMOCYTOMA	4	16	3	7	1	7	1	4
MALIGNANT PHEOCHROMOCYTOMA	-	2	1	-	-	3	-	-
PARATHYROID								
ADENOMA	1	2	-	-	-	2	-	1

KEY: GROUP 1 = CONTROL

GROUP 2 = 15 MG/KG/DAY

GROUP 3 = 45 MG/KG/DAY

GROUP 4 = 135/270 MG/KG/DAY

CONTINUED
 L-158,086: 105-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT 890-099-0
 SUMMARY OF PRIMARY NEOPLASMS

	GROUP 1		GROUP 2		GROUP 3		GROUP 4	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
PITUITARY								
ADENOMA	107	63	63	45	66	55	57	39
CARCINOMA	1	-	-	-	-	-	-	-
THYROID								
FOLLICULAR CELL, ADENOCARCINOMA	-	2	1	-	1	3	-	1
PARAFOLLICULAR CELL, ADENOMA	16	15	7	11	7	3	3	7
FOLLICULAR CELL, ADENOMA	4	4	-	1	-	4	-	3
PARAFOLLICULAR CELL, CARCINOMA	1	-	-	-	1	1	-	1
BENIGN GANGLIONEUROMA	1	-	-	-	-	-	-	-
KIDNEY								
TUBULAR ADENOMA	1	-	-	-	-	1	-	2
HEMANGIOMA	-	-	-	-	-	-	-	1
BENIGN MESENCHYMAL TUMOR	-	-	-	2	1	-	-	-
URINARY BLADDER								
TRANSITIONAL CELL CARCINOMA	-	-	-	-	-	1	-	-
OVARY								
BENIGN SERTOLI CELL TUMOR	1	-	-	-	-	-	-	-
UTERUS								
FIBROMA	-	-	1	-	1	-	-	-
LEIOMYOSARCOMA	-	-	1	-	1	-	-	-
POLYP	2	-	6	-	-	-	1	-
ENDOMETRIAL STROMA, SARCOMA	-	-	-	-	-	-	-	-
VAGINA								
LEIOMYOSARCOMA	-	-	-	-	1	-	-	-
TESTIS								
LEYDIG CELL, ADENOMA	-	11	-	4	-	3	-	3
BENIGN MESOTHELIONA	-	-	-	2	-	-	-	-
PROSTATE								
CARCINOMA	-	-	-	-	-	1	-	-
SKIN								
FIBROMA	5	6	2	1	1	4	2	3
FIBROSARCOMA	1	1	-	2	-	-	2	1
HEMANGIOMA	-	-	1	-	-	-	-	-
MALIGNANT FIBROUS HISTIOCYTOMA	-	-	-	-	1	-	-	-
BENIGN KERATOACANTHOMA	-	4	1	2	-	1	-	2

KEY: GROUP 1 = CONTROL

GROUP 2 = 15 MG/KG/DAY

GROUP 3 = 45 MG/KG/DAY

GROUP 4 = 135/270 MG/KG/DAY

CONTINUED
 L-158,086: 105-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT #90-099-0
 SUMMARY OF PRIMARY NEOPLASMS

	GROUP 1		GROUP 2		GROUP 3		GROUP 4	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
SKIN								
LEIOMYOMA	1	-	-	-	-	-	-	-
LIPOMA	5	4	3	1	1	3	-	2
LIPOSARCOMA	-	-	-	1	-	-	-	-
NEUROFIBROMA	-	-	-	-	-	1	-	-
PAPILLOMA	-	3	-	2	2	2	-	3
RHABDOMYOSARCOMA	-	1	-	-	-	-	-	-
UNDIFFERENTIATED SARCOMA	-	-	-	-	-	-	-	1
MALIGNANT SCHWANNOMA	-	1	-	-	-	-	-	-
SEBACEOUS ADENOMA	-	-	-	-	-	2	-	-
BENIGN TRICHOEPITHELIOMA	-	2	-	1	-	-	-	-
MAMMARY GLAND								
ADENOCARCINOMA	27	-	15	1	18	1	5	2
ADENOLIPOMA	1	-	-	-	-	-	-	-
ADENOMA	9	-	5	1	3	-	3	-
FIBROADENOMA	78	3	37	7	37	6	45	4
LUNG								
ADENOCARCINOMA	-	-	-	-	-	-	-	1
ADENOMA	-	-	-	1	-	1	2	-
PLEURA								
MALIGNANT HIBERNOMA	-	-	1	-	-	-	-	-
HEART								
ATRIUM, EPITHELIAL BENIGN MESOTHELIOMA	-	-	-	-	-	1	-	-
SPLEEN								
HEMANGIOMA	-	-	-	1	-	-	-	-
HEMANGIOSARCOMA	-	1	-	-	-	-	-	-
LEIOMYOMA	-	-	1	-	-	-	-	-
LYMPH NODE								
HEMANGIOMA	-	5	1	-	-	-	1	1
THYRUS								
BENIGN THYROMA	1	-	-	-	-	-	1	-
BONE								
OSTEOSARCOMA	3	1	-	1	-	-	-	-
SKELETAL MUSCLE								
FIBROSARCOMA	-	-	1	-	-	-	-	-

KEY: GROUP 1 = CONTROL
 GROUP 2 = 15 MG/KG/DAY
 GROUP 3 = 45 MG/KG/DAY
 GROUP 4 = 135/270 MG/KG/DAY

CONTINUED
 L-158,086: 105-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT 890-099-0
 SUMMARY OF PRIMARY NEOPLASMS

	GROUP 1		GROUP 2		GROUP 3		GROUP 4	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
BRAIN								
MALIGNANT GLIOMA	4	1	1	-	1	-	1	-
BENIGN GRANULAR CELL TUMOR	3	1	-	1	-	4	-	1
MALIGNANT MENINGIOMA	-	-	-	-	-	1	-	-
EAR								
ZYMBAL'S GLAND, CARCINOMA	1	1	1	-	-	1	1	1
MALIGNANT SCHWANNOMA	-	-	1	-	-	-	-	1
PRIMARY SITE UNDETERMINED								
ADENOCARCINOMA	-	1	-	-	-	-	-	-
HISTIOCYTIC SARCOMA	1	4	1	3	-	3	-	2
GRANULOCYTTIC LEUKEMIA	-	-	-	-	-	-	-	1
LYMPHOMA	2	4	1	8	4	1	2	1

KEY: GROUP 1 = CONTROL

GROUP 2 = 15 MG/KG/DAY

GROUP 3 = 45 MG/KG/DAY

GROUP 4 = 135/270 MG/KG/DAY

14-Week Oral Range Finding Toxicity Study in Mice

Study Facility: MSD Research Laboratories, West Point, PA

Study No: TT #90-058-0

Study Dates: 3/12/90- 7/13/90

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Male and female Crl:CD-1 (ICR) BR mice (39 days old at initiation of study).

Drug Administration: Losartan (Lot # 005H010) was dissolved in deionized water and administered orally by gavage.

Dose Levels: 0 (vehicle), 50, 250 and 500 mg/kg/day (15/sex/dose group)

Observations/Measurements: Mice were observed daily for mortality and clinical signs of toxicity. Body weights were measured prior to treatment, once during Week 1 of treatment and twice weekly, thereafter. Food consumption was measured weekly. Urine was collected from mice during week 13 of treatment for urinalysis. At termination of the study, surviving mice were anesthetized with ether and blood was withdrawn from the vena cava for hematological and serum biochemical analyses. All animals were examined for gross pathology; sections of major organs and tissues from control and high dose animals were sectioned, fixed on slides and examined microscopically.

Results:

Mortality: One high dose (500 mg/kg/day) female mouse died on day 3 of treatment.

Other Treatment-Related Effects:

Measurement		% Difference from Control		
		50	250	500
Body Weight**	M	-5.2	-12.1	-9.4
	F	-1.3	-1.3	-5.0
Body Wt. Gain	M	-16	-31*	-35*
	F	+3	-10	-25*
<u>Hematology</u>				
RBC Counts	M	-6	-4	-4
	F	+2	0	-8
Hct	M	-2	-2	-4
	F	+5	0	-10
Hb	M	-5	-3	-6
	F	+3	0	-9
<u>Serum Chemistry</u>				
Urea Nitrogen	M	+1	+4	+10
	F	-2	+25	+154*
<u>Urinalysis</u>				
Urine Volume	M	-10	-40	-20
	F	-52	-16	-58
<u>Organ Weight</u>				
Heart				
Absolute Wt.	M	-2	-16	-20
	F	-7	-14	-14
Relative Wt.	M	+4	-4	-12
	F	-4	-13	-9

* Significantly different from control ** Not analyzed statistically

Renal Histopathologic Effects

Effect	Incidence							
	Control		Low	Mid Dose		High Dose		
	M	F	M	M	F	M	F	
JG Hyperplasia	0	0	0	2	7	7	13	11
Tubular Focal Basophilia	2	0	0	1	5	5	11	11

Ninety-Two Week Oral Carcinogenicity Study in Mice

Study Facility: MSD Research Laboratories, West Point, PA

Study No: TT #90-133-0

Study Dates: 8/20/90 - 5/20/92

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Male and female Crl:CD-1(ICR)BR mice (22.6-32.7 gm males, 17.7- 27.0 gm females; 36 days old; housed 2-3/cage)

Drug Administration: Losartan (Batch # 086-005H-010 and 086-005H-019) was dissolved in deionized water and administered orally by gavage once daily.

Dose Levels:

Vehicle Control 1		50M, 50F
Vehicle Control 2		50M, 50F
Losartan 20 mg/kg/day	(Low Dose)	50M, 50F
Losartan 100 mg/kg/day	(Mid Dose)	50M, 50F
Losartan 300/200 mg/kg/day*	(High Dose, Males)	50M
Losartan 500/300/200 mg/kg/day*(High Dose, Females)		50F

Note: Due to treatment-related decreases in body weight gain and increases in mortality, the dosage level for the high dose females was lowered from 500 to 300 mg/kg/day in Drug Week 28 and the dosage level for the high dose males and females was lowered from 300 to 200 mg/kg/day in Drug Week 43. An additional 5/sex/group were used as replacement animals for mice that died of causes unrelated to treatment, such as dosing accidents, during the first 8 weeks of the study. After 8 weeks, the remaining animals in these groups were discarded.

Observations/Measurements: Mice were observed daily for mortality and weekly for clinical signs of toxicity. The animals were palpated for masses every 4 weeks beginning in Drug Week 26. Body weights were measured pretest, once in Drug Week 1, twice weekly in Drug Weeks 2 through 13, and once weekly thereafter. Ophthalmoscopic examinations were conducted on all animals prior to treatment and in Drug Weeks 52 and 89. At scheduled sacrifice, mice were anesthetized with ether and venous blood was obtained from the vena cava for hematologic examination. Caval blood samples were obtained at unscheduled necropsies to aid in the diagnosis of leukemias and lymphomas. All animals were necropsied and sections of major organs and tissues were fixed on slides for microscopic examination. The incidences of various tumor types were analyzed for statistically significant trend (P < 0.05) with adjustments made for variations in mortality.

Results:

Mortality and Survival: A higher than expected occurrence of early deaths/early sacrifices (due to gastrointestinal lesions or to undetermined causes) was noted among high dose females prior to Drug Week 28 and in high dose males prior to Drug Week 43, prompting the sponsor to reduce the dosage levels for high dose males and females. At study termination, the number of male and female control and high dose mice which died or were killed were similar. The incidences of early sacrifices (ES) and early deaths (ED) among low and mid dose treated mice were lower than control.

Animal Survival

Dose Group	No. Mice Surviving to End of Study	
	Females	Males
Control 1	24	20
Control 2	21	20
Low Dose	34	27
Mid Dose	29	25
High Dose	17	21

GI and Undetermined Causes of Early Sacrifices/Early Deaths

Dose Group	No. of Early Sacrifices/Early Deaths				
	GI Lesions		Undetermined		Total
	F	M	F	M	
Control 1	0	0	0	0	0
Control 2	0	1	0	0	1
Low Dose	0	1	0	0	1
Mid Dose	0	2	0	2	4
High Dose	5	4	4	7	20

Physical Signs: Dyspnea, decreased locomotor activity, weakness, pallor and abdominal distension were observed in several mid and high dose animals prior to early death or early sacrifice. These signs were often associated with treatment-related gastrointestinal effects (intestinal distension, gastritis and ulcers).

Body Weight: Statistically significant ($P < 0.05$) reductions in body weight gain, as compared to the average of combined concurrent control values, were observed after 91 weeks of treatment in high dose males and in females of all dose groups. Body weights and body weight gains in high dose females were reduced after Drug Weeks 27 and 42 and in high dose males after Drug Week 42. These body weight decreases, in conjunction with the increase in early mortalities and GI toxicity, prompted the lowering of the dosage level for the high dose animals.

Effects on Body Weight and Body Weight Gain

Dose Group		Percent Change from Control* Wt (Wt Gain)		
		27 Weeks	42 Weeks	91 Weeks
Low Dose	M	0	0	-4
	F	-6	-8	-4 (-10)*
Mid Dose	M	-1	-2	0
	F	-6	-10	-9 (-22)*
High Dose	M	-5 (-12)	-8 (-23)	-6 (-22)*
	F	-13 (-39)	-15 (-40)	-13 (-34)*

*Average of 2 concurrent control group values used in calculating change.

* Significant difference from control

Ophthalmoscopic Effects: No treatment-related ocular effects were observed.

Hematological Effects: There were no treatment-related effects on hematologic parameters in animals that died or those sacrificed at termination of the study.

Gross Pathology: Except for the gastrointestinal lesions (gastric fundic erosions, ulceration or hemorrhage of the small and/or large intestine) observed primarily in high dose animals that died or were sacrificed prior to study termination, no treatment-related gross pathology was seen at necropsy.

Microscopic Pathology:

Neoplastic Lesions: There were no significant differences in the number of mice with neoplasms or total neoplasms between losartan-treated groups and concurrent controls.

Summary of Neoplasms in Male Mice

	Number or Incidence				
	Control 1	Control 2	Low Dose	Mid Dose	High Dose
# Mice with Neoplasms					
Malignant	8	11	16	9	15
Benign	19	19	14	22	16
Malignant or Benign	25	23	25	28	26
Total # of Neoplasms					
Malignant	8	12	17	11	20
Benign	25	22	18	29	19
Malignant or Benign	33	34	35	40	39

Summary of Neoplasms in Female Mice

	Number or Incidence				
	Control 1	Control 2	Low Dose	Mid Dose	High Dose
# Mice with Neoplasms					
Malignant	12	12	8	11	7
Benign	14	16	18	11	7
Malignant or Benign	23	26	23	20	13
Total # of Neoplasms					
Malignant	14	14	10	11	7
Benign	15	18	20	13	9
Malignant or Benign	29	32	30	24	16

Positive Tumor Findings In the sponsor's analysis, a statistically significant ($P < 0.05$) increased trend in the incidence of lung adenocarcinoma was detected in male mice. No statistically significant increased trend in the incidence of lung adenocarcinomas was seen in female mice and no increase was observed in either sex for lung adenomas.

Percent Incidence of Pulmonary Adenoma and Adenocarcinoma

	Percent Incidence				
	Control 1	Control 2	Low Dose	Mid Dose	High Dose
<u>Male Mice</u>					
Adenoma	14	12	18	18	12
Adenocarcinoma	4	6	6	6	16
Adenoma or Adenocarcinoma	18	18	24	24	28
<u>Female Mice</u>					
Adenoma	20	10	14	14	10
Adenocarcinoma	6	8	2	0	4
Adenoma or Adenocarcinoma	26	18	16	14	14

FDA Analysis of Pulmonary Adenoma and Adenocarcinoma in Male Mice

Parameter	Tumor Rate				Statistical Test	
	100=C	50=LD	50-MD	50=HD	Trend	Pairwise
No Animals						
Lung Adenocarcinoma	5	3	3	8	.004 (S)	.023 (NS)
Lung Adenoma or Adenocarcinoma	18	12	12	14	.044 (NS)	.055 (NS)

(S)= Statistically significant (NS)= Not statistically significant

Although the incidence of lung adenocarcinoma in high dose males was significantly increased above concurrent control, the sponsor dismisses this finding based on the fact that this incidence is within their range of historical control values. In the 9 most recent carcinogenicity studies from the same laboratory (studies of similar duration with 18 control groups of 50 male mice/group), the sponsor has observed the following mean incidences and ranges for pulmonary neoplasms (individual study results shown in Appendix II).

Sponsor's Historical Incidence on Pulmonary Tumors in Male Mice

	Mean	Median	Range
Adenoma	15%	20%	8-34%
Adenocarcinoma	6.6%	6.0%	0-24%

There was no statistically significant increased trend in the incidence of neoplasms in any other organs or tissues in this study (Appendix III).

Non-Neoplastic Lesions: As previously described, treatment-related gastrointestinal (GI) lesions were observed in several mice of both sexes, primarily in the high dose group but also in some males in the mid dose group. The types and incidences of GI lesions observed are as follows:

Treatment-Related Gastrointestinal Lesions

GI Effect	Incidence (# mice)										
	C-1		C-2		Low		Mid		High		
	F	M	F	M	F	M	F	M	F	M	
Stomach											
Distension	0	0	0	0	0	0	0	0	1	1	
Necrotizing Gastritis	0	0	0	0	0	0	0	0	1	0	
Sm. Intestine											
Distension	0	0	0	1	0	0	0	3	5	3	
Ulcer	0	0	0	0	0	1	1	2	1	2	
Lge. Intestine											
Distension	0	0	0	0	0	0	0	1	3	1	
Ulcer	0	0	0	0	0	0	0	0	0	2	

A dose-related occurrence of renal juxtaglomerular (JG) cell hyperplasia was seen in all losartan-treated groups. The lesions were characterized by an increase in the number and size of these specialized cells comprising the wall of the afferent arteriole of the glomeruli. A slightly higher incidence of chronic nephritis was seen in mid and high dose females and in high dose males.

Renal Effects

Pathology		Incidence (# mice)					
		C-1	C-2	Low	Mid	High	
JG Cell Hyperplasia	F	0	0	10	22	24	
	M	0	0	8	15	32	
Chronic Nephritis	F	24	31	29	43	42	
	M	30	34	28	36	42	

Dose Selection and MTD Considerations

Dose selection for the mouse carcinogenicity study was based on a 14-week oral (gavage) dose rangefinding study in which 3 dose levels (50, 250 and 500 mg/kg/day) of losartan were evaluated. Doses of 250 and 500 mg/kg/day caused significant reductions from control body weight (-12%, -9.4%, respectively) and body weight gains (-31%, -35%, respectively) in males. A dose of 500 mg/kg/day caused significant reductions from control body weight (-5%) and body weight gain (-25%) in females. Doses of 250 and 500 mg/kg/day caused dose-dependent increases in serum urea nitrogen in females and dose-dependent increases in renal JG cell hyperplasia and tubular focal basophilia in males and females. Mean erythrocyte, hemoglobin and hematocrit were decreased by 4% to 10% in high dose males and females. Based on the finding that body weights were significantly lower in males treated with 250 or 500 mg/kg/day, the sponsor selected a dose of 300 mg/kg/day as an appropriate high dose for males in the carcinogenicity study. Because female weights were affected to a lesser degree, the sponsor selected a dose of 500 mg/kg/day as an appropriate high dose for females. After initiation of the carcinogenicity study, treatment-related decreases in body weight gain and a higher incidence of early deaths prompted the sponsor to decrease the high dose in females from 500 to 300 mg/kg/day in Drug Week 28 and lower the 300 mg/kg/day dose in both males and females to 200 mg/kg/day in Drug Week 43 (the sponsor's and the FDA's analyses of the results of the carcinogenicity study revealed a statistically significant, increased trend for mortality in female mice; much of this difference was associated with a higher incidence of treatment-related early deaths with the high dose group). The increased incidences of early deaths/early sacrifices at 300 mg/kg/day is strong evidence that the 200 mg/kg/day dose administered for the final 49 weeks of the study is at-or-near the maximally tolerated level for this agent by this route in this species.

MTD Conclusions

Male mouse	MTD: Yes Basis: Early deaths/early sacrifices associated with GI toxicity in 92-wk study with 300 mg/kg/day. Significant weight gain decrement in high dose group at end of 92-wk. study.
Female mouse	MTD: Yes Basis: Early deaths/early sacrifices associated with GI toxicity in 92-wk study with 500 and 300 mg/kg/day. Significant weight gain decrements in mid and high dose groups at end of 92-wk study.

Tumor and Other Histopathologic Findings

Sponsor's and FDA's analyses of the results of the carcinogenicity study showed a statistically significant increased trend in the incidence of lung adenocarcinoma in males. The incidences of lung adenocarcinoma in female mice were not significantly different from control. No increase in lung adenoma was observed for either sex. A pairwise comparison of the high dose males and control groups of males mice showed no statistically significant difference in the incidence of lung adenocarcinoma. In addition, historical control incidence data for this tumor type from sponsor's 18 most recent control groups of mice showed that the 16% incidence rate seen in high dose males is within the sponsor's historical control range (0%-24%). Because of (1) the absence of a significant pairwise difference (high dose vs. control) in lung adenocarcinoma incidence, (2) the lack of increased incidence of lung adenocarcinoma in female mice and (3) the fact that the high dose male incidence is within the sponsor's historical control range, it is reasonable to conclude that this finding represents a false positive and is unlikely to be treatment-related. There was no statistically significant increased trend in the incidence of neoplasms in any other organ in this study.

Non-neoplastic drug-related pathologies in mice included dose-dependent increases in the incidences of JG cell hyperplasia and increased incidence of gastric and intestinal lesions, primarily in high dose males and females and in mid dose males. The losartan-related increase in JG cell hyperplasia is regarded as an adaptive response of the renin-angiotensin system in response to blockade of angiotensin II activity; such a response is similarly seen with ACE inhibitors.

Appendix II

Historical Incidence of Benign and Malignant Pulmonary Tumors in Control Male CD-1 (ICR)BR Mice from Nine Recently Conducted Carcinogenicity Studies

Study	Group	Malignant Adenocarcinoma		Benign Adenoma	
		Incidence*	% Incidence	Incidence*	% Incidence
1	C-1	0/50	0	11/50	22
	C-2	0/50	0	8/50	16
2	C-1	12/50	24	4/50	8
	C-2	7/49	14	8/49	16
3	C-1	0/50	0	10/50	20
	C-2	0/50	0	6/50	12
4	C-1	1/50	2	9/50	18
	C-2	2/50	4	8/50	16
5	C-1	5/50	10	17/50	34
	C-2	6/50	12	10/50	20
6	C-1	5/50	10	8/50	16
	C-2	7/50	14	9/50	18
7	C-1	3/50	6	8/50	16
	C-2	3/50	6	12/50	24
8	C-1	2/50	4	11/50	22
	C-2	4/50	8	10/50	20
9	C-1	1/50	2	11/50	22
	C-2	1/47	2	10/47	21

All groups on study for 92 weeks except groups from study #7 which were on study for 73 weeks.

*Represents # mice with tumor/# mice necropsied

Appendix III Primary Neoplasms in Mice

L-158,086; 92-WEEK ORAL CARCINOGENICITY STUDY IN MICE. TT 890-133-0
SUMMARY OF PRIMARY NEOPLASMS

NUMBER NECROPSIED	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5		GROUP 6	
	F	M	F	M	F	M	F	M	F	M	F	M
	50	50	50	50	50	50	50	50	-	50	50	-
STOMACH												
NONGLANDULAR MUCOSA, PAPILLOMA	-	-	-	-	1	-	-	-	-	-	-	-
SMALL INTESTINE												
ADENOCARCINOMA	-	-	-	-	-	-	1	-	-	-	-	-
HEMANGIOMA	-	-	-	1	-	-	-	-	-	-	-	-
POLYP	-	-	1	1	-	-	-	1	-	-	-	-
LARGE INTESTINE												
ANUS, SQUAMOUS CELL CARCINOMA	-	-	-	-	-	-	1	-	-	-	-	-
LIVER												
HEMANGIOMA	-	-	3	-	1	-	-	-	-	-	-	-
HEMANGIOSARCOMA	-	1	-	1	-	1	-	-	-	-	-	-
HEPATOCELLULAR ADENOMA	-	6	1	3	1	2	-	5	-	6	-	-
HEPATOCELLULAR CARCINOMA	2	3	-	6	-	8	-	4	-	7	-	-
PANCREAS												
ISLET, ADENOMA	-	-	-	1	-	-	-	-	-	-	-	-
ADRENAL												
CORTEX, ADENOMA	-	2	-	1	-	1	-	-	-	-	-	-
MALIGNANT PHEOCHROMOCYTOMA	1	-	-	-	-	-	-	-	-	-	-	-
BENIGN SPINDLE CELL TUMOR	1	-	-	-	-	-	1	-	-	-	1	-
PITUITARY												
ADENOMA	2	-	-	-	-	-	1	1	-	-	-	-
THYROID												
FOLLICULAR CELL, ADENOMA	-	2	-	1	-	-	1	-	-	1	-	-
KIDNEY												
PELVIC EPITHELIUM, TRANSITIONAL CELL CARCINOMA	-	-	-	-	-	-	1	-	-	-	-	-
OVARY												
PAPILLARY ADENOMA	-	-	-	-	1	-	-	-	-	-	-	-
BENIGN GRANULOSA CELL TUMOR	-	-	1	-	-	-	1	-	-	-	-	-
MALIGNANT GRANULOSA CELL TUMOR	-	-	-	-	1	-	-	-	-	-	-	-

KEY: GROUP 1 = CONTROL 1

GROUP 3 = 300/200 MG/KG/DAY

GROUP 2 = CONTROL 2

GROUP 6 = 500/300/200 MG/KG/DAY

GROUP 3 = 20 MG/KG/DAY

GROUP 4 = 100 MG/KG/DAY

L-158.086 (CONTINUED): 92-WEEK ORAL CARCINOGENICITY STUDY IN MICE. TT 890-133-0
SUMMARY OF PRIMARY NEOPLASMS

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5		GROUP 6	
	F	M	F	M	F	M	F	M	F	M	F	M
UTERUS												
HEMANGIOMA	-	-	-	-	1	-	-	-	-	-	1	-
LEIOMYOMA	-	-	-	-	2	-	-	-	-	-	-	-
POLYP	1	-	2	-	3	-	1	-	-	-	-	-
ENDOMETRIAL STROMA, SARCOMA	1	-	-	-	-	-	-	-	-	-	1	-
VAGINA												
LEIOMYOSARCOMA	1	-	-	-	-	-	-	-	-	-	-	-
TESTIS												
RETE TESTIS, ADENOMA	-	1	-	-	-	-	-	-	-	-	-	-
HEMANGIOMA	-	-	-	1	-	-	-	-	-	-	-	-
BENIGN INTERSTITIAL CELL TUMOR	-	1	-	1	-	1	-	2	-	1	-	-
EPIDIDYMIS, LEIOMYOSARCOMA	-	-	-	-	-	-	-	-	-	1	-	-
SEMINAL VESICLE												
PAPILLARY ADENOMA	-	1	-	-	-	-	-	-	-	-	-	-
SKIN												
HEMANGIOMA	-	-	1	-	-	-	-	-	-	-	-	-
HEMANGIOSARCOMA	-	1	-	-	-	-	-	-	-	-	-	-
BENIGN HIBERNOMA	-	-	-	-	-	-	1	-	-	-	-	-
LIPOMA	-	-	-	1	-	-	-	-	-	-	-	-
OSTEOGENIC SARCOMA	-	1	-	-	-	-	-	-	-	-	-	-
RHABDOMYOSARCOMA	-	-	-	-	2	-	-	-	-	-	-	-
MAMMARY GLAND												
MALIGNANT ADENOACANTHOMA	1	-	2	-	-	-	-	-	-	-	-	-
ADENOCARCINOMA	2	-	3	-	1	-	1	-	-	-	1	-
LUNG												
ADENOCARCINOMA	3	2	4	3	1	3	-	3	-	8	2	-
ADENOMA	10	7	5	6	7	9	7	9	-	6	5	-
OSTEOMA	1	-	-	-	-	-	-	-	-	-	-	-
HEART												
HEMANGIOMA	-	-	1	-	-	-	-	-	-	-	-	-
SPLEEN												
HEMANGIOSARCOMA	-	-	-	1	-	-	-	1	-	-	-	-
BONE												
OSTEOMA	-	-	1	-	-	-	-	-	-	-	-	-
OSTEOSARCOMA	-	-	1	-	-	-	-	-	-	-	-	-

KEY: GROUP 1 = CONTROL 1

GROUP 5 = 300/200 MG/KG/DAY

GROUP 2 = CONTROL 2

GROUP 6 = 500/300/200 MG/K/DAY

GROUP 3 = 20 MG/KG/DAY

GROUP 4 = 100 MG/KG/DAY

L-15P,086 (CONTINUED): 92-WEEK ORAL CARCINOGENICITY STUDY IN MICE. TT 890-133-0
SUMMARY OF PRIMARY NEOPLASMS

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5		GROUP 6	
	F	M	F	M	F	M	F	M	F	M	F	M
SKELETAL MUSCLE												
HEMANGIOSARCOMA	-	-	-	-	-	1	-	-	-	-	-	-
RHABDOMYOSARCOMA	1	-	-	-	-	-	1	-	-	-	-	-
NERVE												
MALIGNANT SCHWANNOMA	-	-	-	-	-	-	-	-	-	1	-	-
EYE												
LABYRINTHIN GLAND, ADENOMA	-	5	2	5	3	5	1	10	-	5	2	-
PRIMARY SITE UNDETERMINED												
HISTIOCYTIC SARCOMA	1	-	1	1	-	1	1	-	-	1	1	-
MYELOID LEUKEMIA	-	-	-	-	-	1	-	-	-	-	-	-
LYMPHOMA	1	-	3	-	5	2	4	3	-	2	2	-
MALIGNANT PLASMA CELL MYELOMA	-	-	-	-	-	-	1	-	-	-	-	-

KEY: GROUP 1 = CONTROL 1

GROUP 5 = 300/200 MG/KG/DAY

GROUP 2 = CONTROL 2

GROUP 6 = 500/300/200 MG/KG/DAY

GROUP 3 = 20 MG/KG/DAY

GROUP 4 = 100 MG/KG/DAY

NOV 14 1994

Review *Konsum*
11-15-94

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE:

NOV 14 1994

FROM: Epidemiologist, Epidemiology Branch, HFD-733

SUBJECT: **CONSULT** Losartan and renal cancer, NDA 20-386

THROUGH: Acting Branch Chief, Epidemiology Branch, HFD-733

Acting Director, Division of Epidemiology and
Surveillance, HFD-730

TO: Director, Division of Cardiorenal Drug
Products, HFD-110

This memorandum responds to your request for a review of the sponsor's submissions that addressed the incidence of renal cancer in the losartan NDA. In addition to reviewing the July 21 and August 18 submissions, this issue was discussed in several teleconferences with the sponsor, in the August 3 and September 22 meetings between the sponsor and HFD-110, and in several in-house meetings.

Summary

The incidence of renal cancer with losartan exposure (97% of person-time was in hypertensive patients) is no greater than that observed by the sponsor with enalapril/lisinopril (EL) exposure in hypertensive populations (relative risk [RR] for losartan compared to EL after first year = 1.0, 95% CI; 0.2, 6.0). The incidence rates were both about 2 cases per 1000 person-years in patients with more than one year of exposure. The first year of exposure should not be counted as person-time at risk because baseline medical screening may have removed patients with renal cancer that could have been diagnosed shortly after randomization. If the observed number of cases with losartan and EL are separately compared to that expected based upon the incidence in SEER, the standardized morbidity ratios (SMRs) are 10.3 and 12.5 in patients with more than one year of exposure, respectively. While some increase in renal cancer incidence would have been expected because hypertension is associated with an increased incidence of renal cancer, the magnitude of both SMRs was surprising. Estimates of the relative risk in hypertensive populations compared to the general population range from 2-5 or several fold less than these SMRs.

In the EL data submitted by the sponsor, about 57% of the

exposure was in hypertensive patients. In these data, the incidence of renal cancer was about 3 times greater in patients with hypertension with only 1 case occurring in a patient without hypertension. In the SOLVD study, which randomized patients to enalapril or placebo to evaluate the benefits of ACE therapy in a CHF population, the incidence of renal cancer was about 0.3 per 1000 person-years of enalapril exposure. In addition to examining the SOLVD and SHEP databases, sponsors of several recently approved channel blockers and ACE inhibitors were queried regarding renal cancer incidence. However, none of the data were helpful because of limited exposure and concerns regarding adequacy of follow-up.

In summary, losartan appears to have the same incidence of renal cancer as EL and there is no evidence to suggest that ACE inhibitors are associated with an increase in renal cancer in the absence of hypertension. The limitation in power in comparing losartan to EL is probably no greater than exists in other NDAs for excluding increased rates of a specific cancer. The most likely explanation for the increased rates observed with losartan and EL above that expected in a hypertensive population, is better surveillance for cancer that may exist in clinical trial settings and specifically with this sponsor. Better surveillance may have resulted in a lead-time bias.

Background

Before reviewing the sponsor's losartan and EL data, it may be helpful to briefly comment on the literature regarding renal cancer and hypertension, as well as that focusing on latency times (including induction) for some environmental exposures that cause solid tumors. Latency, the time from effective biological cancerous change till diagnosis, may be more of an issue with a solid tumor like renal cancer. These cancers are reported to be slow growing and frequently diagnosed at a relatively large size. Given such characteristics one would expect renal cancers to have a long latency. Lead-time bias occurs when cancers with a lengthy latency are detected earlier in the study population than in the comparative population causing an apparent increase in incidence in the study population. If the study population is followed long enough, the overall incidence will return to that expected. This type of bias has been discussed extensively for breast cancer screening with mammography and in the UAW pattern workers who were screened for colon cancer.

Renal Cancer and Hypertension

The sponsor provided a good review of the published studies that have estimated the relative risk of renal cancer in hypertensive populations. While the incidence of renal cancer is consistently increased in patients with hypertension, even after excluding the first several years of follow-up (exclusion necessary because of

potential detection bias and misclassification), the relationships between selected antihypertensive drugs (mostly diuretics and beta blockers) and renal cancer have been inconsistent. We have not found any published studies that specifically examined renal cancer risk in hypertensives using ACE inhibitors. NCI recently completed a large case-control study of incident renal cancer cases in Wisconsin that collected ACE inhibitor exposure, however the findings have not yet been submitted for publication.

Several studies have made a great deal of the observation that RR increases in patients reporting a history of physician-diagnosed hypertension and antihypertensive therapy compared to patients with a history of physician-diagnosed hypertension. (In the Seventh Day Adventist study the RR was 2.9 in patients reporting a history of physician-diagnosed hypertension and 4.5 for those with a history and taking any antihypertensive.) Such an observation does not necessarily mean that drug therapy is associated with increased risk. In fact, many researchers when conducting observational studies, use a drug therapy in conjunction with a diagnosis to increase the specificity of that diagnosis. If a history of hypertension along with antihypertensive drug therapy was more specific for hypertension than a history of hypertension alone (fewer false positives giving a higher positive predictive value), then the RR would be expected to increase because of less misclassification even if there was no risk with drug therapy.

In summary, our interpretation of the literature is that the association between hypertensive populations and renal cancer is compelling, but the association with specific drug therapies is weak. However, it is difficult methodologically to separate effects due to disease from that due to drugs used to treat the disease without randomization.

Cancer Induction with environmental exposure

There are several environmental exposures that have been causally related to the development of solid tumors (excluding lymphoma). Thyroid and breast cancer both are increased following significant doses of ionizing radiation. The time from sufficient exposure to occurrence of thyroid cancer is moderately long, estimated at 7-10 years while breast cancer occurring from ionizing radiation may have an even longer induction and latency. The induction and latency of hepatic angiosarcoma occurring after vinyl chloride exposure has been estimated at 5-20 years.

The shortest latency that we could identify between any environmental exposure and solid cancer occurrence was for endometrial cancer occurring after either estrogen or tamoxifen exposure. The mean time to diagnosis after first exposure to either usually falls in the range of 3-6 years. A recent study

reported that the mean time to diagnosis was 41 months following tamoxifen first exposure. Thus, an increase in incidence of a solid tumor like renal cancer within 2 years of first exposure would be surprising and maybe unprecedented in humans.

Recent discussions in the cancer literature have raised questions regarding direct regulation of cancer cell growth by drugs, in particular for aspirin and drugs with antihistaminic activity. Rapid growth of existing cancers is a possible explanation for observing an increased incidence of a solid tumor shortly after exposure. In some cases, antihistamine receptor blockade has been associated with rapid cancer cell growth in vitro. (Brandes in his publications has referred to this phenomena as promotion, but it is more aptly referred to as growth regulation since the cancer cells are present prior to exposure.) Although this hypothesis is interesting, we are aware of no drugs that are accepted as growth regulators except for possibly tamoxifen.

Review of Sponsor's Data

Because of the apparent increase in renal cancer incidence with losartan compared to that in the general population, the sponsor elected to estimate the incidence in their enalapril and lisinopril databases. About 55% and 66% of the person-time for enalapril and lisinopril was observed in hypertensive trials, respectively (57% when combined). Overall, there were 2 renal cancers with enalapril and 3 with lisinopril. One of the enalapril cancers occurred in a patient without hypertension, while all four other cancers occurred in patients with hypertension. The incidence rate for enalapril/lisinopril combined (EL) in non-hypertensives was 0.3 per 1000 person-years and based only on one case (1/2972 person-years). In hypertensives exposed to EL, it was 1 per 1000 person-years (4/3926 person-years). Most of the increase in incidence with EL was due to the 3 lisinopril cases observed in about 50% as much person time as enalapril. After the first year of exposure, lisinopril made an even greater contribution to the EL combined incidence with 2 cases observed in 190.6 person-years of exposure. While the question could be raised of whether it is appropriate to combine enalapril and lisinopril, the sponsor made this decision a priori. In addition, the precision of comparing enalapril to lisinopril would be limited by small numbers of cases and limited person-time.

Table 1 provides case counts, person-time, incidence rates and SMRs for losartan and EL in hypertensive patients. Overall, there have been 9 cases of renal cancer diagnosed during exposure to losartan, enalapril or lisinopril in hypertensive patients. Cases that occurred that were no longer exposed to one of the drugs were not captured nor has this person-time been defined.

A similar pattern in the incidence rates occurs over time for

both losartan and EL. Both incidence rates increase by several fold after the first year of exposure. Such increases offer compelling evidence that both exposures (EL combined) are associated with the development of renal cancer, if it is appropriate to compare early exposure with latter exposure. However, such comparison is probably not appropriate because medical screening at baseline may have excluded patients with prevalent cancers that would have been diagnosed shortly after randomization, biasing the first year rates low. One way of addressing this would be to determine the number of exclusions that occurred for findings consistent with renal cancer. Because of this concern, we have excluded the first year of observation from estimates of relative risk (SMRs) in the following discussions.

Also shown in Table 1 are the SMRs for losartan and EL when the renal cancer incidence in each population was compared to the incidence in the SEER population. SMRs provide relative risk estimates and are calculated by indirectly standardizing (age and gender) the losartan and EL populations to the SEER population. Both SMRs are greater than 10 after excluding the first year of observation. These SMRs are the largest relative risk estimates that we are aware of in any hypertensive population. Because the expected number of cases is specific to each exposed population's age/gender distribution, a direct comparison of the magnitude of the SMRs is not valid.

Table 1. Incidence Rates and SMRs based upon
Data Submitted by Sponsor

	Losartan		Enalapril/Lisinopril	
	0-52 Weeks	>52 Weeks	0-52 Weeks	>52 Weeks
Person-Time in PYRs	2154.6	1953.7	2613.4	1425.5
Observed Case Counts	1	4	1	3
Rate per 1000 PYRs	0.5	2.0	0.4	2.1
Expected Case Counts	0.4	0.4	0.5	0.2
SMR	2.3	10.3	2.0	12.5
Exact probability		.001		.002

*one tailed poisson - exact probability

To make a direct comparison, the sponsor provided incidence rate

ratios by strata of observation time. There was no difference in the incidence, although the confidence limits were moderately wide (RR = 1.0 for exposure >52 weeks, 95% CI; 0.2,6.0). Thus, if 80% power were necessary to detect a relative risk of 2 when losartan was compared to EL, then the data are significantly underpowered. However, this lack of power is likely to be no different than that in most NDAs when evaluating the occurrence of rare events.

Thus, based upon the data submitted by the sponsor we reached three conclusions. First, baseline hypertension appears to increase the incidence of renal cancer observed during EL exposure (1 case in a patient with CHF without hypertension). A precise estimate of baseline incidence would be necessary to examine for a drug-disease interaction. If the incidence of renal cancer during drug exposure in the absence of hypertension was the same as in the general population, there would be no evidence of any drug effect.

Second, losartan had a similar incidence of renal cancer as hypertensive patients taking EL, although the precision of this comparison was also limited. Baseline rates for losartan in the absence of hypertension were not meaningful since only 3% of the person-time was observed in patients without hypertension at baseline.

Finally, both losartan and EL have the highest relative risk estimates for renal cancer in hypertensive populations that we could find in the literature raising the question of whether both classes of drugs are associated with an increased renal cancer incidence. Unfortunately, none of the published studies observing an increased incidence of renal cancer in hypertension occurred in a clinical trial setting and none were recent enough to include ACE inhibitor exposure. If a clinical trial setting were more efficient at detecting renal cancers, then a lead-time bias would be a possible explanation for the magnitude of the losartan and EL SMRs.

To address the magnitude of the SMRs observed with losartan and EL three other sources of data were developed that may have been collected in settings comparable to that employed by this sponsor for losartan and EL:

- 1) The sponsor estimated the incidence of renal cancer for enalapril exposure in the SOLVD study. SOLVD randomized patients to enalapril or placebo to study the effects of an ACE inhibitor on mortality in patients with CHF. Although the baseline screening and surveillance after randomization may not have been as rigorous as in efficacy trials, it is the only data we know of for any ACE inhibitor outside of NDA data.

- 2) The Division of Epidemiology and Surveillance contacted the

coordinating center for the SHEP study. SHEP randomized patients with systolic hypertension to placebo or diuretic with atenolol as stepped therapy. The SHEP study obtained all information on hospitalizations that occurred during the long follow-up period and tried to exclude cancer at baseline. Thus, if renal cancer is also related to patients with isolated systolic hypertension (not addressed in the literature), then the SHEP study may have more comparable methods to those in a clinical trial setting and provide more comparable rates than that observed in the general population.

3) HFD-110 contacted sponsors for several hypertensive NDAs for selected calcium channel blockers and ACE inhibitors. Each sponsor was asked for person-time data and total cancer listings. To be of value, there would have to be significant person-time after the first year and sponsors would have to employ good surveillance methods. To help evaluate any differences in surveillance between sponsors, we compared the SMRs for all cancers (excluding basal and squamous skin cancers) in each NDA that provided appropriate person-time data.

Incidence of renal cancer in the SOLVD and SHEP study populations

The sponsor provided rates and SMRs for enalapril in the SOLVD study which randomized patients with CHF (some had hypertension at baseline) to either enalapril or placebo. Overall there were 2 cases observed in enalapril treated patients and 3 with placebo. The crude incidence for any enalapril exposure was about 0.3 per 1000 person-years after 52 weeks of exposure. In patients with hypertension irrespective of treatment, the rate was about 0.8 per 1000 person-years after the first year of observation. There was one renal cancer case in patients with hypertension randomized to enalapril. The incidence excluding the first year of observations was about 0.4 per 1000 person-years. (1/2283 person years). The SMRs were all slightly less than 1.

In the SHEP study 5 cases of renal cancer were observed. The crude rate was 0.5 per 1000 person years of exposure for those randomized to active therapy. In the placebo arm 2 cases were observed giving a crude rate of 0.2 per 1000 person-years. We obtained the age and gender breakdown for cases and overall person-time and calculated SMRs using SEER rates. Using the SEER rates, 4 cases would have been expected in the active treated group giving an SMR of 1.2.

While the SOLVD study was reassuring from the standpoint of providing no evidence of increased renal cancer with enalapril exposure, it seems doubtful that the baseline screening or follow-up was as rigorous as in the sponsor's losartan and EL study populations. There was one case of renal cancer with enalapril after 1 year in the SOLVD study and in the sponsor's enalapril data, but there was about 2.5 times as much person-time

in the SOLVD database.

Incidence of renal cancer in other hypertensive NDAs

Sponsors of recent NDAs for selected calcium channel blockers and ACE inhibitors were asked to provide cancer case counts and stratified person-time tables. The data provided for quinipril was the only response that included significant person time after the first year of exposure. There were no renal cancers identified, but there were 5 cancer cases that were coded as undefined cancer. The sponsor of losartan and EL also analyzed their NDA data for felodipine in hypertensive patients. There were no cases of renal cancer, but the amount of exposed person-time was limited.

Since surveillance mechanisms used by the sponsors would have to be comparable to use their data comparatively, we used SEER rates to obtain the expected number of cancers (excluding squamous and basal cell skin cancers) given the person-time distribution of exposure for several of the drugs. The sponsor of losartan, EL and felodipine provided SMRs directly to HFD-110. In the losartan database, 43 cancers were observed with 37 expected while in the EL database, 57 were observed with 60 expected. For felodipine, 7 were observed while 11 cancers would have been expected.

For quinipril, 15 cancers were observed with about 35 expected. For moexipril, the sponsor observed 17 with 13 expected. For perindopril, none were observed with about 5 expected.

Thus, none of the data submitted by other sponsors provide valid rates of renal cancer in hypertension for ACE inhibitors or for calcium channel blockers to compare to that observed with losartan or EL. Based upon the SMRs for all cancers, there is significant variation in surveillance mechanisms used by sponsors to detect cancer occurrence. The sponsor of quinipril, which had to be potential to provide meaningful rates beyond 1 year of exposure, captured the lowest percentage of expected. The sponsor of losartan and EL appears to be one of the better sponsors for detecting cancer in its study populations.

Discussion

Since hypertension is associated with renal cancer, it would not have been surprising to have seen an increased incidence of renal cancer in any antihypertensive NDA, assuming that careful monitoring of the population was employed. For losartan and EL, it is the magnitude of the relative risk estimates that were surprising. Both losartan and EL have the highest estimates of relative risk for renal cancer in patients with hypertension that we are aware of, and when losartan is directly compared with EL, there was little difference in renal cancer incidence.

Given what is known about solid cancer occurrence following environmental exposures, it seems implausible that solid tumors, particularly renal cancer, could be increased within 1-2 years of any exposure without a biased estimate of incidence. Given the differences in medical monitoring that occurs in some clinical trial settings compared to that in the general population, it would not be surprising to see increased detection of renal cancer with the former.

Providing support that ACE inhibitors are not causing renal cancer was the internal analysis of the sponsor's EL dataset where hypertension was associated with renal cancer incidence. There was only 1 case of renal cancer in a patient without hypertension that was exposed to either enalapril or lisinopril. To evaluate for a drug-disease interaction, this baseline rate would have to be compared to that expected, but with only 1 case such comparison would not be meaningful without more person-time. This was the also the case with losartan where 97% of the person-time was in patients with hypertension. The SOLVD study was reassuring in that there was no increase in renal cancer incidence with enalapril exposure compared to that in the general population. However, the rates observed with SOLVD may not be directly comparable to those in the sponsor's data because it is unlikely that the SOLVD population underwent the same degree of medical monitoring.

One limitation of the data presented by the sponsor is that only exposed cases of renal cancer and exposed person-time have been observed. Person-time in patients who discontinued use of any of the three drugs was not observed. This means that renal cancer cases occurring subsequent to the discontinuation of exposure were not ascertained. Whether such restriction has resulted in any bias can not be determined from the data currently available. Follow-up of all patients ever exposed to either losartan, enalapril or lisinopril could be consume significant resources and may not even be feasible.

By asking sponsors of recent antihypertensives to provide person-time data and cancer listings, we were able to compare each sponsor's degree of ascertainment of cancer. The drug with the most exposure after 1 year was quinipril and could have provided valuable information about renal cancer incidence during exposure to another ACE inhibitor in patients with hypertension. Had we observed the same rates, it would have been reassuring, although a drug-disease interaction would still be a possible explanation since we were unlikely to have enough person-time in patients without hypertension to get reliable baseline rates. While no renal cancers were observed with quinipril, the sponsor only captured about 50% of the cancers expected.

The sponsor of losartan, enalapril and lisinopril appears to be one of the better sponsors at ascertaining cases of cancer

NDA 020386

FIRM:

MERCK

7 OF 10

TRADE NAME:

COZAAR (LOSARTAN POTASSIUM) 25/50 MG TAB

GENERIC NAME:

LOSARTAN POTASSIUM

occurrence with antihypertensives. Because of such careful monitoring, it is unlikely that any retrospective data source will provide valid rates for comparison. Thus, the most comparable database for losartan is the sponsor's EL database.

In summary, the most likely explanation for the magnitude of the SMRs for renal cancer observed with losartan and EL is the careful monitoring that occurs in clinical trial settings and specifically by this sponsor that may have lead to a lead-time bias. Cancers that would have been detected later were detected earlier. Hypothetically, if there is a lead time bias and one followed the losartan, enalapril and lisinopril populations long enough, the overall incidence would return to that expected.

Conclusion

The incidence of renal cancer observed with losartan is no greater than that observed in hypertensive patients exposed to EL. However, the incidence rates observed for both are the highest incidence that we have observed in the literature. The mostly likely explanation for the magnitude of the incidence with losartan and EL, is better detection in the study population than occurs in the general population.

 11-3-94

Greg Burkhardt, M.D., M.Sc.
Epidemiology Branch
Division of Epidemiology and Surveillance
Office of Epidemiology and Biostatistics
534-5468

BIO/DISSOLUTION

REVIEW

NDA: 20-386
Priority: 1 S
COZAAR® (Losartan Potassium)
Tablets (25, 50 and 100 mg)

SUBMISSION DATES: DEC. 3, 1993
JUNE 17, 1994
AUG. 4, 1994,
OCT 3, 1994

MERCK RESEARCH LABORATORIES.

REVIEWER: Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: Original NME

SYNOPSIS:

The sponsor has adequately studied the pharmacokinetics (single and multiple dose), metabolism and excretion of losartan, a new angiotensin II receptor antagonist, and has established the dose proportionality of losartan to include the dosing range covered in the proposed package insert. Acceptable studies have also been performed to study renal and liver impairment as well as age and gender effects. Drug interaction between the drug and phenobarbital, cimetidine, warfarin, digoxin and hydrochlorothiazide were studied. Food effect was studied. An acceptable in vitro dissolution method has been provided.

RECOMMENDATION:

The Division of Biopharmaceutics recommends that the sponsor's NDA 20-386 be accepted for meeting the Biopharmaceutics requirements provided the comments below (pages 8-10) are satisfactorily addressed by the sponsor.

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Appendix II:

Note: Appendix II contains more data/information such as individual subject data and statistical analyses. This information is being retained in the Division of Biopharmaceutics, and can be obtained upon request.

BACKGROUND: Losartan is a synthetic compound with structure shown in Figure 1.

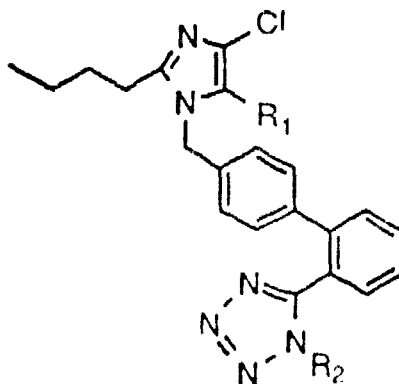
Losartan and its active metabolite block all physiologically relevant actions of angiotensin II by binding to the AT₁ receptor. It is proposed to be used for the treatment of hypertension, and dizziness and orthostatic effects are the major side effects. The sponsor has submitted 18 studies in support of the NDA and the 18 studies were reviewed. The recommended dosing is 50 to 100 mg once a day for up to 8-6 weeks.

Losartan is an acidic polar compound with a solubility of >500 mg/ml in water (resulting pH of 9.7), 2.5 mg/g in acetonitrile, and about 35 mg/g in 2-propanol. The average partition coefficient in octanol-water (phosphate buffer, pH 7; initial aqueous phase concentrations 0.01M and 0.001M) system is 15 ± 1 . The pH of a solution of losartan potassium (1% w/w) in water is about 8.2. The pKa value in aqueous solution containing 1% methanol is 4.1 as determined by ultraviolet spectroscopy using buffers from pH 1 to 13.

Structures of Losartan Potassium and L-158,641

OR
E-3174

(ACTIVE METABOLITE)



	R1	R2	Molecular Formula	Molecular Weight
Losartan potassium	CH ₂ OH	K	C ₂₂ H ₂₇ ClKN ₆ O	461.0
L-158,641	COOH	H	C ₂₂ H ₂₁ ClN ₆ O ₂	436.9

SUMMARY OF BIOAVAILABILITY/PHARMACOKINETICS/PHARMACODYNAMICS

I. BIOAVAILABILITY/BIOEQUIVALENCE:

A. **Absolute Bioavailability:** With reference to a 30 mg IV bolus dose, the absolute bioavailability of Losartan given as 1 X 100 mg non-market (clinically tested) capsule averaged 24.6% (CV 43.0%) while that of the tablet (used for Phase III studies) averaged 22.9% (CV 43.1%) (Study # 022). With reference to a 20 mg IV bolus dose, the absolute bioavailability of Losartan given as 1 X 50 mg final market image tablet averaged 32.6% (CV 43.4%) (Study # 074). With reference to a 30 mg IV bolus dose, the absolute bioavailability of Losartan given as 100 mg oral solution averaged 38.9% (CV 37.7%) (Study # 060).

B. **Bioequivalence:** Bioequivalence was evaluated on log-transformed parameters and 90% confidence intervals were reported. Study #022 compared the 100 mg capsule formulation used for early Phase I and Phase II studies to the 100 mg tablet formulation used for Phase III studies. The two one-sided test procedure on the AUC (0.69 - 1.24), C_{max} (0.55 - 1.32) for losartan, and AUC (0.96 - 1.09), C_{max} (0.93 - 1.23) for the active metabolite show that the clinically tested capsule and 100 mg tablet for Phase III are bioinequivalent with respect to losartan but bioequivalent with respect to the active metabolite. Study #075 compared the 50 mg tablet formulation manufactured by Merck and used for Phase III studies to the 50 mg tablet formulation manufactured by DuPont-Merck Pharmaceutical Corporation (DMPC) for marketing (in USA). The two one-sided test procedure on the AUC (0.89 - 1.07), C_{max} (0.69 - 1.17) for losartan, and AUC (0.91 - 1.05), C_{max} (0.81 - 1.02) for the active metabolite show that the 50 mg Merck and DMPC tablets are bioinequivalent with respect to losartan but bioequivalent with respect to the active metabolite. Study #075 also compared 50 mg losartan capsule formulation (prepared by DMPC) to the Merck Phase III tablet. The two one-sided test procedure on the AUC (0.99 - 1.19), C_{max} (0.92 - 1.56) for losartan, and AUC (1.00 - 1.15), C_{max} (0.97 - 1.22) for the active metabolite show that the 50 mg DMPC Losartan Capsules and 50 mg Merck Losartan Tablets are bioinequivalent with respect to losartan but bioequivalent with respect to the active metabolite.

C. **Food effect:** The effect of food on the absorption of losartan administered AM as single 1 X 100 mg tablet was evaluated (Study #015). After coadministration of a standard meal (caloric content = 469 Kcal) the T_{max} increased from 1.3 hours to 2.9 hours, C_{max} decreased by 52% and AUC decreased by 18% for losartan; T_{max} increased from 3.1 hours to 4.8 hours, C_{max} decreased by 24% and AUC decreased by 13% for the active metabolite but the T_{1/2} remained unchanged for losartan and the active metabolite.

II PHARMACOKINETICS:

After a single AM 2 X 50 mg capsule dose, the mean C_{max} was 315 ng/ml (CV 40%), the mean AUC_(0-∞) 816 ng*hr/ml (CV 44%), and the mean T_{max}, 1.5 hours (CV 60%) for losartan; the mean C_{max} was 568 (CV 36%), the mean AUC_(0-∞) 3642 ng*hr/ml (CV 30%),

and the mean Tmax, 3.4 hours (CV 24%) for the active metabolite (Study #007). On multiple dose administration of 2 X 50 mg capsules qd for 9 days, the Cmax was 437 ng/ml (CV 71%), the mean AUC_(0-∞) 662 ng*hr/ml (CV 42%), and the mean Tmax, 0.9 hours (CV 56%) for losartan; the mean Cmax was 547 (CV 33%), the mean AUC_(0-∞) 3341 ng*hr/ml (CV 28%), and the mean Tmax, 2.7 hours (CV 33%) for the active metabolite (Study #007). The accumulation factor was 0.81 for losartan; and 0.93 for the active metabolite (Study #007). On multiple dose administration of 2 X 50 mg capsules qd for 9 days, the renal clearance for losartan increased from 74.3 ml/min to 91.9 ml/min but there was no change in the mean renal clearance of the active metabolite (Study #007). The terminal half-life for losartan across studies was consistent and approximately 2 hours. 11.5% of the dose was recovered in the urine on administration of a 30 mg IV dose, and 4.8% after 100 mg oral solution on AM administration; > 92% of the total radioactivity was recovered in urine and feces over 168 hours following IV and oral losartan (Study #060). The volume of distribution was about 47 liters and the systemic clearance was 558.7 ml/minute for losartan; and the renal clearance (74 ml/min) accounts for about 13% of plasma clearance. Following single IV doses (10 - 80 mg) of the active metabolite to healthy volunteers (Study #060, Study #017) across the studies, the systemic clearance was 50 ml/minute, the volume of distribution was 12 liters, the half-life was about 6.6 hours, the renal clearance was 26 ml/minute and about 53% of the dose was recovered from urine over 96 hours.

III. **METABOLISM:** Metabolic profiling confirms the presence of three major metabolites in urine and feces, the carboxylic acid metabolite (active), ω-1 hydroxylated metabolite and ω-3 hydroxylated metabolite. The three metabolites, together with losartan account for 85% and 87% of radioactivity in urine (28% and 35% of the dose) for oral and IV doses respectively. The percentage of IV or PO losartan dose converted to the active metabolite is 14%. In vitro studies with specific enzyme inhibitors and recombinant isoforms of human cytochrome P450 indicate that both CYP2C9 and CYP3A4 isoforms are involved in the biotransformation of losartan to its metabolites. About 1% (4 out of about 500) subjects have so far been found who are unable to metabolize losartan (the 4 subjects are all caucasians).

IV. **DOSE AND DOSAGE FORM PROPORTIONALITY:**

The Cmax and AUC of losartan and its active metabolite were dose proportional between 10 mg and 200 mg single oral doses, as determined by linear regression (Study #003).

V. **SPECIAL POPULATIONS:**

A. **Renal Impairment:** Renally insufficient patients with creatine clearances ranging from < 10 ml/min (hemodialysis) to ≥ 75 ml/min were administered AM multiple (100 mg QD for 7 days) oral doses of losartan. Cmax increased (854 to 1615 ng/ml for losartan and 681 to 715 for the active metabolite) with decreasing renal function (Study #012). The AUC increased (1109 to 2066 ng*hr/ml for losartan and 4362 to 5012 ng*hr/ml for the metabolite) but there was no significant change in the Tmax and the half-life in patients with Clcr < 10 ml/min as compared with normal renal function (Study #012). Losartan and the active

metabolite do not appear to be cleared by hemodialysis.

B. Hepatic Impairment: Patients with hepatic insufficiency were administered AM single doses of 50 mg losartan tablet, 10 mg losartan IV solution and 10 mg of the active metabolite IV solution (Study #067). Compared to normal subjects (Study #060, #022, #074) systemic clearance decreased from 559 ml/min (Study #060) to 285 ml/min (Study #067) for losartan and from 47 ml/min (Study #060) to 33 ml/min (Study #067) for the active metabolite; the volume of distribution decreased from 47 liters (Study #060) to 20 liters (Study #067) for losartan and from 10 liters (Study #060) to 9 liters (Study #067) for the active metabolite; the AUC following oral administration of losartan increased (about 5-fold for losartan and about 1.7-fold for the active metabolite); the oral bioavailability of losartan increased by about 100%. The fractional conversion of losartan in systemic circulation to the active metabolite was similar in hepatic and healthy subjects (13 and 14% respectively). Adjustment to lower doses of losartan to patients with hepatic insufficiency should be considered.

C. Elderly and Gender: Hypertensive patients (5 males and 5 females) aged 65 - 75 years were administered AM single doses of 50 mg losartan tablet and 10 mg losartan IV solution (Study #063). Compared to young healthy males (Study #007, #015, #022) the AUC of losartan following oral administration in the elderly increased by between 15 - 32% while the AUC of the metabolite increased between 34 - 59%. Compared to young healthy males the volume of distribution decreased from 40 liters (Study #022) to 29 liters in elderly males (Study #067) for losartan. There is no difference in the systemic clearance of losartan between the young healthy males and the elderly but the renal clearance is decreased in the elderly hypertensive males by about 50%. The renal clearance of the active metabolite is about 17% lower in the elderly. The absolute bioavailability of oral losartan increased from 27% in young, healthy males to 34% in elderly male hypertensives.

Gender analysis of the data for the elderly patients shows that there are differences in the AUC (after PO) of losartan (males - 478 ng/ml.hr; females - 1008 ng/ml.hr), AUC of the active metabolite (males - 2477 ng/ml.hr; females - 2887 ng/ml.hr), systemic clearance (males - 597 ml/min; females - 416 ml/min), renal clearance (males - 46.6 ml/min; females - 32.8 ml/min) and absolute bioavailability (males - 33%; females - 49%). There was no significant difference in the mean volumes of distribution (males - 29 liters, females - 30 liters).

VI. DRUG INTERACTIONS:

A. Warfarin: In Study #070 healthy male volunteers were administered losartan, 100 mg/day for 7 days, or placebo, and administered a single 30 mg dose of warfarin on Day 7, with plasma samples collected for measurement of (R) and (S) warfarin and prothrombin time over the next 6 days as losartan or placebo were continued. Losartan did not affect the pharmacokinetics of (R) and (S) warfarin (AUC, C_{max}, T_{max}, T_{1/2}, λ) and the pharmacodynamic response (prothrombin time) to warfarin.

B. Phenobarbital: After chronic administration of phenobarbital (100 mg q.h.s. for 16 days)

followed by a single dose of losartan (100 mg) there was an induction of cytochrome P-450 (Study #072). Although this resulted in an increase in the amount of 6- β -hydroxycortisol excreted in the urine there was a reduction of about 20% each in the AUC for losartan and its active metabolite; and a reduction of about 20% each in the amounts excreted in the urine for losartan and its active metabolite.

C. Cimetidine: The results of Study #024 in which volunteers received single dose of losartan (100 mg) with and without prior and concurrent administration of cimetidine (400 mg) indicated that with co-administration of cimetidine there is an increase of about 23% in AUC and 36% in Cmax of losartan but no difference in the pharmacokinetics of the active metabolite of losartan.

D. Digoxin: Study #079 was a double-blind, two-period crossover design in which subjects received 50 mg losartan or placebo for 15 days in each period and single 0.5 mg IV (Day 4) and oral (Day 11) doses of digoxin. There were no significant differences in the pharmacokinetics of digoxin after intravenous or oral digoxin with and without losartan.

E. Hydrochlorothiazide (HCTZ): Study #073 was a randomized, three-period crossover design in which subjects received losartan (50 mg), HCTZ (12.5 mg) or losartan/HCTZ (50 mg/12.5 mg) single oral doses for 7 consecutive days on three separate occasions. The pharmacokinetics of losartan and its active metabolite are not significantly altered by HCTZ but the AUC₀₋₂₄ for HCTZ is decreased by about 17% when co-administered with losartan.

VII. PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIP: The nature of the interactions between losartan (a competitive angiotensin II antagonist) and its active metabolite (a non-competitive angiotensin II antagonist) makes it extremely difficult to simply estimate the specific contribution of losartan or E-3174 to the activity of the drug following single dose administration to humans. Following IV administration (Study #006) of single doses of losartan (40, 80, 120 mg), the systolic BP responses (% inhibition) to exogenous angiotensin II and concentration of E-3174 during 9 hours after dosing were fit to a Hill-Sigmoid-Emax model. The 9-hour areas under the E-3174 concentration and inhibition vs. time curve were fit to an Emax model. A plot of supine diastolic blood pressure change versus E-3174 concentration in hypertensive patients dosed with 20 mg IV infusion of E-3174 (Study #069) resulted in an open hysteresis with a somewhat linear portion up to achievement of maximal concentrations, followed by additional decreases in blood pressure as concentration declined. Following oral losartan (0-150 mg/day) to patients with mild to moderate hypertension for 8 weeks (Study #011), both drug concentration (E-3174) and effect increased with increasing dose of losartan but single measurements of drug concentration at peak, or trough are not highly correlated with drug effect after multiple-dose administration of losartan.

VIII. FORMULATION: The three tablet formulations to be marketed (25, 50 and 100 mg) are compositionally proportional. Their compositions are shown in Table 1 (Attached).

IX. **DISSOLUTION:** The proposed dissolution method of USP Appartus II at 50 rpm, in water is acceptable but the specification should be changed from Q = at 45 minutes to Q = at 30 minutes.

X. **ASSAY:** The sponsor used validated HPLC methods to measure losartan and its active metabolite in all the studies. Overall, the analytical validation was satisfactory.

XI. **PLASMA PROTEIN BINDING:** Both losartan and its active metabolite were extensively bound to plasma protein. The unbound fractions of losartan and its active metabolite for human plasma were 1.3% and 0.2% respectively. Binding of the two drugs was concentration-independent over a wide concentration range (0.1-10 $\mu\text{g/ml}$), and over the pH range 6.95 to 8.58. Studies with purified human serum albumin and α_1 -acid glycoprotein revealed that serum albumin is the major component of plasma protein responsible for the binding of both drugs.

XII. **LABELING:** The clinical pharmacology section of the labeling is deficient and the firm has been advised to modify it accordingly (see comments below).

XIII. **INFLUENCE OF RACE:** The pharmacokinetics of losartan and its active metabolite has not been described in various race groups.

GENERAL COMMENTS TO THE MEDICAL OFFICER:

The sponsor has not demonstrated bioequivalence in terms of Cmax of losartan between (a) the 100 mg capsule used for early Phase I and Phase II studies and the 100 mg tablet used for Phase III studies; (b) the 50 mg tablet formulation manufactured by Merck and used for Phase III studies and the 50 mg tablet formulation manufactured by DuPont-Merck Pharmaceutical Corporation for marketing in USA. It was however noted that the tablet formulation for Phase III and to-be-marketed products are identical except for color. Additionally, PK/PD analysis shows Cmax of losartan to be a less important parameter than AUC and Cmax of the active metabolite for which bioequivalence has been demonstrated. In the light of these facts the demonstration of bioequivalence in terms of Cmax of losartan may not be very critical for deciding on the approval of the NDA.

GENERAL COMMENTS TO THE PHARMACOLOGIST:

The pharmacologist is requested to please note that under the "*Carcinogenesis, Mutagenesis, Impairment of Fertility*" section of the labeling the toxicology data in animals in relation to humans should be related to exposure rather than doses.

COMMENTS TO BE SENT TO THE FIRM:

1. In the analyses of Cmax and AUC (Study #022, #074, #075) the firm normalized the

C_{max} and AUC for losartan and E-3174 to assayed contents of the oral and IV formulations used for the studies. The firm should note that this approach is not acceptable for biostudies; instead the labelled strength of the formulations should be used.

2. DISSOLUTION: Based on the dissolution data submitted by the sponsor, the dissolution specification should be changed from not less than _____ of the labelled amount of losartan potassium dissolved in 45 min to " not less than _____ of the labelled amount of losartan potassium dissolved in 30 min "

3. RARE SUBJECTS: Four subjects have been identified as rare subjects because of their inability to metabolize losartan. The sponsor submitted a protocol to evaluate the cytochrome P-450 system in these subjects in March 1993 and through a telephone conversation with the firm (Dr. Bell) the reviewer was informed that the studies are not yet completed. The firm submitted a preliminary information on 2 of the subjects on October 3, 1994. The sponsor is requested to submit to the Agency the full reports on these rare subjects as soon as they are available.

LABELING COMMENTS:

1. The Clinical Pharmacology section of the labeling should be written under the following sub-sections: *Mechanism of Action, Pharmacokinetics - introductory paragraph (with most important pharmacokinetic features), absorption, distribution, metabolism, excretion, special populations, gender, race, renal insufficiency, hepatic insufficiency, drug interactions as shown below:*

Mechanism of Action
As in the labeling.

Pharmacokinetics:

Losartan's activity is primarily due to the parent drug and the carboxylic acid metabolite. Studies with radiolabeled drug have demonstrated that orally administered losartan is well absorbed into the systemic circulation with approximately 92% of the radiolabel recovered in urine and feces. Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6-9 hours, respectively. During once-daily dosing at 100 mg, neither losartan nor its active metabolite accumulate significantly in plasma.

Absorption

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The absolute bioavailability of losartan is approximately 33%. Losartan's low bioavailability is due to its high presystemic first pass metabolism. Mean peak concentrations of losartan and its active

metabolite are reached in 1 hour and in 3-4 hours respectively. Administration of losartan with standardized meal (18.8 g of protein, 53.8 g of carbohydrate, 19.5 g of fat; caloric content = 469 Kcal) showed that AUC decreased by 18%, C_{max} decreased by 52%, and T_{max} increased from 1.3 to 2.9 hours for losartan; AUC decreased by 13%, C_{max} decreased by 24%, and T_{max} increased from 3.1 to 4.8 hours for the active metabolite.

Distribution

The volume of distribution of losartan is approximately 47 liters while that of its active metabolite is approximately 12 liters. Both losartan and its active metabolite are $\geq 99\%$ bound to plasma proteins, primarily albumin. The unbound fractions of losartan and its active metabolite are respectively 1.3% and 0.2%. Plasma protein binding is constant over the concentration range achieved with recommended doses. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Metabolism

Losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, inactive metabolites are formed, including the ω -1 hydroxylated metabolite and ω -3 hydroxylated metabolite, and a minor metabolite, an N-2 tetrazole glucuronide. The active carboxylic acid metabolite has been evaluated along with losartan in receptor binding studies and has a demonstrated potency about 5 to 10 times of the parent drug. About 14% of an intravenous- or orally-administered dose losartan is converted to the active metabolite. Following oral and intravenous administration of ¹⁴C-labeled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and its active metabolite. In vitro studies with specific enzyme inhibitors and recombinant isoforms of human cytochrome P450 indicate that both CYP2C9 and CYP3A4 isoforms are involved in the biotransformation of losartan to its metabolites. Minimal conversion of losartan to the active metabolite (less than 1% of the dose compared to 14% of the dose in normal subjects) was seen in about one percent of individuals studied.

Excretion

Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% of the dose is excreted in urine as active metabolite. Biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following oral dose of ¹⁴C-labeled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the feces. Following an intravenous dose of ¹⁴C-labeled losartan in man, about 43% of radioactivity is recovered in the urine and 50% in the feces. The pharmacokinetics of losartan and its active metabolite are linear with single oral losartan potassium doses up to 200 mg.

Special Populations

Pediatric

Losartan pharmacokinetics have not been investigated in patients < 18 years of age.

Geriatric and Gender

Losartan Pharmacokinetics have been investigated in the elderly (65-75 years). The renal clearance of losartan is decreased by about 50% in elderly male hypertensives when compared to young healthy males. Plasma concentrations of losartan were about 2-fold higher in female hypertensives as compared to male hypertensives. Concentrations of the active metabolite were not different in males and females.

Race

Pharmacokinetic differences due to race have not been identified.

Renal Insufficiency

Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 ml/min. Compared to patients with normal renal function, the AUC of losartan is approximately 2-fold greater in hemodialysis patients. Plasma concentrations of the active metabolite are not significantly altered in patients with renal impairment or in hemodialysis patients. Neither losartan nor its active metabolite can be removed by hemodialysis.

Hepatic Insufficiency

Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were respectively, 5-fold and 1.7-fold greater than those seen in young male volunteers. Compared to normal subjects the volume of distribution of losartan in patients with ~~renal~~ ^{hepatic} insufficiency decreased by about 50% but the oral bioavailability increased by about 100%.

Drug Interactions

Losartan did not affect the pharmacokinetics and pharmacodynamics of warfarin. Losartan did not affect the pharmacokinetics of oral or intravenous digoxin. Coadministration of losartan and cimetidine led to an increase of about 23% in AUC of losartan but no difference in the pharmacokinetics of its active metabolite. Coadministration of losartan and phenobarbital led to a reduction of about 20% in the AUC of losartan and that of its active metabolite. There is no interaction between losartan and hydrochlorothiazide.

2. Pharmacodynamics

The following statement should be added to paragraph 4 of the pharmacodynamics section:
" However individual peak or trough concentrations of losartan or the active metabolite do not correlate with antihypertensive effects".


Emmanuel O. Fadiran, Ph.D.
Pharmacokinetics Evaluation Branch

FT Initialed by A. Parekh, Ph.D. Ameeta Parekh 1/27/95
Biopharm Day 9/28/94: Collins, Ludden, Malinowski, Fleischer, Chen, Hepp, Parekh

cc: NDA 20-386, HFD-110, HFD-426 (Fadiran, Fleischer), HFD-427 (M. Chen), Chron,
Drug, Review, FOI (HFD-19), HFD-340 (Vish), DI, F, G, A, RI, PK/PD, H, M

APPENDIX I

METABOLIC PROFILING

STUDY NUMBER: 060-001 **VOLUME:** 1.42 **PAGES:** 1106 - 1360

INVESTIGATOR AND LOCATION:

STUDY PERIOD: June 1992 - July 1992.

OBJECTIVES: (1) To determine the metabolite profiles in plasma and urine after administration of ¹⁴C-losartan to humans; (2) to determine the absorption, distribution, metabolism and elimination of ¹⁴C-losartan when administered by oral and IV routes; (3) to determine if any route of administration-dependent differences in losartan metabolism exists; (4) to determine the fraction of losartan that is metabolized to the active metabolite (E-3174).

FORMULATIONS:

Radioactive losartan Injection, 30 mg, Formulation # R0954 HSS002A001
Radioactive losartan Injection, 30 mg (used orally), Formulation # R0954 HSS002A001
Losartan Injection, 50 mg (used orally), Formulation # 0954 HSS001A001
E-3174 (Active metabolite) Injection, 50 mg, Formulation # 9519 HSS001A001

STUDY DESIGN:

A randomized, open, three-period cross-over study in 6 healthy volunteers with a washout period of 7 days. ¹⁴C-losartan was administered in the first and third periods as single 100 mg oral (Treatment A) dose (100 μ Ci) and as a single 30 mg IV (Treatment B) dose (100 μ Ci). E-3174 (without isotope) was administered as a single 20 mg IV (Treatment C) dose during the second period. For Treatment A, blood samples (11 ml) were collected at 0, .25, .5, .75, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36, and 48 hours; for Treatment B blood samples (11 ml) were collected at 0, 10, 20, 30 minutes, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36, and 48 hours; and for Treatment C blood samples (6 ml) were collected at 0, 10, 20, minutes, 1, 2, 4, 6, 9, 12, 18, 24, 30, and 36 hours. For Treatments A and B urine samples were collected predose (blank) and at 0-2, 2-4, 4-6, 6-8, 8-12, 12-18, 18-24, 24-36, 36-48, 48-72, 72-96 hours; and for Treatment C predose (blank), and at 0-3, 3-6, 6-12, 12-24, 24-36 and 36-48 hours. Feces were collected over 168-hour period following Treatments A and B and fecal samples were assayed radiometrically until negligible radioactivity was observed.

ASSAYS: HPLC with UV detection.

PLASMA SAMPLES - LOSARTAN (MK-954) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curve from 5 to 1000 ng/ml.

Accuracy: Satisfactory. 96.0% at 20 ng/ml, 92.1% at 800 ng/ml for MK-954, and 98.0% at

20 ng/ml, 97.2% at 800 ng/ml for E-3174.

Precision: Satisfactor . %CV - 9.9% at 20 ng/ml, 6.3% at 800 ng/ml for MK-954, and 3.3% at 20 ng/ml, 5.7% at 800 ng/ml for E-3174.

Sensitivity: LOQ - 5 ng/ml.

Specificity: Satisfactory. Chromatograms submitted.

URINE SAMPLES - LOSARTAN (MK-954) AND ACTIVE METABOLTE (E-3174):

Linearity: Satisfactory. Standard curve from 10 to 2000 ng/ml for E-3174 and 20 to 2000 ng/ml for DuP 753..

Accuracy: Satisfactory. 102.0% at 40 ng/ml, 97.5% at 1600 ng/ml for MK-954, and 100.8% at 40 ng/ml, 101.8% at 1600 ng/ml for total E-3174.

Precision: Satisfactory. %CV - 4.2% at 40 ng/ml, 1.0% at 1600 ng/ml for DuP 753, and 1.5% at 40 ng/ml, 2.0% at 1600 ng/ml for E-3174.

Sensitivity: LOQ - 10 ng/ml for E-3174 and 20 ng/ml for MK-954.

Specificity: Satisfactory. Chromatograms submitted.

The assays have been validated over the range of plasma and urine concentrations observed in the study.

DATA ANALYSIS: AUC, Cmax, Tmax, Vdss, λ , CL, CLr, %Dose excreted and bioavailability were calculated.

RESULTS:

Total R-radioactivity and Metabolic Profiling (% dose)

	I.V. Losartan 30 mg (30 μ Ci)		Oral Losartan 100 mg (100 μ Ci)	
	Urine	Feces	Urine	..Feces
Total Radioactivity	43.3 $\pm$ 8.4	49.5 $\pm$ 13.3	35.2 $\pm$ 6.2	57.7 $\pm$ 7.9
Metabolic Profile		AN001	AN002	
Losartan	11.4 $\pm$ 4.0	12.8	7.77	4.91 $\pm$ 2.27
L-158,795	9.35 $\pm$ 1.73	8.20	8.38	9.09 $\pm$ 1.79
L-158,641	6.44 $\pm$ 2.45	6.92	13.38	6.41 $\pm$ 2.22
L-158,796	8.24 $\pm$ 1.76	7.37	9.44	7.64 $\pm$ 1.80
L-158,783	0.267 $\pm$ 0.109	0.794	1.31	-

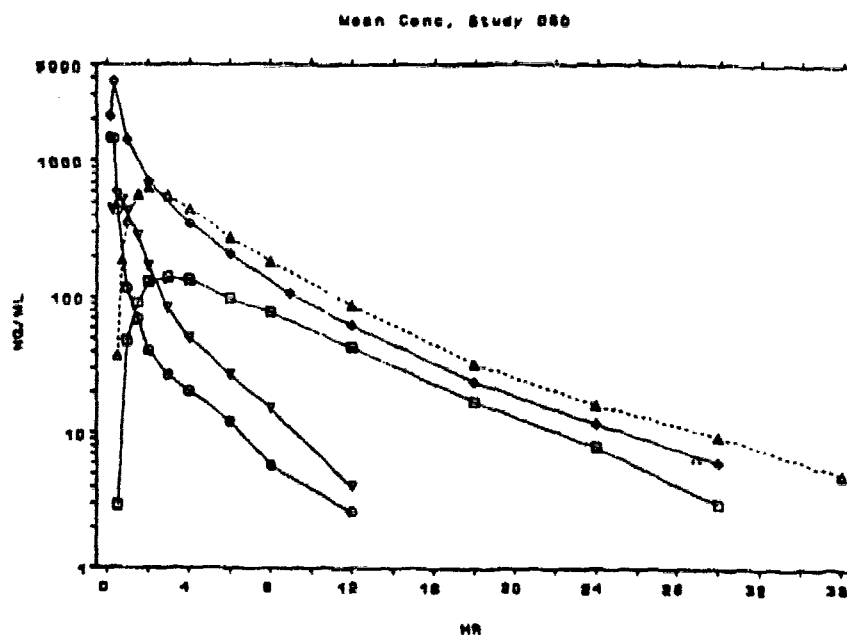
Pharmacokinetics Parameters (mean±S.D.) of Losartan and L-158,641

	Intravenous L-158,641 20 mg	Intravenous Losartan 30 mg (100 µCi)		Oral Losartan (Solution) 100 mg (100 µCi)	
	L-158,641	Losartan	L-158,641	Losartan	L-158,641
C _{20min} , ng/ml	3720.7 ± 342.2	1452.8 ± 636.4	-	-	-
C _{max} , ng/ml	-	-	148.9 ± 78.9	639.1 ± 244.0	652.6 ± 259.1
T _{max} , hr	-	-	4.0 ± 2.1	0.46 ± 0.29	2.33 ± 0.52
AUC _{0-∞} , ng/mL·hr	5969.27 ± 709.03	851.18 ± 234.54	1331.96 ± 490.24	1091.35 ± 397.46	4072.54 ± 1252.91
λ, hr ⁻¹	0.1105 ± 0.0228	0.2181 ± 0.0531	0.1304 ± 0.0501	0.2418 ± 0.0502	0.0881 ± 0.0092
t _{1/2} , hr ^a	6.27 ± 1.36	3.18 ± 0.78	5.32 ± 2.12	2.87 ± 0.57	7.87 ± 0.82
V _{dss} , L	10.33 ± 1.09	46.59 ± 20.50	-	-	-
CL, mL/min	46.93 ± 5.79	558.71 ± 188.01	-	-	-
CL _T , mL/min	25.88 ± 5.59	64.39 ± 25.96	25.25 ± 7.00	64.63 ± 17.28	27.00 ± 6.10
Recovered in Urine (mg)	9.129 ± 1.414	3.020 ± 0.836	1.911 ± 0.616	4.297 ± 1.878	6.516 ± 2.186
% Dose ^c	55.07 ± 8.95	11.50 ± 3.49	7.59 ± 2.30	4.77 ± 2.08	7.63 ± 2.58
F, % ^b	-	-	-	38.90 ± 14.67	-

^a Harmonic mean and pseudo standard deviation.

^b Oral bioavailability, geometric mean was 36.47% with 90% confidence interval limits of 26.11% to 50.94%.

^c % dose recovered in the urine as losartan.



Mean Plasma Concentrations of MK-954 and E-3174 in Six Subjects Following the Administration of A Single Intravenous Dose of 30-mg MK-954 (○ = MK-954, □ = E-3174), A Single 100-mg Oral Dose of MK-954 (▽ = MK-954, △ = E-3174), and A Single Intravenous Dose of 20-mg E-3174 (◊ = E-3174)

CONCLUSION: The study supports the sponsor's labeling claim for the metabolic profiling of losartan following oral or intravenous administration.

DOSE PROPORTIONALITY STUDY (I.V.)

STUDY NUMBER: 013

VOLUME: 1.42

PAGES: 1369 - 1793

INVESTIGATOR AND LOCATION:

OBJECTIVES: To evaluate the safety, tolerability and pharmacokinetics of losartan following administration of the intravenous preparation at several doses.

FORMULATIONS:

Losartan (10 ml fill), Batch No. C-W352, Formulation No. 0954 HSS001A001

Placebo (10 ml fill), Batch No. C-W352, Formulation No. P954 HSS001P001

STUDY DESIGN: Double-blind, randomized, rising-dose, placebo-controlled study in two alternating panels of 9 healthy male subjects per panel. On each study day 6 subjects in each panel received losartan and 3 placebo according to a randomized allocation schedule. Panel I received 1, 10, and 40 mg losartan or placebo and Panel II received 5, and 20 mg losartan or placebo. All doses were administered as a 20-minute infusion with each dose in each subject separated by a 7-day washout period. Plasma samples were drawn at 0, 5, 10, 15, 20, 25, 30, 45, 60, 80, 100 minutes, 2, 3, 4, 5, 6, 8, 10, 16, 24, 30, and 36 hours post-initiation of infusion of losartan. Urine samples were collected at 0-6, 6-12, 12-24, 24-36, and 36-48-hour intervals post-initiation of infusion of losartan.

ASSAYS: HPLC with UV detection.

PLASMA SAMPLES-LOSARTAN (MK-954) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curves from 5 to 1000 ng/ml

Accuracy: Satisfactory. 108.0% at 20 ng/ml, 103.0% at 800 ng/ml for MK-954; and 111.5% at 20 ng/ml, 105.6% at 800 ng/ml.

Precision: Satisfactory. %CV- 6.6% at 20 ng/ml, 4.9% at 800 ng/ml for MK-954; and 4.0% at 20.0 ng/ml, 4.2% at 800 ng/ml.

Sensitivity: LOQ - 5 ng/ml for MK-954 and E-3174.

Specificity: Satisfactory. Chromatograms submitted.

URINE SAMPLES-LOSARTAN (MK-954) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curves from 20 to 2000 ng/ml for MK-954; and

10 to 2000 ng/ml for E-3174.

Accuracy: Satisfactory. 91.0% at 40 ng/ml, 97.8% for 1600 ng/ml for MK-954; and 110.8% at 40 ng/ml, 98.2 % at 1600 ng/ml.

Precision: Satisfactory. %CV- 9.2% at 40 ng/ml, 0.8% at 1600 ng/ml for MK-954; and 11.6% at 40 ng/ml, 0.3% at 1600 ng/ml for E-3174.

Sensitivity: LOQ - 20 ng/ml for MK-954; 10 ng/ml for E-3174.

Specificity: Satisfactory, Chromatograms submitted.

The assays have been validated over the range of plasma and urine concentrations observed in the study.

DATA ANALYSIS: AUC, C_{20min} , $t_{1/2}$, CL, CL_r , V_{dss} , and % Dose excreted in urine were calculated for 10 and 40 doses of losartan.

RESULTS:

Summary of Pharmacokinetic Analysis

Parameter*	Losartan				L-158,641			
	10 mg		40 mg		10 mg		40 mg	
C_{20} (ng/mL)	594	(131)	2501	(564)	—	—	—	—
C_{max} (ng/mL)	—	—	—	—	40	(14)	241	(63)
T_{max} (hr)	—	—	—	—	4.0	(0.9)	2.6	(0.9)
$AUC_{(0-\infty)}$ (ng.hr/mL)	307	(56)	1187	(254)	433	(122)	1786	(369)
$t_{1/2}$ (hr)	2.1	(0.7)	2.2	(0.7)	6.2	(2.3)	6.7	(1.6)
V_{dss} (L)	33	(11)	26	(10)	—	—	—	—
Cl (mL/min)	563	(93)	585	(102)	—	—	—	—
Cl_r (mL/min)	87	(26)	80	(31)	25	(12)	25	(6)
% Dose	15	(2)	16	(4)	5	(1)	7	(1)

* Values are mean (SD) except for $t_{1/2}$ (harmonic mean [pseudo standard deviation])

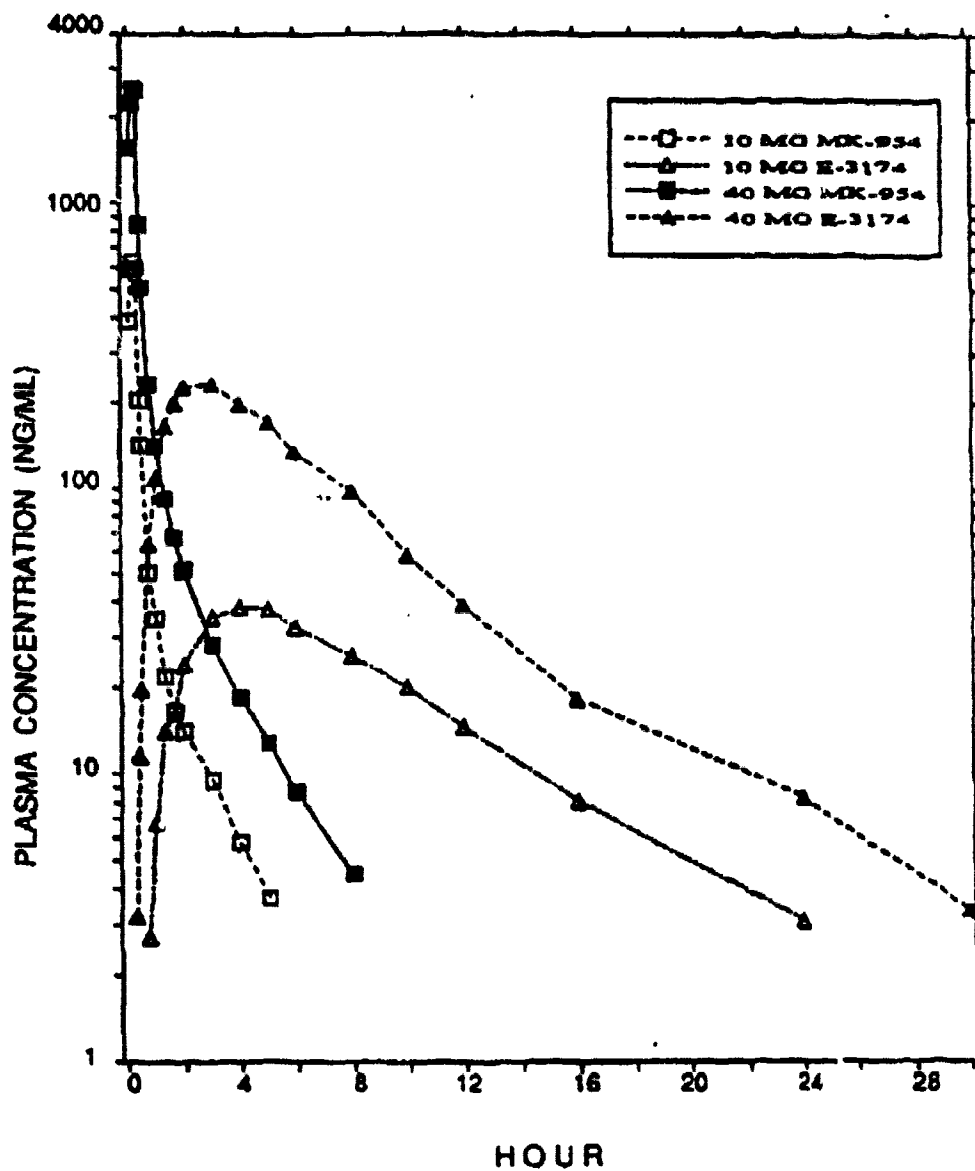
C_{20} = Concentration at end of infusion

Cl = Systemic clearance

Cl_r = Renal clearance

% dose = Percent of dose found in urine (0-48 hours)

Mean Plasma Concentrations of Losartan
and L-158,641 (E-3174) Following 10 mg and 40 mg Losartan (n=6)



CONCLUSION: The study supports the sponsor's claim that the pharmacokinetics of losartan and its active metabolite were dose-independent between the 10- and 40-mg IV doses of losartan.

DOSE PROPORTIONALITY STUDY (METABOLITE)

STUDY NUMBER: 017

VOLUME: 1.43

PAGES: 1794 - 2295

INVESTIGATOR AND LOCATION:

OBJECTIVES: To evaluate the safety, tolerability and pharmacokinetics of E-3174 following administration of the intravenous preparation of E-3174 at several doses.

FORMULATIONS:

E-3174 IV Injection (5 mg/ml; HCl salt), Formulation No. 9519 HSS001a001 (DuPont Lot #901463).

STUDY DESIGN: Double-blind, randomized, rising-dose, placebo-controlled study in two alternating panels of 8 healthy male subjects per panel. On each study day 6 subjects in each panel received E-3174 and 2 placebo according to a randomized allocation schedule. Panel I received 0.1, 1, 10, and 40 mg E-3174 or placebo and Panel II received 0.5, 5, 20, and 80 mg E-3174 or placebo. All doses were administered as a 20-minute infusion with each dose in each subject separated by a 7-day washout period. At doses 1, 5, 10, 20, 40 and 80 mg, plasma samples were drawn at 0, 5, 10, 15, 20, 30, 45, 60, 80, 100 minutes, 2, 3, 6, 9, 12, 16, 24, 30, and 36 hours post-initiation of infusion of E-3174. Urine was collected at 0-6, 6-12, 12-24, 24-36, and 36-48-hour intervals post-initiation of infusion of E-3174.

ASSAYS: HPLC with UV detection.

PLASMA SAMPLES

Linearity: Satisfactory. Standard curve from 5 to 1000 ng/ml.

Accuracy: Satisfactory. 90.0% at 20 ng/ml, 103.8% at 800 ng/ml .

Precision: Satisfactory. %CV - 11.1% at 20 ng/ml, 2.3% at 800 ng/ml.

Sensitivity: LOQ - 5 ng/ml.

Specificity: Satisfactory. Chromatograms submitted.

URINE SAMPLES

Linearity: Satisfactory. Standard curve from 10 to 2000 ng/ml

Accuracy: Satisfactory. 103.5% at 20 ng/ml, 100.8% at 800 ng/ml .

Precision: Satisfactory. %CV - 4.8% at 20 ng/ml, 3.4% at 800 ng/ml .

Sensitivity: LOQ - 10 ng/ml.
 Specificity: Satisfactory. Chromatograms submitted.

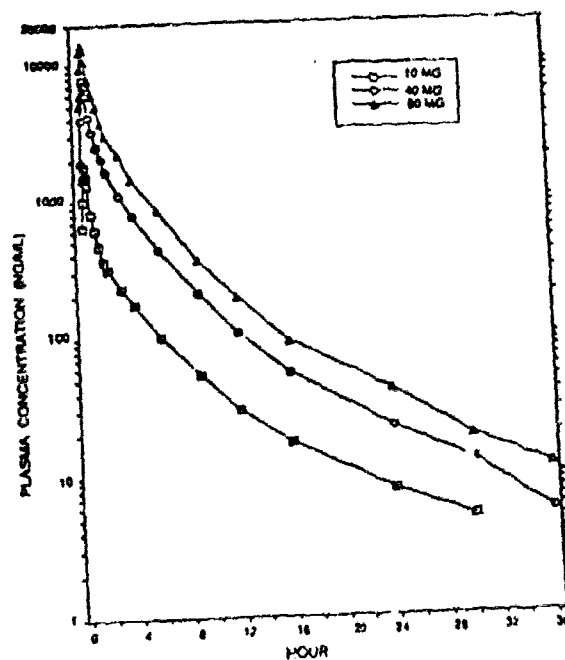
The assays have been validated over the range of plasma and urine concentrations observed in the study.

DATA ANALYSIS: AUC_{∞} , C_{20min} , $t_{1/2}$, CL, CL_r , V_{dss} , and % Dose excreted in urine were calculated for 10, 40 and 80 mg doses of E-3174.

RESULTS:

	10 mg	40 mg	80 mg
$C_{20 min}$ (ng/mL)	1818 ± 132	7814 ± 1129	14,305 ± 2676
AUC_{∞} (ng·hr/mL)	2897 ± 407	12,808 ± 2688	24,310 ± 4147
$t_{1/2}$ (hr ^a)	6.9 ± 5.0	6.5 ± 1.2	6.6 ± 1.2
v_{dss} (L)	16.4 ± 5.6	10.3 ± 2.4	9.8 ± 1.3
CL (mL/min)	53.0 ± 7.4	48.8 ± 9.5	51.4 ± 11.9
CL_{renal} (mL/min)	27.5 ± 6.1	23.8 ± 4.7	27.9 ± 5.4
% Dose in urine	52.6 ± 2.7	49.2 ± 6.6	54.9 ± 9.7

^aHarmonic mean and pseudo standard deviation.



CONCLUSION: The study supports the sponsor's claim that the pharmacokinetics of the active metabolite of losartan were dose-independent between the 10-, 40- and 80-mg IV doses.

DOSE PROPORTIONALITY STUDY

STUDY NUMBER: 003

VOLUME: 1.43 - 1.45

PAGES: 2296 - 3674

INVESTIGATOR AND LOCATION:

STUDY PERIOD: DECEMBER 1989 - MAY 1990.

OBJECTIVES: (i) to determine the safety, tolerability of single doses of losartan (Dup 753) ranging from 10 to 300 mg/day, (ii) to determine preliminary pharmacokinetics, dose proportionality of single doses of DuP 753.

FORMULATIONS:

5 mg losartan capsules, Formulation # DuP 753, lot # 891351

20 mg losartan capsules, Formulation # DuP 753, lot # 891352

50 mg losartan capsules, Formulation # DuP 753, lot # 891353

Placebo capsules lot # 891354

STUDY DESIGN: Single center, double-blind, parallel, placebo-controlled study with 29 male subjects divided into four treatment groups and 7 days washout period between treatments. Each subject received received four single-dose treatments of study drug (three active, one placebo) in rising dose order with respect to active drug and placebo inserted into the sequence according to a random allocation schedule. Group 1 received single doses of 10 mg, 20 mg, and 40 mg; Group 2 received 40 mg, 80 mg, and 120 mg; Group 3 received 120 mg, 150 mg, and 200 mg; and Group 4 received 200 mg, 250 mg and 300 mg. Prior to the start of the active treatment periods, each subject received a single dose of placebo (open label) and blood pressure and ECG recording were measured for a 24-hour period. Blood samples (7ml) were drawn at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 30 hours post dose.

ASSAYS: HPLC with UV detection.

Linearity: Satisfactory. Standard curves from 20 to 1000 ng/ml.

Accuracy: Satisfactory. 99.2% at 83.1 ng/ml, 107.3% at 842.1 ng/ml for DuP 753; and 96.0% at 24.9 ng/ml, 106.52% at 851.3 ng/ml for E-3174.

Precision: Satisfactory. %CV - 2.0% at 83.1 ng/ml, 5.0% at 842.1 ng/ml for DuP 753; and 1.0% at 102.2 ng/ml, 1.9% at 851.3 ng/ml for E-3174.

Sensitivity: LOQ - 20 ng/ml.

Specificity: Satisfactory. Chromatograms submitted.

The assays have been validated over the range of plasma concentrations observed in the study.

DATA ANALYSIS: AUC, $\lambda^{(n)}$, C_{max} , $t_{1/2}$, and T_{max} were calculated.

RESULTS:

Dose (mg)		DuP 753					E-8174				
		C_{max} (ng/mL)	T_{max}^a (hr)	AUC (ng-hr/mL)	$\lambda^{(n)}$ (hr ⁻¹)	$t_{1/2}^b$ (hr)	C_{max} (ng/mL)	T_{max}^a (hr)	AUC (ng-hr/mL)	$\lambda^{(n)}$ (hr ⁻¹)	$t_{1/2}^b$ (hr)
10	Mean	21.1	1.00	94.1	0.4418	1.6	39.3	0.00	434.3	0.0393	17.6
	S.D.	15.9 (0.25-1.50)		NA	NA	NA	15.0 (4.0-8.0)		170.0	NA	NA
	n	7	5	2	2	2	7	6	6	1	1
20	Mean	71.6	0.50	137.0	0.7437	0.9	66.4	4.00	777.0	0.1266	5.5
	S.D.	35.2 (0.5-2.0)		57.0	0.5327	0.7	35.4 (3.0-6.0)		122.0	0.0102	0.0
	n	7	7	7	4	4	7	6	6	6	6
40 ^c	Mean	214.0	0.75	391.5	0.4539	1.5	186.7	4.00	1720.0	0.1607	4.3
	S.D.	123.4 (0.5-1.5)		225.5	0.2062	0.7	89.9 (3.0-4.0)		509.2	0.0450	1.3
	n	15	15	15	14	14	15	14	14	14	14
80	Mean	537.5	0.75	932.7	0.5202	1.3	480.0	3.00	3039.3	0.1009	4.1
	S.D.	226.1 (0.5-1.5)		519.2	0.2209	0.6	101.5 (2.0-4.0)		1451.7	0.0390	1.0
	n	8	8	8	7	7	8	8	8	8	8
120 ^c	Mean	866.5	1.00	1277.7	0.6111	1.2	907.7	2.00	5333.7	0.1701	3.9
	S.D.	371.3 (0.5-1.5)		572.7	0.2974	0.6	206.2 (1.5-3.0)		1664.1	0.0715	1.6
	n	15	15	15	15	15	15	15	15	15	15
150	Mean	1141.1	1.00	1670.0	0.4029	1.7	1241.6	1.75	6006.9	0.1610	4.3
	S.D.	364.3 (0.5-2.0)		296.0	0.1194	0.5	236.2 (1.5-3.0)		1735.2	0.0672	1.9
	n	8	8	8	8	8	8	8	8	8	8
200 ^c	Mean	2177.3	0.75	2371.0	0.4030	1.5	1710.0	1.50	8110.0	0.1454	4.0
	S.D.	826.0 (0.5-1.5)		704.1	0.2471	0.8	452.5 (1.0-3.0)		2110.3	0.0445	1.5
	n	16	15	15	15	15	15	15	15	15	15
250	Mean	2118.7	1.00	2567.3	0.5410	1.3	2039.9	2.00	9067.0	0.1693	4.1
	S.D.	1442.6 (0.5-2.0)		1062.1	0.3750	1.1	639.3 (1.5-2.0)		2910.9	0.0647	1.6
	n	7	7	7	7	7	7	7	7	7	7
300	Mean	2070.3	0.50	3492.4	0.5471	1.3	2327.1	2.00	10546.0	0.1420	4.0
	S.D.	1660.0 (0.5-1.0)		1593.0	0.3090	0.9	669.5 (1.5-3.0)		3219.1	0.0233	0.0
	n	7	7	7	7	7	7	7	7	7	7

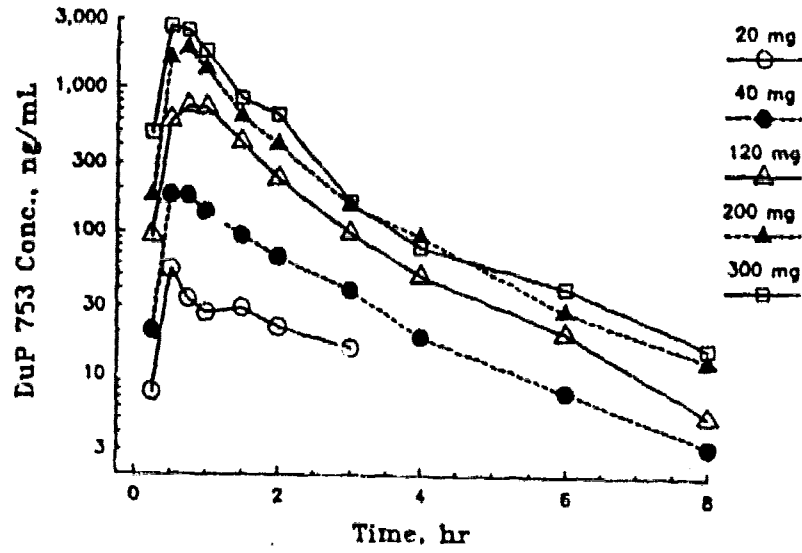
^a Median and range.

^b Harmonic mean and pseudo standard deviation based on the jackknife variance.

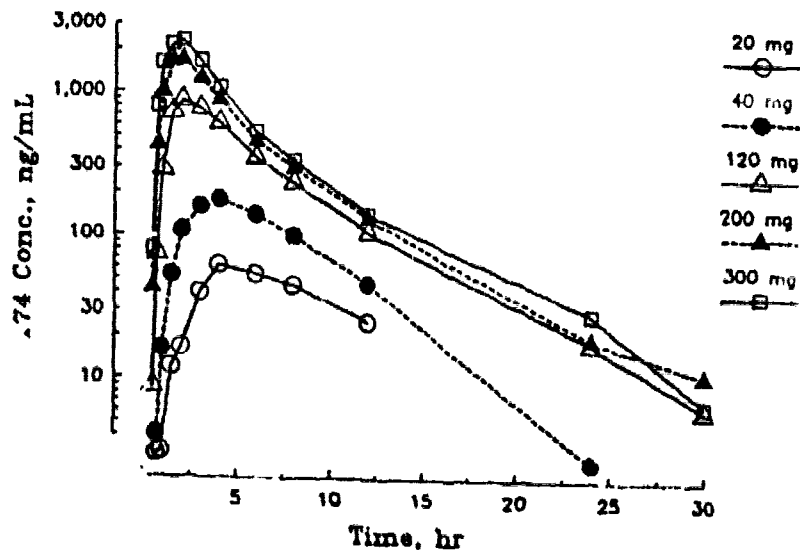
^c Mean and S.D. of all subjects in two groups for this dose.

NA: Not applicable.

Mean Concentration



Mean Concentration



CONCLUSION: The study supports the sponsor's claim that the disposition of losartan (DuP 753) is linear when administered as single, oral doses from 10 - 200 mg to healthy volunteers.

DOSE PROPORTIONALITY STUDY IN PATIENTS

STUDY NUMBER: 004

VOLUME: 1.45 - 1.46

PAGES: 3675 - 4584

INVESTIGATOR AND LOCATION:

STUDY PERIOD: DECEMBER 1989 - JANUARY 1990.

OBJECTIVES: (i) to determine the safety, efficacy, and tolerability of single oral doses of losartan (Dup 753) ranging from 5 to 120 mg/day, (ii) to assess the preliminary pharmacokinetics single doses DuP 753.

FORMULATIONS:

5 mg losartan capsules, Formulation # DuP 753, lot # 891351

20 mg losartan capsules, Formulation # DuP 753, lot # 891352

50 mg losartan capsules, Formulation # DuP 753, lot # 891353

Placebo capsules lot # 891354

STUDY DESIGN: Single center, double-blind, parallel, placebo-controlled study with 20 male patients with mild to moderate essential hypertension divided into two treatment groups and 7 days washout period between treatments. Each patient received received five single-dose treatments of study drug (four active, one placebo) in rising dose order with respect to active drug and placebo inserted into the sequence according to a random allocation schedule. Group 1 received single doses of 5 mg, 20 mg, and 60 and 100 mg; and Group 2 received 10, 40 mg, 80 mg, and 120 mg. all escalations were made in a sequential order relative to the active doses and Group 2 was started three days after Group 1 had started so that the doses were given in a leader follow design. Prior to the start of the active treatment periods, each subject received a single dose of placebo and blood pressure and ECG recording were measured for a 24-hour period. Blood samples (7ml) were drawn at 0, 0.5, 1, 2, 4, 8, 12, and 24 hours post dose.

ASSAYS: HPLC with UV detection.

Linearity: Satisfactory. Standard curves from 15 to 1000 ng/ml.

Accuracy: Satisfactory. 99.2% at 83.1 ng/ml, 107.3% at 842.1 ng/ml for DuP 753; and 96.0% at 24.9 ng/ml, 106.52% at 851.3 ng/ml for E-3174.

Precision: Satisfactory. %CV - 2.0% at 83.1 ng/ml, 5.0% at 842.1 ng/ml for DuP 753; and 1.0% at 102.2 ng/ml, 1.9% at 851.3 ng/ml for E-3174.

Sensitivity: LOQ - 20 ng/ml for DuP 753 and 17 ng/ml for E-3174.

Specificity: Satisfactory. Chromatograms submitted.

The assays have been validated over the range of plasma concentrations observed in the study.

DATA ANALYSIS: AUC_{∞} , C_{max} , $t_{1/2}$, CL_o , T_{max} , and $\lambda_{(o)}$ were calculated.

RESULTS:

Pharmacokinetic Parameters

DuP 753							
Dose (mg)		C_{max} (ng/mL)	T_{max}^a (hr)	AUC_{∞}^b (ng·hr/mL)	CL_o (L/min)	$\lambda_{(o)}$ (hr ⁻¹)	$t_{1/2}^b$ (hr)
5	Mean	13.9	0.75	NA ^c	NA	NA	NA
	S.D.	17.1	(0.5-2.0)	NA	NA	NA	NA
	n	10		NA	NA	NA	NA
10	Mean	26.7	0.5	119.3	1.794	NA	NA
	S.D.	24.1	(0.5-1.0)	41.6	0.576	NA	NA
	n	8		8	8	NA	NA
20	Mean	134.2	0.5	367.2	1.229	0.500	1.4
	S.D.	63.8	(0.5-2.0)	245.8	0.785	0.373	0.8
	n	10		10	10	10	10
40	Mean	266.5	0.5	423.4	1.792	0.498	1.4
	S.D.	130.3	(0.5-1.0)	143.0	0.472	0.344	0.8
	n	8		8	8	8	8
60	Mean	521.1	0.5	574.8	1.267	0.477	1.0
	S.D.	225.1	(0.5-1.0)	280.4	0.343	0.411	0.7
	n	10		10	10	10	10
80	Mean	471.8	1.0	582.4	1.406	0.554	1.2
	S.D.	257.6	(0.5-1.0)	212.0	0.478	0.228	0.5
	n	8		8	8	8	8
100	Mean	582.0	0.75	1523.9	1.367	0.464	1.0
	S.D.	486.8	(0.5-2.0)	729.4	0.779	0.311	0.5
	n	10		10	10	10	10
120	Mean	511.0	0.75	1406.1	1.490	0.484	1.0
	S.D.	288.2	(0.5-1.0)	322.1	0.362	0.252	0.4
	n	8		8	8	8	8

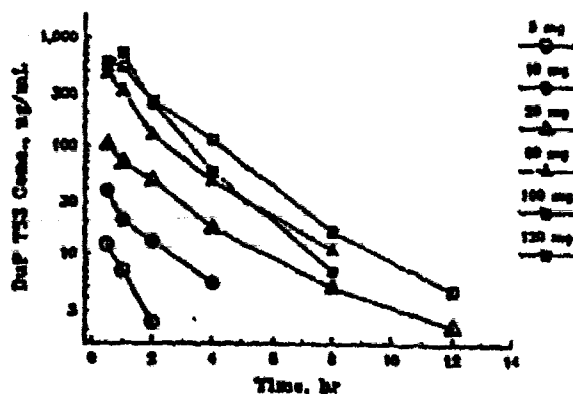
^aMedian and Range.
^bHarmonic mean and pseudo standard deviation based on jackknife variance.
^cNot available.

Pharmacokinetic Parameters

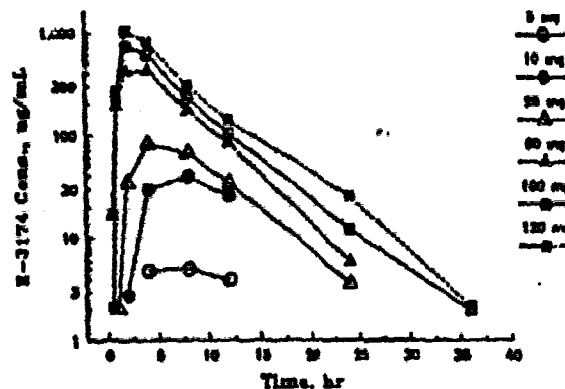
E-3174						
Dose (mg)		C_{max} (ng/mL)	T_{max}^a (hr)	AUC_{∞}^b (ng·hr/mL)	$\lambda_{(o)}$ (hr ⁻¹)	$t_{1/2}^b$ (hr)
5	Mean	7.2	1.1	268.4	NA ^c	NA
	S.D.	11.8	(4.0-12.0)	107.4	NA	NA
	n	10		10	NA	NA
10	Mean	29.5	0.0	526.1	NA	NA
	S.D.	12.0	(0.0)	122.1	NA	NA
	n	8		8	NA	NA
20	Mean	89.9	4.0	955.7	0.125	5.5
	S.D.	64.8	(4.0-8.0)	412.5	0.084	2.8
	n	10		10	10	10
40	Mean	166.6	4.0	2113.4	0.122	5.2
	S.D.	80.0	(4.0)	698.0	0.027	1.1
	n	8		8	8	8
60	Mean	466.5	4.0	3583.0	0.200	3.8
	S.D.	234.2	(1.0-8.0)	1075.8	0.060	1.0
	n	10		10	10	10
80	Mean	565.7	4.0	4329.1	0.176	3.8
	S.D.	237.7	(2.0-4.0)	1340.1	0.047	1.2
	n	8		8	8	8
100	Mean	530.0	3.0	5056.6	0.209	3.3
	S.D.	282.3	(1.0-4.0)	1170.0	0.070	1.1
	n	10		10	10	10
120	Mean	1036.7	3.0	6774.4	0.168	4.1
	S.D.	274.8	(2.0-4.0)	2116.5	0.034	0.8
	n	8		8	8	8

^aMedian and Range.
^bHarmonic mean and pseudo standard deviation based on jackknife variance.
^cNot available.

Mean Concentration



Mean Concentration



CONCLUSION: The study supports the sponsor's claim that the disposition of losartan (DuP 753) is linear when administered as single, oral doses from 5 - 120 mg to patients with mild to moderate essential hypertension.

MULTIPLE DOSE PHARMACOKINETICS STUDY

STUDY NUMBER: 007-001

VOLUME: 1.46 - 1.47

PAGES: 4585 - 5150

INVESTIGATOR AND LOCATION:

STUDY PERIOD: SEPTEMBER 1990 - SEPTEMBER 1990.

OBJECTIVES: To determine whether the pharmacokinetics of losartan change with multiple dosing; to investigate the possibility of drug and/or metabolite accumulation during multiple dose administration, to determine the safety, tolerability, and hemodynamic effects of losartan in normotensive volunteers and to investigate the effects of losartan on renin, angiotensin II, and aldosterone.

FORMULATIONS:

50 mg losartan capsules, lot # C-W166, Formulation # 0954DFC002C003;

Matching Placebo capsules lot # C-166, Formulation # P095DFC001C002.

STUDY DESIGN: Double-blind, parallel, placebo-controlled, three-phase study with 14 male subjects and a placebo run-in day, followed by 1-day single dose phase and a 7-day multiple dose phase. Ten of the subjects received 2x50 mg losartan capsules once daily on Days 1, 3 - 9; while the other four subjects received placebos. Plasma samples were drawn at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 7, 8, 12, 18, 24, 30, and 36 hours post dose; trough predose samples were drawn on Days 5, 7, and 8. Urine was collected at 0-6-, 6-12-, 12-24-, 24-36-, and 36-48-hour intervals on Day 1 and at 0-6-, 6-12- and 12-24-hour intervals on Day 9. Subjects were fasted the nights before Days 1 and 9. Plasma samples for plasma renin activity, angiotensin II, aldosterone, norepinephrine and epinephrine were collected periodically.

ASSAYS: HPLC with UV detection.

PLASMA SAMPLES - LOSARTAN (DuP 753) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curves from 5 to 1000 ng/ml.

Accuracy: Satisfactory. 96.0% at 20 ng/ml, 92.1% at 800 ng/ml for DuP 753, and 98.0% at 20 ng/ml, 97.2% at 800 ng/ml for E-3174.

Precision: Satisfactory. %CV - 9.9% at 20 ng/ml, 6.3% at 800 ng/ml for DuP 753, and 3.3% at 20 ng/ml, 5.7% at 800 ng/ml for E-3174.

Sensitivity: LOQ - 5 ng/ml.

Specificity: Satisfactory. Chromatograms submitted.

URINE SAMPLES - LOSARTAN (DuP 753) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curve from 10 to 2000 ng/ml for E-3174 and 20 to 2000

ng/ml for DuP 753..

- Accuracy: Satisfactory. 102.0% at 40 ng/ml, 97.6% at 1600 ng/ml for DuP 753, and 100.8% at 40 ng/ml, 9101.8% at 1600 ng/ml for E-3174.
- Precision: Satisfactory. %CV - 4.2% at 40 ng/ml, 1.0% at 1600 ng/ml for DuP 753, and 1.5% at 40 ng/ml, 2.0% at 1600 ng/ml for E-3174.
- Sensitivity: LOQ - 10 ng/ml for E-3174 and 20 ng/ml for Dup 753.
- Specificity: Satisfactory. Chromatograms submitted.

The assays have been validated over the range of plasma and urine concentrations observed in the study.

DATA ANALYSIS: AUC_{24} , AUC_{∞} , C_{max} , $t_{1/2}$, CL_r , T_{max} , % Dose excreted in urine and accumulation factors for DuP 753 and E-3174 were calculated.

The accumulation factor was calculated for the final dose from:

$$\frac{AUC_{24} (Day9)}{AUC_{24} (Day1)}$$

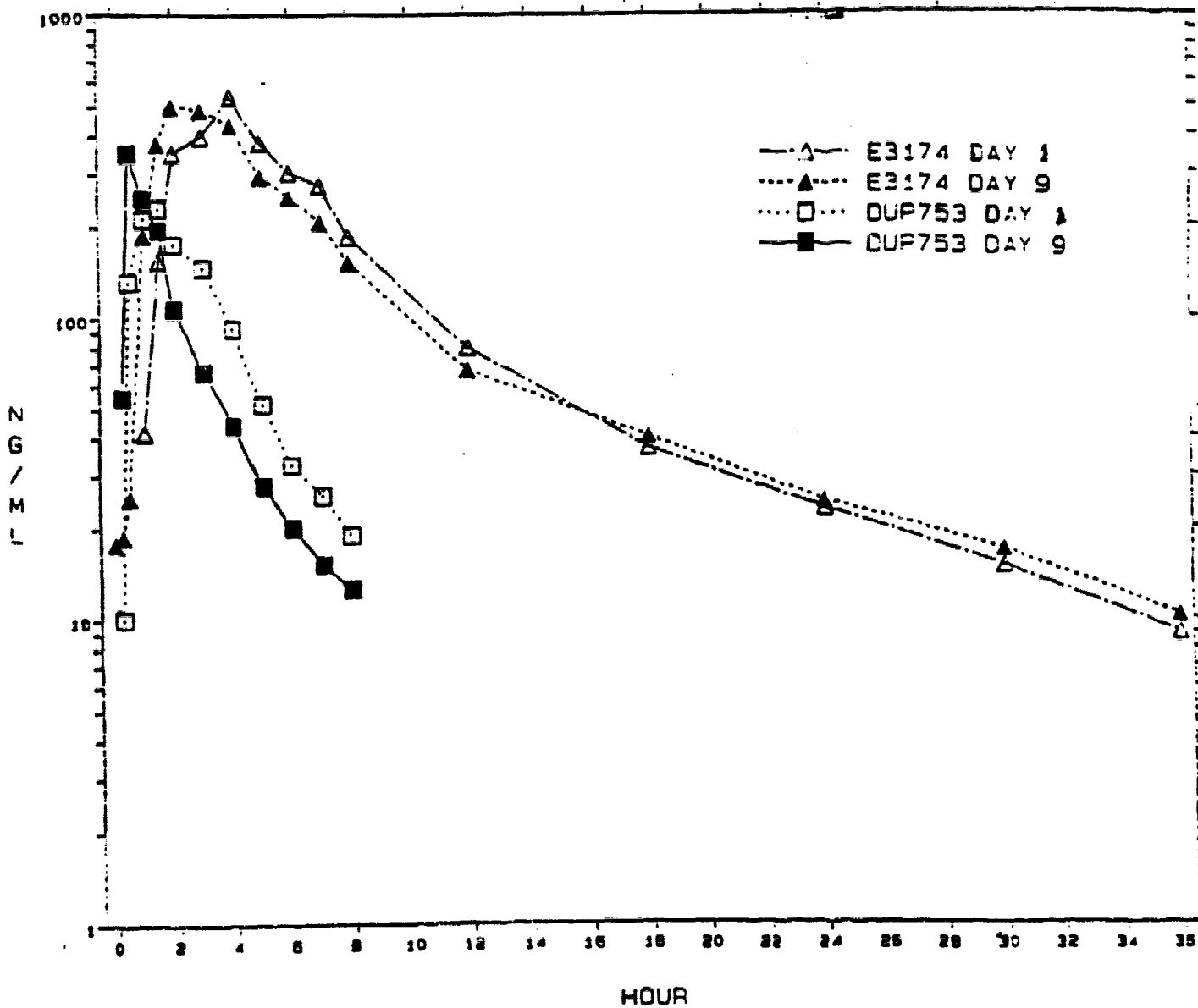
or

$$\frac{AUC_{24} (Day9)}{AUC_{\infty} (Day1)}$$

RESULTS:

	DuP 753		E-3174	
	Day 1	Day 9	Day 1	Day 9
C_{max} , ng/ml	315 ± 126	437 ± 312	568 ± 205	547 ± 179
T_{max} , hr	1.5 ± 0.9	0.9 ± 0.5	3.4 ± 0.8	2.7 ± 0.9
AUC_{24} , ng·hr/ml	814 ± 355	662 ± 276	3342 ± 1031	3341 ± 924
AUC_{∞} , ng·hr/ml	816 ± 357	--	3642 ± 1105	--
$t_{1/2}$, hr	2.0 ± 0.7	2.2 ± 0.8	9.0 ± 1.7	9.1 ± 1.6
CL_r , ml/min.	74 ± 18	92 ± 24	25 ± 5	27 ± 6
% Dose	3.5 ± 1.0	3.6 ± 1.7	5.6 ± 1.7	5.8 ± 2.1
$\frac{AUC_{24} (Day 9)}{AUC_{24} (Day 1)}$		0.95 ± 0.17*		1.02 ± 0.13
$\frac{AUC_{24} (Day 9)}{AUC_{\infty} (Day 1)}$		0.95 ± 0.17*		0.93 ± 0.11

*Corrected by renal clearances.



CONCLUSION: The study supports the sponsor's labeling claim that during once-daily dosing at 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.

COMMENT:

Losartan renal clearance increased by about 24% upon multiple dose administration and the sponsor corrected for this increase in the calculation of the accumulation factor for losartan. There is no rationale for this correction. Without the correction the accumulation factor for losartan will be 0.81.

ABSOLUTE ORAL BIOAVAILABILITY

STUDY NUMBER: 074

VOLUME: 1.47

PAGES: 5151 - 5423

INVESTIGATOR AND LOCATION:

STUDY PERIOD: SEPTEMBER 1992 - OCTOBER 1992.

OBJECTIVES: (i) to assess the absolute bioavailability of oral losartan using final process biobatch tablets, (ii) to compare the plasma concentration profile of the metabolite L-158,641 (E-3174) following administration of losartan, 50 mg orally and 20 mg intravenously.

FORMULATIONS:

50 mg losartan Tablet, Formulation # 0954FCT017C001

5 mg/ml losartan Injection, Formulation # 0954HSS001A003

STUDY DESIGN: Randomized, open, two-period, crossover study with 12 subjects and a wash period of 7 days. Subjects received a single dose of 50 mg losartan tablet during the first period (Treatment A) and 20 mg losartan solution (20 minute IV infusion, Treatment B) during the second period. Subjects fasted from midnight before and until 3 hours postdose on both study days. Blood samples (8 ml) were collected 0, .25, .5, .75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 30, and 36 hours after the oral administration of losartan; and at 0, 5, 10, 15, 20, 23, 26, 30, 45 and 90 minutes, 2, 3, 4, 5, 6, 8, 12, 18, 24, and 30 hours after IV administration. Urine samples were collected predose (blank) and at 0-3, 3-6, 6-12, 12-36, and 36-48 hours.

ASSAYS: HPLC with UV detection.

PLASMA SAMPLES - LOSARTAN (DuP 753) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curves from 5 to 1000 ng/ml.

Accuracy: Satisfactory. 96.0% at 20 ng/ml, 98.8% at 800 ng/ml for DuP 753; and 105.0% at 20 ng/ml, 105.2% at 800ng/ml for E-3174.

Precision: Satisfactory. %CV - 4.0% at 20 ng/ml, 1.5% at 800 ng/ml for DuP 753; and 4.6% at 20 ng/ml, 3.6% at 800 ng/ml for E-3174.

Sensitivity: LOQ - 5 ng/ml.

Specificity: Satisfactory. Chromatograms submitted.

URINE SAMPLES - LOSARTAN (DuP 753) AND ACTIVE METABOLTE (E-3174):

Linearity: Satisfactory. Standard curves from 10 to 2000 ng/ml.

Accuracy: Satisfactory. 92.0% at 40 ng/ml, 96.6% at 1600 ng/ml for DuP 753, and 103.0% at 40 ng/ml, 100.7% at 1600 ng/ml for E-3174.

Precision: Satisfactory. %CV - 3.4% at 40 ng/ml, 0.8% at 1600 ng/ml for DuP 753, and 3.4% at 40 ng/ml, 2.7% at 1600 ng/ml for E-3174.

Sensitivity: LOQ - 10 ng/ml .

Specificity: Satisfactory. Chromatograms submitted.

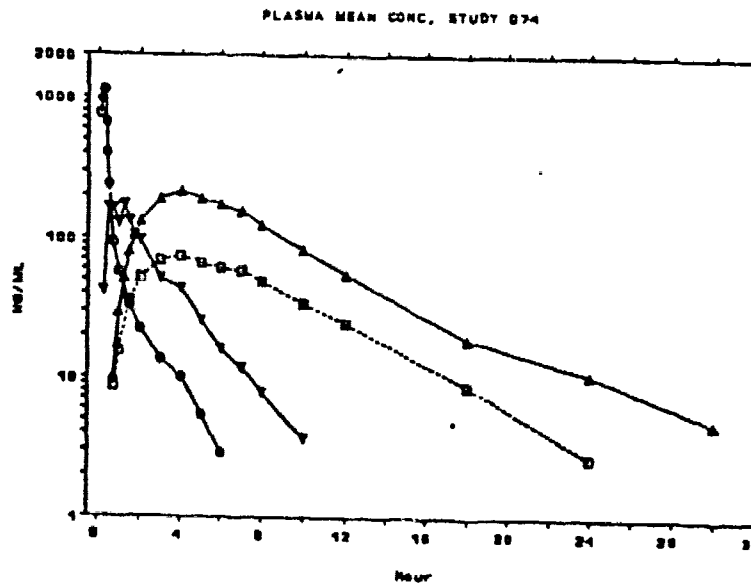
The assays have been validated over the range of plasma and urine concentrations observed in the study.

DATA ANALYSIS: AUC_{∞} , C_{max} , $t_{1/2}$, Cl, CLr, T_{max} , vdss, %Dose excreted in urine, absolute bioavailability and $\lambda_{(a)}$ were calculated.

RESULTS:

	Losartan 20 mg Intravenous Dose		Losartan 50 mg Oral Dose	
	Losartan	L-158,641	Losartan	L-158,641
C_{max} , ng/mL ^a	--	76.4 ± 30.4	296.4 ± 217.0	249.4 ± 73.7
T_{max} , hr	--	4.17 ± 0.58	1.02 ± 0.52	4.09 ± 1.56
$T\%$, hr ^b	1.81 ± 0.60	4.55 ± 1.30	2.13 ± 0.54	6.42 ± 2.29
AUC, ng·hr/mL ^a	538.69 ± 94.87	744.40 ± 272.36	475.56 ± 199.55	1915.25 ± 537.82
AUC, ng·hr/mL (geometric mean) ^a	531.3	--	433.6	--
λ , hr ⁻¹	0.3836 ± 0.1253	0.1524 ± 0.0438	0.3260 ± 0.0829	0.1080 ± 0.0379
Vd _{ss} , L	28.36 ± 13.61	--	--	--
CL, mL/min	635.95 ± 107.40	--	--	--
CL _r , mL/min	72.14 ± 20.76	28.36 ± 5.95	72.04 ± 20.60	25.91 ± 6.90
Urinary Recovery	mg	2.353 ± 0.501	1.195 ± 0.355	2.061 ± 0.853
	% dose	11.97 ± 2.50	6.54 ± 2.33	4.20 ± 1.74
Absolute Bioavailability	--	--	32.6(25.3, 42.1) ^c	--

^a Data normalized to 20.0 mg I.V. and 50.0 mg p.o. dose based on assay potency.
^b Harmonic mean and pseudo standard deviation.
^c Geometric mean with 90% confidence interval.



CONCLUSION: The study supports the sponsor's labeling claim of an absolute bioavailability of about 33%.

BIOEQUIVALENCE / BIOAVAILABILITY STUDY

STUDY NUMBER: 075

VOLUME: 1.48

PAGES: 5424 - 5893

INVESTIGATOR AND LOCATION:

STUDY PERIOD: OCTOBER 1992 - NOVEMBER 1992.

OBJECTIVES: (i) to assess the bioequivalence of 50 mg DuPont-Merck losartan tablet (DMPC) compared to the 50 mg Merck losartan tablet (MRL), (ii) to assess the relative bioavailability of the 50 mg DuPont-Merck capsule compared to the 50 mg losartan tablet, (iii) to compare the plasma concentration profile of the metabolite L-158,641 following administration of the 50 mg Merck losartan tablet, 50 mg DuPont-Merck losartan capsule and 50 mg DuPont-Merck losartan tablet.

FORMULATIONS:

50 mg losartan Tablet (MRL), Formulation # 0954FCT005C003 (Used for Phase III studies)
50 mg losartan Tablet (DMPC), Formulation # 0954FCT018C001 (To be marketed in US)
50 mg losartan Capsule (DMPC), Formulation # 0954DFC002C013 (Used for Phase IIb dose-response study).

STUDY DESIGN: Randomized, three-period, crossover study with 30 subjects and a wash period of 7 days. Subjects received single dose of the 50 mg Merck tablet (Treatment A), the DuPont-Merck tablet (Treatment B) and the DuPont-Merck capsule (Treatment C). Subjects fasted from midnight before and until 3 hours postdose on all of the study days. Blood samples (8 ml) were collected 0, .25, .5, .75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 30, and 36 hours after the oral administration of losartan. A sequential approach was employed towards the data analysis and analysis was completed at Stage I (N= 18 subjects).

ASSAYS: HPLC with UV detection.

Linearity: Satisfactory. Standard curves from 5 to 1000 ng/ml.

Accuracy: Satisfactory. 97.5% at 20 ng/ml, 97.1% at 800 ng/ml for DuP 753; and 100.5% at 20 ng/ml, 101.2% at 800ng/ml for E-3174.

Precision: Satisfactory. %CV - 2.7% at 20 ng/ml, 1.9% at 800 ng/ml for DuP 753; and 3.5% at 20 ng/ml, 3.6% at 800 ng/ml for E-3174.

Sensitivity: LOQ - 5 ng/ml.

Specificity: Satisfactory. Chromatograms submitted.

The assays have been validated over the range of plasma concentrations observed in the study.

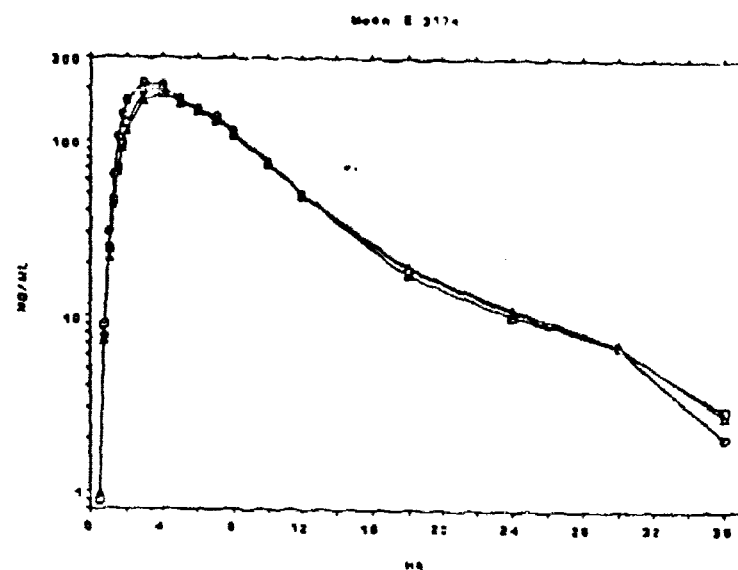
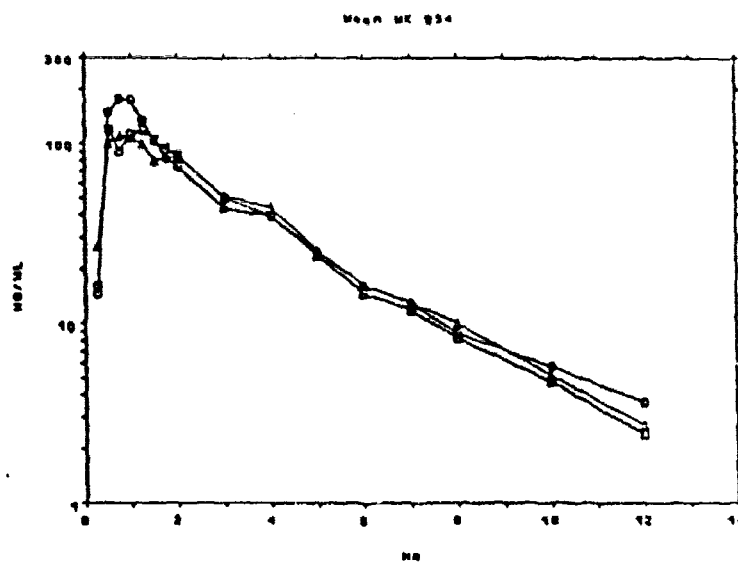
DATA ANALYSIS: AUC_{∞} , C_{max} , $t_{1/2}$, λ and T_{max} , were calculated.

RESULTS:

	MK-954*		
	Merck Tablet, n = 18	DuPont-Merck Tablet, n = 17	DuPont-Merck Capsule, n = 18
C_{max} , ng/ml	204.0 ± 99.4	183.4.0 ± 79.8	245.0 ± 110.3
T_{max} , hr	1.24 ± 0.86	1.23 ± 1.02	0.91 ± 0.41
AUC_{∞} , ng-hr/ml	417.28 ± 115.23	419.08 ± 125.94	451.31 ± 118.45
λ , hr ⁻¹	0.2990 ± 0.1320	0.2631 ± 0.1148	0.2699 ± 0.1421
$t_{1/2}$, hr ^b	2.32 ± 1.03	2.58 ± 1.12	2.57 ± 1.38

	E-3174*		
	Merck Tablet, n = 17	DuPont-Merck Tablet, n = 16	DuPont-Merck Capsule, n=17
C_{max} , ng/ml	225.4 ± 116.7	203.1 ± 90.1	236.5 ± 99.1
T_{max} , hr	4.47 ± 1.70	4.69 ± 1.89	3.82 ± 1.55
AUC_{∞} , ng-hr/ml	1778.33 ± 434.30	1769.55 ± 414.26	1854.95 ± 343.32
λ , hr ⁻¹	0.0753 ± 0.0179	0.0788 ± 0.0189	0.0828 ± 0.0211
$t_{1/2}$, hr ^b	9.21 ± 2.23	8.8 ± 2.24	8.37 ± 2.16

* C_{max} and AUC_{∞} normalized to 50.0 mg based on assayed potencies of the formulations.
^b Harmonic mean and pseudo standard deviation.



Mean Plasma Concentrations (ng/ml) of MK-954 and E-3174 Following Oral Administration of 50-mg Merck Tablet (□), DuPont-Merck Tablet (Δ) and DuPont-Merck Capsule (○)

RESULTS:**Bioequivalence:****DMPC Tablet vs. Merck Tablet**

Compound	Variable	N	Ratio Analyses		Difference Analyses	
			Geometric Mean Ratio	Conf. Int. W/O Zero	Diff. in Arith. Means	Conf. Int. W/O Zero
Losartan	AUC (ng*hr/mL)	17	0.97	(0.89,1.07)	-	-
	C _{max} (ng/mL)	17	0.90	(0.69,1.17)	-23.3	(-76.9,+30.3)
	T _{max} (hours)	17	-	-	+0.06	(-0.46,+0.58)
L-158,641	AUC (ng*hr/mL)	16	0.97	(0.91,1.05)	-	-
	C _{max} (ng/mL)	16	0.90	(0.81,1.02)	-22.9	(-45.5,-0.3)
	T _{max} (hours)	16	-	-	+0.17	(-0.61,+0.95)

Relative Bioavailability:**DMPC Capsule vs. Merck Tablet**

Compound	Variable	N	Ratio Analyses		Difference Analyses	
			Geometric Mean Ratio	Conf. Int. w/o Zero	Diff. in Arith. Means	Conf. Int. w/o Zero
Losartan	AUC (ng*hr/mL)	18	1.09	(0.99,1.19)	-	-
	C _{max} (ng/mL)	18	1.20	(0.92,1.56)	+41.0	(-11.8,+93.8)
	T _{max} (hours)	18	-	-	-0.33	(-0.84,+0.18)
L-158,641	AUC (ng*hr/mL)	17	1.08	(1.00,1.15)	-	-
	C _{max} (ng/mL)	17	1.09	(0.97,1.22)	+11.4	(-10.9,+33.7)
	T _{max} (hours)	17	-	-	-0.66	(-1.43,+0.11)

CONCLUSIONS: (i) DuPont-Merck tablet is bioinequivalent to Merck tablet with respect to losartan but bioequivalent with respect to the active metabolite (E-3174); (ii) DuPont-Merck capsule is bioinequivalent to Merck tablet with respect to losartan but bioequivalent with respect to the active metabolite (E-3174).

BIOEQUIVALENCE / BIOAVAILABILITY STUDY

STUDY NUMBER: 022

VOLUME: 1.48

PAGES: 5894 - 6147

INVESTIGATOR AND LOCATION:

STUDY PERIOD: APRIL 1991 - MAY 1991.

OBJECTIVES: (i) to assess the bioequivalence of 100 mg losartan tablets as compared to the 100 mg losartan capsule, (ii) to assess the absolute bioavailability of oral, (iii) to compare the plasma concentration profile of the metabolite L-158,641 following administration of the 100 mg tablet, as compared to 100 mg losartan capsule, and (iv) to compare the plasma concentration profile of the metabolite L-158,641 following administration of losartan, 100 mg orally and 30 mg intravenously.

FORMULATIONS:

100 mg losartan Capsule, Batch # C-W737, Formulation # 0954DF001D003 (Used for Phases I & II Studies)

100 mg losartan Tablet, Batch # C-W738, Formulation # 0954FCT004D001 (Used for Phase III Studies)

5 mg/ml losartan Solution, Batch # C-W739, Formulation # 0954HSS001a001

STUDY DESIGN: Randomized (Periods I and II only), open, three-period, crossover study with 8 subjects and a wash period of 7 days. Subjects received 100 mg losartan tablet (Treatment A) and 100 mg losartan capsule (Treatment B) during Periods I and II. During Period III, subjects received 30 mg losartan solution (Treatment C) as a 20-minute IV infusion. Subjects fasted from midnight before and until 3 hours postdose on all of the study days. Blood samples (8 ml) were collected 0, 10, 30, 40, 50 minutes, 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 10, 12, 18, 24, 30, and 36 hours after the oral administration of losartan; and at 0, 2, 4, 8, 12, 16, 20, 22, 26, 30, 50, 60, 80, 100, minutes, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, and 30 after IV administration. Urine samples were collected predose (blank) and at 0-3, 3-6, 6-12, 12-24, 24-36, and 36-48 hours.

ASSAYS: HPLC with UV detection.

PLASMA SAMPLES - LOSARTAN (MK-954) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curves from 5 to 1000 ng/ml.

Accuracy: Satisfactory. 98.0% at 20 ng/ml, 102.5% at 800 ng/ml for MK-954 and 96.5% at 20 ng/ml, 98.6% at 800ng/ml for E-3174.

Precision: Satisfactory. %CV - 5.9% at 20 ng/ml, 5.4% at 800 ng/ml for MK-954; and

Sensitivity: LOQ - 5 ng/ml.
 Specificity: Satisfactory. Chromatograms submitted.

URINE SAMPLES - LOSARTAN (MK-954) AND ACTIVE METABOLITE (E-3174):

Linearity: satisfactory. Standard curve from 10 to 2000 ng/ml for E-3174 and 20 to 2000 ng/ml for MK-954..

Accuracy: Satisfactory. 103.8% at 40 ng/ml, 101.4% at 1600 ng/ml for MK-954; and 105.0% at 40 ng/ml, 100.3% at 1600 ng/ml for total E-3174.

Precision: Satisfactory. %CV - 6.3% at 40 ng/ml, 1.6% at 1600 ng/ml for MK-954; and 2.8% at 40 ng/ml, 1.4% at 1600 ng/ml for E-3174.

Sensitivity: LOQ - 10 ng/ml for E-3174 and 20 ng/ml for MK-954.

Specificity: Satisfactory. Chromatograms submitted.

DATA ANALYSIS: AUC_{∞} , C_{max} , T_{max} , $t_{1/2}$, vd_{ss} , Cl, Cl_r, F, and % Dose excreted in urine were calculated.

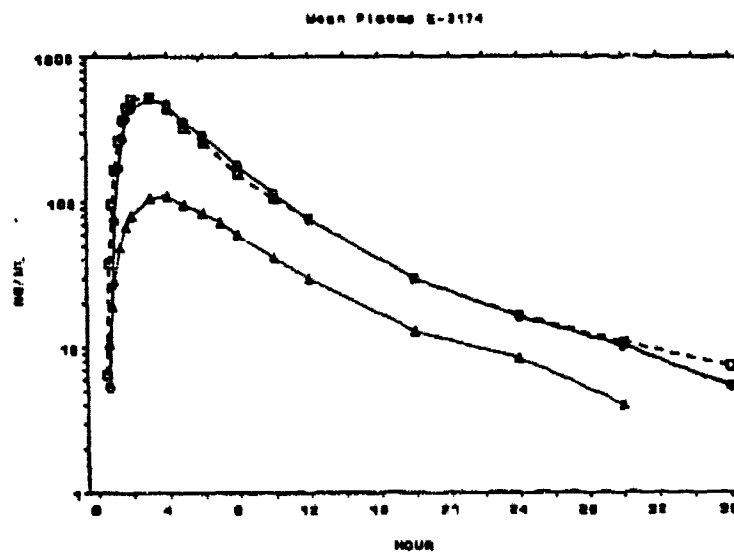
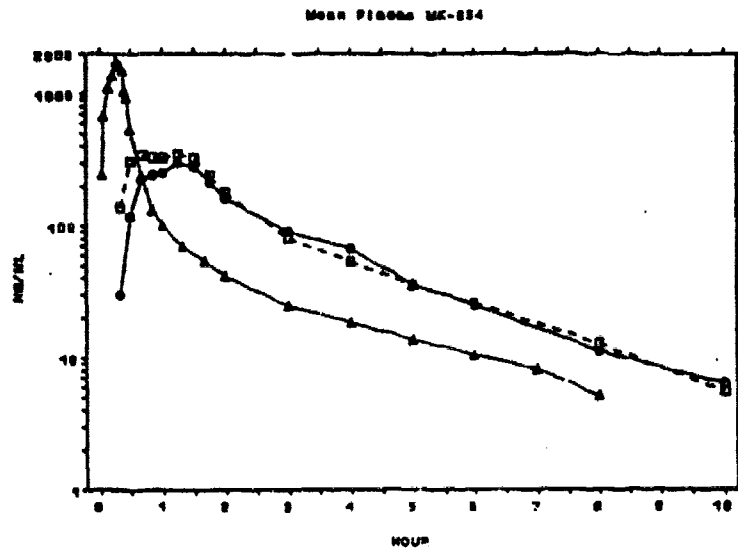
RESULTS:

	MK-954 ^a		
	Tablet	Capsule	I.V.
C_{max} , ng/ml	486.2 ± 231.7	570.1 ± 260.3	-
T_{max} , hr	1.4 ± 0.8	0.9 ± 0.5	-
AUC_{∞} , ng·hr/ml	722.4 ± 375.8	821.0 ± 421.3	925.6 ± 349.7
$t_{1/2}$, hr	1.9 ± 0.5	2.1 ± 0.40	2.3 ± 0.9
Vd_{ss} , L	-	-	40.2 ± 13.0
Cl, ml/min	-	-	618 ± 247
Cl _{renal} , ml/min	90 ± 42	79 ± 35	76 ± 39
% Dose in urine	3.7 ± 1.3	3.6 ± 1.0	11.6 ± 2.5
F _{tab}	0.23 (0.17 - 0.30) ^b		-
F _{cap}	0.25 (0.18 - 0.34) ^b		
F _{rel} (tab/cap)	0.93 (0.69 - 1.24) ^b		
C_{max} ratio (tab/cap)	0.86 (0.55 - 1.32) ^b		

	E-3174 ^a		
	Tablet	Capsule	I.V.
C_{max} , ng/ml	584 ± 120	547 ± 105	-
T_{max} , hr	3.1 ± 1.0	2.6 ± 0.6	-
AUC_{∞} , ng·hr/ml	3561 ± 686	3458 ± 542	1066 ± 198
$t_{1/2}$, hr	8.3 ± 1.2	9.1 ± 1.2	7.7 ± 1.8
Cl _{renal} , ml/min	23 ± 6	25 ± 6	24 ± 5
% Dose in urine	5.0 ± 1.7	5.4 ± 1.6	5.3 ± 1.5
C_{max} ratio (tab/cap)	1.07 (0.93 - 1.23) ^b		
AUC ratio (tab/cap)	1.02 (0.96 - 1.09) ^b		

^a C_{max} and AUC values for MK-954 and E-3174 were normalized to nominal doses of 100.0 mg (oral) and 30.0 mg (i.v.) based on actual doses given.

^b90% confidence interval limits.



Mean Plasma Concentrations of MK-954 and E-3174 Following 100 mg of MK-954 Tablet (o, n = 8), 100 mg of MK-954 Capsule (□, n = 8) and 30 mg of MK-954 I.V. Infusion (Δ, n = 7).

CONCLUSIONS: (i) the absolute bioavailability of the 100 mg tablet used for Phase III studies is 23%; (ii) the absolute bioavailability of the 100 mg capsule used for Phases I & II studies is 25%; (iii) the 100 mg capsule used for Phases I & II studies is bioequivalent to 100 mg tablet used for Phase III studies with respect to losartan but bioequivalent with respect to the active metabolite (E-3174).

FOOD EFFECT STUDY

STUDY NUMBER: 015

VOLUME: 1.49

PAGES: 6148 - 6476

INVESTIGATOR AND LOCATION:

STUDY PERIOD: DEC. 1990 - FEB. 1991.

OBJECTIVES: (i) to investigate the effect of a standard meal on the plasma concentration profiles of losartan following administration of a single oral dose of losartan 100 mg; (ii) to determine whether any food effect on absorption has pharmacodynamic consequences as measured by an effect on losartan-induced increases in plasma renin activity and angiotensin II activity; (iii) to provide preliminary data on the absorption of losartan following administration of the tablet formulation.

FORMULATIONS:

100 mg losartan (MK-954) Tablet, Batch # C-W438, Formulation # 0954FCT004D001.

STUDY DESIGN: Randomized, open, two-period crossover study with 8 subjects and a wash period of 5-7 days. Subjects received a single 100 mg oral dose of losartan on two occasions (once under fasting conditions and once under fed conditions). Subjects fasted overnight prior to dosing, the fed were given a standard meal immediately prior to dosing and then fasted for at least four hours while the fasted group remained fasting for at least four hours post dose. Blood samples (8 ml) were collected 0, 10, 30, 40, 50 minutes, 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 10, 12, 18, 24, 30, and 36 hours post dose.

The standard meal consisted of :

- 1 fried egg
- 2 pieces of toast
- 20 g jelly or marmalade
- 2 strips of bacon
- 150 ml of whole milk
- 100 ml orange juice

Caloric content = 469 Kcal (18.8 g of protein, 53.8 g of carbohydrate, 19.5 g of fat).

Blood samples for measurement of plasma renin activity and angiotensin II concentration were obtained at -1, 2, 4, 6, 8, 12 and 24 hours post dose.

ASSAYS: HPLC with UV detection

Linearity: Satisfactory. Standard curves from 5 to 1000 ng/ml.

Accuracy: Satisfactory. 98.0% at 20 ng/ml, 97.4% at 800 ng/ml for MK-954; and 97.9% at 20 ng/ml, 99.6% at 800ng/ml for E-3174.

Precision: Satisfactory. %CV - 6.2% at 20 ng/ml, 4.2% at 800 ng/ml for MK-954; and 7.5% at 20 ng/ml, 5.3% at 800 ng/ml for E-3174.

Sensitivity: LOQ - 5 ng/ml.

Specificity: Satisfactory. Chromatograms submitted.

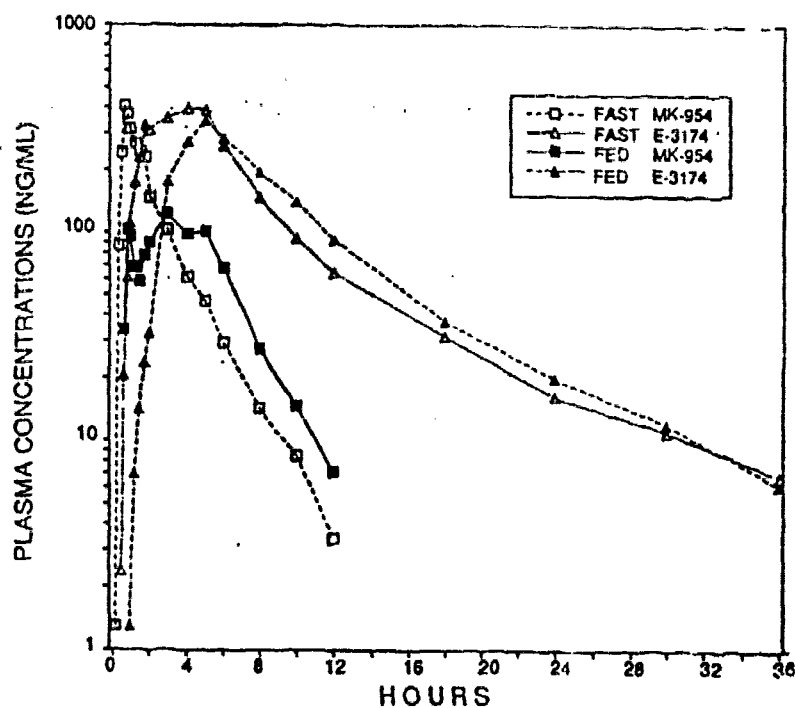
The assays have been validated over the range of plasma concentrations observed in the study.

DATA ANALYSIS: AUC_{∞} , C_{max} , T_{max} and $t_{1/2}$ were calculated.

RESULTS:

	MK-954		E-3174	
	Fasted	Fed	Fasted	Fed
C_{max} , ng/ml	514 ± 199	267 ± 166	502 ± 124	415 ± 189
T_{max} , hr	1.3 ± 0.8	2.9 ± 1.7	3.1 ± 1.3	4.8 ± 1.2
AUC_{∞} , ng·hr/ml	826 ± 181	681 ± 163	3097 ± 633	2766 ± 877
$t_{1/2}$, hr	2.2 ± 0.6	2.1 ± 0.6	8.3 ± 0.8	8.0 ± 1.7
$\frac{AUC_{\infty} (Fed)}{AUC_{\infty} (Fasted)}$		0.82*		0.87*
$\frac{C_{max} (Fed)}{C_{max} (Fasted)}$		0.48*		0.76*

*Geometric mean.



CONCLUSIONS: (i) Administration of losartan with food results in decrease in C_{max} and AUC_{∞} (52% and 18% respectively) and a delay of 1.6 hour in T_{max} of losartan; and a decrease in C_{max} and AUC_{∞} (24% and 13% respectively) and a delay of 1.7 hour in T_{max} of the active metabolite (E-3171).

PHARMACOKINETICS STUDY IN THE ELDERLY

STUDY NUMBER: 063

VOLUME: 1.49

PAGES: 6477 - 6772

INVESTIGATOR AND LOCATION:

OBJECTIVES: (i) To determine the pharmacokinetics of 50 mg losartan tablets and 10 mg IV losartan in elderly hypertensive patients, (ii) to compare the bioavailability and systemic clearance of losartan in elderly hypertensive patient with young normal volunteers, (iii) to compare the plasma concentration profiles of losartan in the elderly to those in young, normal volunteers, (iv) to assess the tolerability of single dose treatments of losartan in elderly hypertensive patients.

FORMULATIONS:

Losartan 50 mg Tablet, Formulation No. 0954 FCT005C001

Losartan (5 mg/ml fill) IV solution, Formulation No. 0954 HSS001A001

STUDY DESIGN: Randomized, open, two-period, cross-over study in 10 (5 males, 5 females) elderly (> 65 years) hypertensive patients and a washout period of 14 days. On each study day, patients received either the 50 mg tablet or the 10 mg losartan IV solution administered over a 20-minute interval after an overnight fast. Blood samples were drawn following oral losartan at 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 30, and 36 hours and following IV losartan administration at 0, 5, 10, 15, 20, 23, 26, 30, 45, 60, 90 minutes and 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 30 and 36 hours. Urine was collected at 0-3, 3-6, 6-12, 12-24, 24-36, and 36-48-hours post dose.

ASSAYS: HPLC with UV detection.

PLASMA SAMPLES - LOSARTAN (MK-954) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curves from 5 to 1000 ng/ml.

Accuracy: Satisfactory. 93.5% at 20 ng/ml, 98.6% at 800 ng/ml for MK-954 and 97.5% at 20 ng/ml, 100.8% at 800ng/ml for E-3174.

Precision: Satisfactory. %CV - 8.8% at 20 ng/ml, 1.8% at 800 ng/ml for MK-954; and 4.8% at 20 ng/ml, 3.5% at 800 ng/ml for E-3174.

Sensitivity: LOQ - 5 ng/ml.

Specificity: Satisfactory. Chromatograms submitted.

URINE SAMPLES - LOSARTAN (MK-954) AND ACTIVE METABOLTE (E-3174):

Linearity: Satisfactory. Standard curves from 10 to 2000 ng/ml.

Accuracy: Satisfactory. 92.8% at 40 ng/ml, 96.4% at 1600 ng/ml for MK-954; and 101.5%

at 40 ng/ml, 101.2% at 1600 ng/ml for total E-3174.
 Precision: Satisfactory. %CV - 2.8% at 40 ng/ml, 2.1% at 1600 ng/ml for MK-954; and
 6.0% at 40 ng/ml, 3.4% at 1600 ng/ml for E-3174.
 Sensitivity: LOQ - 10 ng/ml .
 Specificity: Satisfactory. Chromatograms submitted.

The assays have been validated over the range of plasma and urine concentrations observed in the study.

DATA ANALYSIS: AUC_{∞} , C_{max} , $t_{1/2}$, CL, CL_r , V_{dss} , T_{max} , F, and % Dose excreted in urine were calculated.

RESULTS:

MK-954				
	50-mg Tablet		10 mg LV.	
	Male (n = 5)	Female (n = 5)	Male (n = 5)	Female (n = 5)
C_{max} , ng/ml	249.1 ± 123.0	533.1 ± 217.2	-	-
T_{max} , hr	1.15 ± 0.68	1.10 ± 0.55	-	-
AUC, ng·hr/ml	478.15 ± 150.17	1008.38 ± 271.48	284.97 ± 33.10	410.72 ± 57.68
$t_{1/2}$, hr ^a	2.06 ± 0.39	2.92 ± 1.41	1.64 ± 0.62	2.30 ± 0.47
V_{dss} , L	-	-	29.33 ± 12.20	29.63 ± 9.78
CL, ml/min	-	-	597.16 ± 69.95	415.99 ± 54.85
CL_r , ml/min	46.57 ± 17.08	32.82 ± 11.31	46.13 ± 19.00 ^b	38.25 ± 9.16
% Dose in Urine	2.73 ± 0.35	4.10 ± 1.47	8.66 ± 1.76 ^c	9.84 ± 2.39 ^b
Bioavailability,% ^c	33.4 (25.9-43.0)	49.4 (37.9-64.5)	-	-

^aHarmonic mean and pseudo standard deviation.

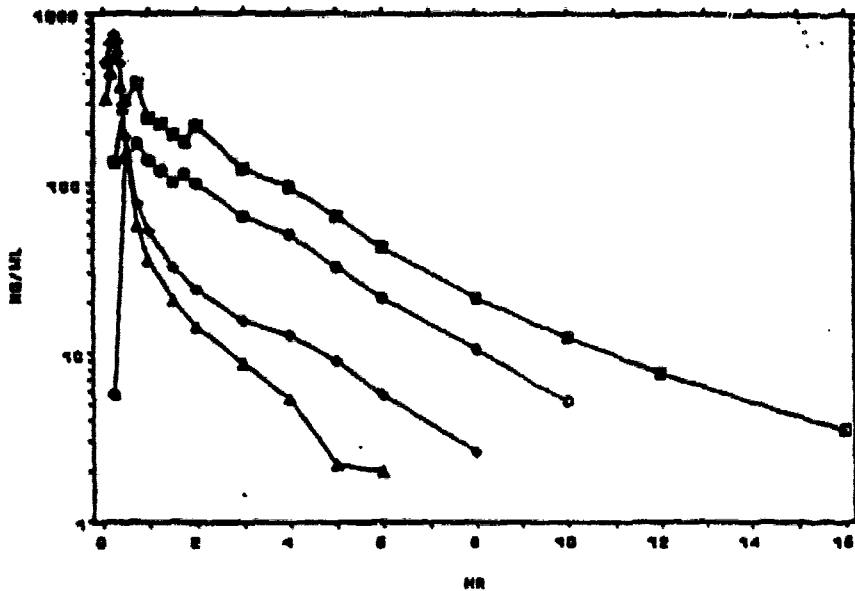
^bn = 4.

^cGeometric mean and 90% confidence interval limits.

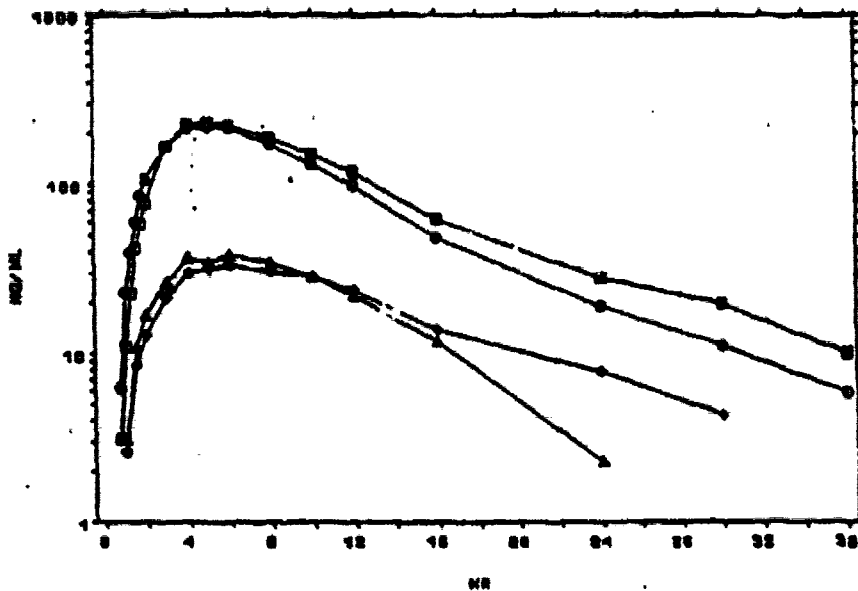
E-3174				
	50-mg Tablet		10 mg LV.	
	Male (n = 5)	Female (n = 5)	Male (n = 5)	Female (n = 5)
C_{max} , ng/ml	247.2 ± 55.2	246.0 ± 75.4	41.3 ± 12.4	33.9 ± 14.3
T_{max} , hr ^a	4.8 ± 1.3	4.6 ± 1.1	5.4 ± 1.7	7.2 ± 1.8
AUC, ng·hr/ml	2476.81 ± 559.69	2886.59 ± 962.61	502.14 ± 194.33	576.25 ± 253.11
$t_{1/2}$, hr ^a	6.53 ± 1.55	8.01 ± 2.29	5.67 ± 1.93	7.58 ± 4.95
CL_r , ml/min	19.22 ± 7.24	15.50 ± 5.85	21.30 ± 8.28	14.60 ± 6.05
% Dose in Urine	5.83 ± 1.26	5.46 ± 1.80	5.63 ± 0.81	4.84 ± 1.78

^aHarmonic mean and pseudo standard deviation.

Mean MK-954, Study 003



Mean E-3174, Study 003



Mean Plasma Concentrations of MK-954 and E-3174 in Elderly Hypertensives Following L.V. MK-954 (□-Female, △-Male) and P.O. MK-954 (□-Female, ○-Male)

MK-954 and E-3174 Data Following Oral MK-954 in Studies #063, #004, #007, #015 and #022 (Data Normalized to 50 mg^a)

Study	MK-954					E-3174				
	C _{max} ng/ml	T _{max} hr	AUC, ng-hr/ml	t _{1/2} ^b hr	CL _r ml/min	C _{max} ng/ml	T _{max} hr	AUC, ng-hr/ml	t _{1/2} ^b hr	CL _r ml/min
Elderly Pooled Study #063, n = 10	391 ± 224	1.1 ± 0.6	743 ± 348	2.4 ± 0.8	40 ± 15	247 ± 62	4.7 ± 1.2	2682 ± 773	7.2 ± 1.9	17 ± 7
Elderly Female Study #063, n = 5	533 ± 217	1.1 ± 0.6	1006 ± 271	2.9 ± 1.4	33 ± 11	246 ± 75	4.6 ± 1.1	2887 ± 963	8.0 ± 2.3	16 ± 6
Elderly Male Study #063, n = 5	249 ± 123	1.2 ± 0.7	478 ± 150	2.1 ± 0.4	47 ± 17	247 ± 55	4.8 ± 1.3	2477 ± 560	6.5 ± 1.6	19 ± 7
Male Patients Study #004, n = 13 ^c	NC	NC	572 ± 200	NC	ND	NC	NC	2613 ± 735	NC	ND
Female Patients Study #004, n = 5 ^c	NC	NC	823 ± 317	NC	ND	NC	NC	2953 ± 714	NC	ND
Young Subjects Study #007, n = 10 ^d	NC	NC	413 ± 181	2.0 ± 0.7	74 ± 18	NC	NC	1843 ± 599	9.0 ± 1.7	25 ± 5
Young Subjects Study #015, n = 8 ^d	259 ± 100	1.3 ± 0.8	416 ± 91	2.2 ± 0.6	ND	253 ± 63	3.1 ± 1.3	1561 ± 319	8.3 ± 0.8	ND
Young Subjects Study #022, n = 8 ^d	243 ± 116	1.4 ± 0.8	361 ± 188	1.9 ± 0.5	90 ± 42	292 ± 60	3.1 ± 1.0	1780 ± 343	8.3 ± 1.2	23 ± 6

^aIndividual data from Studies #004, #007, #015 and #022 can be found in Tables 1-4 in Appendix 5.

^bHarmonic mean and pseudo standard deviation.

^cData from Study #004 (hypertensives)—male mean age 52 yr (range 32-65), female mean age 52 yr (range 43-58), capsule formulations.

^dHealthy young male volunteers—capsule formulation (Study #007), tablet formulations (Studies #015 and #022).

NC - Not compared.

ND - Not determined.

MK-954 and E-3174 Data Following I.V. MK-954 in Studies #063 and #022*

Study	MK-954				E-3174	
	CL _r , ml/min	Vdss, L	Cl _r , ml/min	t _{1/2} ^b , hr	CL _r , ml/min	t _{1/2} ^b , hr
Elderly Pooled Study #063, n = 10	507 ± 112	30 ± 10	42 ± 14	1.9 ± 0.7	18 ± 8	6.5 ± 2.9
Elderly Female Study #063, n = 5	416 ± 55	30 ± 10	38 ± 9	2.3 ± 0.5	15 ± 6	7.6 ± 5.0
Elderly Male Study #063, n = 5	597 ± 73	29 ± 12	46 ± 19	1.6 ± 0.6	21 ± 8	5.7 ± 1.9
Young Male Study #022, n = 8	618 ± 247	40 ± 13	76 ± 39	2.3 ± 0.9	24 ± 5	7.7 ± 1.8

*Individual data from Study #022 can be found in Table 4 in Appendix 5.

^bHarmonic mean and pseudo standard deviation.

The key pharmacokinetic results (LSmeans) for losartan (normalized 50 mg dose) and L-158,641 for the elderly patients and healthy, male volunteers:

	AUC _{0-∞} (ng/ml-hr)		F (%)		CL _r (ml/min)		CL _T (ml/min)	
	Mean	LSmean	Mean	LSmean	Mean	LSmean	Mean	LSmean
Losartan								
Elderly Study 063								
Both	743	743	43	43	507	507	39.7	39.7*
Female	1008	-	51	-	416	-	32.8	-
Male	478	-	34	-	597	-	46.6	-
Healthy Males								
Study 007	413	678	-	-	-	-	74.2	67.4
Study 015	416	681	-	-	-	-	-	-
Study 022	361	626	25	33	618	527	90	83.2
L-158,641								
Elderly Study 063								
Both	2682	2682*	-	-	-	-	17.4	17.4
Female	2887	-	-	-	-	-	15.5	-
Male	2477	-	-	-	-	-	19.2	-
Healthy Males								
Study 007	1843	2048	-	-	-	-	24	23.2
Study 015	1561	1766	-	-	-	-	-	-
Study 022	1780	1985	-	-	-	-	22.5	20.7

*Significantly different from pooled data in young p<0.01.

Age range for healthy, male volunteers 18-31 yr (Study #007), 19-29 yr (Study #015), and 21-35 yr (Study #022).

CONCLUSION: The data obtained from the study shows that there are gender differences in the clearance of losartan in elderly patients, with systemic clearance greater in the elderly males and bioavailability greater in the elderly females. Comparison of the data from this study to those from Study #022 shows that the renal clearance of losartan is decreased in elderly male patients when compared to young, healthy males. These differences should be included in the labeling.

LIVER IMPAIRMENT STUDY

STUDY NUMBER: 067

VOLUME: 1.49

PAGES: 6773 - 7101

INVESTIGATOR AND LOCATION: THEODORE HERMAN, M.D.
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BUFFALO, NY 14209
USA.

OBJECTIVES: (i) To determine the pharmacokinetics of 50 mg losartan tablets and 10 mg IV losartan in patients with hepatic insufficiency, (ii) to compare the bioavailability and systemic clearance of losartan in patients with hepatic insufficiency to that in normal volunteers, (iii) to determine the percentage of the metabolite (L-158,641 or E-3174) produced after an intravenous dose of losartan, (iv) to compare the plasma concentration profiles of losartan and L-158,641 following administration of 50 mg losartan tablet and 10 mg IV losartan in patients with hepatic insufficiency with the profiles seen in normal volunteers, (v) to assess the tolerability of single dosetreatments of losartan in patients with hepatic insufficiency.

FORMULATIONS:

Losartan (MK-954) 50 mg Tablet, Formulation No. 0954 FCT005C003

Losartan (MK-954) IV Solution (5 mg/ml), Formulation No. 0954 HSS001A002

L-158,641 (E-3174) IV Solution (5 mg/ml), Formulation No. 9519HSS001A001

STUDY DESIGN: Randomized, open, three-period, cross-over study in 9 patients with hepatic insufficiency and a washout period of 7 days. On each study day, patients received the 50 mg tablet or the 10 mg losartan IV solution or 10 mg E-3174 solution administered over a 20-minute interval after an overnight fast. Blood samples were drawn following oral losartan at 0, 20, 40 minutes, and 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 16, 24, 30, and 36 hours; and following IV losartan administration at 0, 7, 14, 20, 30, and 40 minutes and 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 16, 24 and 30 hours; and following IV E-3174 at 0, 7, 14, 20 and 30 minutes and 1, 1.5, 2, 4, 6, 9, 12, 24, 30 and 36 hours. Urine was collected at 0-3, 3-6, 6-12, 12-24, 24-36, and 36-48-hours post dose.

ASSAYS: HPLC with UV detection.

PLASMA SAMPLES - LOSARTAN (MK-954) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curves from 5 to 1000 ng/ml.

Accuracy: Satisfactory. 103.0% at 20 ng/ml, 104.3% at 800 ng/ml for MK-954 and 96.0% at 20 ng/ml, 107.2% at 800ng/ml for E-3174.

Precision: Satisfactory. %CV - 6.4% at 20 ng/ml, 2.0% at 800 ng/ml for MK-954; and

10.8% at 20 ng/ml, 4.1% at 800 ng/ml for E-3174.
 Sensitivity: LOQ - 5 ng/ml.
 Specificity: Satisfactory. Chromatograms submitted.

URINE SAMPLES - LOSARTAN (MK-954) AND ACTIVE METABOLITE (E-3174):
 Linearity: Satisfactory. Standard curves from 10 to 2000 ng/ml for E-3174; 20 to 2000 ng/ml for MK-954.
 Accuracy: Satisfactory. 103.0% at 40 ng/ml, 107.2% at 1600 ng/ml for MK-954; and 110.8% at 40 ng/ml, 107.0% at 1600 ng/ml for total E-3174.
 Precision: Satisfactory. %CV - 4.2% at 40 ng/ml, 1.8% at 1600 ng/ml for MK-954; and 9.1% at 40 ng/ml, 2.2% at 1600 ng/ml for E-3174.
 Sensitivity: LOQ - 10 ng/ml for E-3174; 20 ng/ml for MK-954.
 Specificity: Satisfactory. Chromatograms submitted.

The assays have been validated over the range of plasma and urine concentrations observed in the study.

DATA ANALYSIS: AUC_{∞} , C_{max} , $t_{1/2}$, CL , CL_r , Vd_{ss} , T_{max} , F , and % Dose excreted in urine were calculated.

RESULTS:

	Intravenous E-3174	Intravenous MK-954		Oral MK-954	
	E-3174	MK-954	E-3174	MK-954	E-3174
$C_{20\ min}$, ng/ml ^a	2405.8 ± 350.4	1056.1 ± 249.5	-	-	-
C_{max} , ng/ml ^b	-	-	50.3 ± 26.5	1171.8 ± 667.1	296.2 ± 108.9
T_{max} , hr	-	-	4.9 ± 1.8	0.98 ± 0.47	4.56 ± 0.88
AUC_{∞} , ng·hr/ml ^a	5626.39 ± 1764.97	653.72 ± 230.44	623.27 ± 288.73	2162.83 ± 1095.38	3131.19 ± 1219.56
λ , hr ⁻¹	0.1368 ± 0.0581	0.3889 ± 0.1542	0.1187 ± 0.0376	0.2885 ± 0.0778	0.1065 ± 0.0246
$t_{1/2}$, hr ^b	5.07 ± 2.40	1.78 ± 0.74	5.84 ± 1.91	2.40 ± 0.67	6.51 ± 1.54
Vd_{ss} , L	8.57 ± 2.53	19.65 ± 9.77	-	-	-
CL_r , ml/min	33.18 ± 13.17	283.04 ± 97.46	-	-	-
CL_r , ml/min	19.08 ± 7.80	44.27 ± 17.01	23.43 ± 12.23	55.41 ± 20.39	21.38 ± 8.17
% Dose recovered in urine	59.05 ± 13.89	19.69 ± 9.98	8.14 ± 2.97	16.21 ± 11.00	7.84 ± 1.93
Oral bioavailability, % ^c	-	-	-	64.8 ± 21.8	-

^aData normalized to 10.0-mg I.V. E-3174 free acid dose and 10.0-mg I.V. and 50.0-mg oral dose of MK-954.

^bHarmonic mean and pseudo standard deviation.

^cGeometric mean was 61.3%, with 90% confidence interval limits of 49.1% to 76.6%.

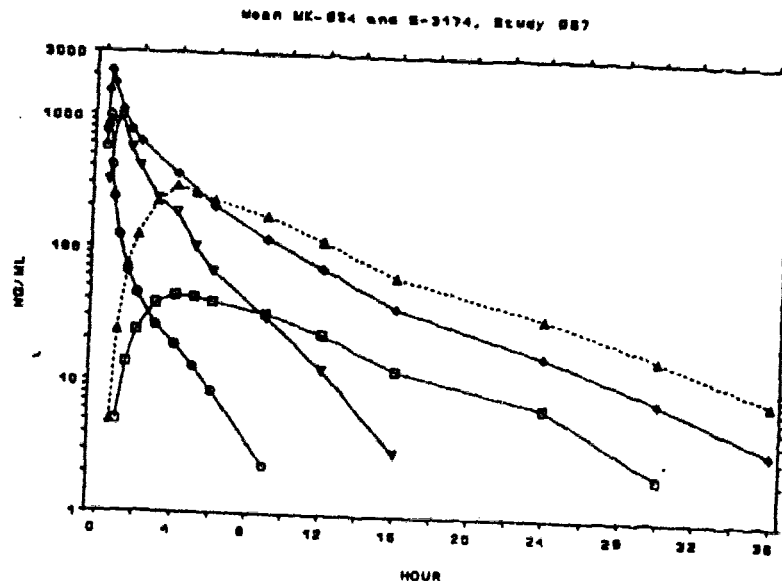


Figure 1. Mean Plasma Concentrations of MK-954 and E-3174 in Nine Patients Following the Administration of A Single Intravenous Infusion Dose of 10-mg MK-954 (○ = MK-954, □ = E-3174), A Single 50-mg Tablet Oral Dose of MK-954 (▽ = MK-954, △ = E-3174), and A Single Intravenous Infusion Dose of 10-mg E-3174 (○ = E-3174)

MK-954 and E-3174 Data Following a Single Oral Dose of 50-mg MK-954 Tablet in Studies #067, #074 and #075 (Data Normalized to 50.0 mg From Assayed Potency)*

Study	MK-954						E-3174				
	C _{max} [†] ng/ml	T _{max} [†] hr	AUC [‡] ng-hr/ml	t _{1/2} [§] hr	CL _r [†] ml/min	F [†] %	C _{max} [†] ng/ml	T _{max} [†] hr	AUC [‡] ng-hr/ml	t _{1/2} [§] hr	CL _r [†] ml/min
Hepatic Study #067, n = 9	1172 ± 667	1.0 ± 0.5	2163 ± 1095	2.4 ± 0.7	55 ± 20	61 (49, 77)	296 ± 109	4.6 ± 0.9	3131 ± 1220	6.5 ± 1.5	21 ± 8
Healthy Subjects Study #074, n = 12	296 ± 217	1.0 ± 0.5	476 ± 200	2.1 ± 0.5	72 ± 21	33 (26, 42)	249 ± 74	4.1 ± 1.6	1915 ± 538	6.4 ± 2.3	26 ± 7
Healthy Subjects Study #075, n = 17	209 ± 100	1.2 ± 0.9	403 ± 100	2.2 ± 0.9	N.D.	N.D.	225 ± 117	4.5 ± 1.7	1778 ± 434	9.2 ± 2.2	N.D.

*Individual data from Studies #074 and #075 can be found in Tables 1 and 2 in Appendix 3.
[†]Harmonic mean and pseudo standard deviation.
[‡]Geometric mean and 90% confidence interval limits.
[§]N.D. - Not Determined.

MK-954 and E-3174 Data Following I.V. MK-954 in Studies #067, #060 and #074*

Study	Dose, mg	MK-954				E-3174			
		CL, ml/min	Vd _{ss} , L	Cl _r , ml/min	t _{1/2} ^b , hr	CL _r , ml/min	t _{1/2} ^b , hr	f _m , %	f _m ^c , %
Hepatic Study #067, n = 9	9.2 ± 0.7	285 ± 97	20 ± 10	44 ± 17	1.8 ± 0.7	23 ± 12	5.8 ± 1.9	13 ± 4	16 ± 5
Healthy Subjects Study #060, n = 6	26.4 ± 1.0	359 ± 188	47 ± 21	64 ± 26	3.2 ± 0.8	25 ± 7	5.3 ± 2.1	14 ± 4	16 ± 4
Healthy Subjects Study #074, n = 12	19.7 ± 1.8	636 ± 107	28 ± 14	72 ± 21	1.8 ± 0.6	28 ± 6	4.6 ± 1.3	N.D.	N.D.

*Individual data from Studies #060 and #074 can be found in Tables 1 and 3 in Appendix 5.

^bHarmonic mean and pseudo standard deviation.

N.D. - Not determined.

Table 21. E-3174 Data Following I.V. E-3174 in Studies #067 and #060*

Study	Dose ^a , mg	E-3174			
		CL, ml/min	Vd _{ss} , L	Cl _r , ml/min	t _{1/2} ^b , hr
Hepatic Study #067, n = 9	8.9 ± 0.6	33 ± 13	8.6 ± 2.5	19 ± 8	5.1 ± 2.4
Healthy Subjects Study #060, n = 6	16.6 ± 0.3	47 ± 6	10.3 ± 1.1	26 ± 6	6.3 ± 1.4

*Individual data from Study #060 can be found in Table 4 in Appendix 5.

CONCLUSION: Comparison of the data from this study to those from healthy male subjects (Study #074, #075, #060) shows that (i) the systemic clearance of losartan is reduced to about 50%, (ii) the oral bioavailability of losartan is increased (from 33% to 65%), (iii) the C_{max} and AUC for losartan following oral administration are about 5-fold greater, (iv) the AUC for E-3174 following oral losartan is about 1.7-fold greater. These differences should be included in the labeling.

RENAL IMPAIRMENT STUDY

STUDY NUMBER: 012

VOLUME: 1.50

PAGES: 7103 - 7457

INVESTIGATOR AND LOCATION:

OBJECTIVES: (i) To determine the effect of renal insufficiency on the pharmacokinetics of losartan (MK-954) and E-3174 following chronic 100-mg doses of MK-954, (ii) to determine to what extent MK-954 and E-3174 are cleared by hemodialysis, (iii) to investigate in hypertensive patients with four degrees of renal function the chronic-dose effects of MK-954 on blood pressure and pulse, (iv) to evaluate the safety of multiple doses of MK-954 in patients with different levels of renal function.

FORMULATIONS:

Losartan (MK-954) 50 mg Capsule, Formulation No. 0954 DFC 002C002

Losartan (MK-954) 100 mg Capsule, Formulation No. 0954 DFC 002D001

STUDY DESIGN: Open label study in 24 patients (from two centers) with various levels of renal function and divided into four groups based on 24-hour creatine clearance (CL_{cr}) determined during baseline: Group I - normal renal function (CL_{cr} ≥ 75 ml/min); Group II - mild to moderate renal insufficiency (CL_{cr} = 30-74 ml/min); Group III - severe renal insufficiency (CL_{cr} = 10-29 ml/min); Group IV - hemodialysis patients (CL_{cr} < 10 ml/min). Following 1 week washout after discontinuation of antihypertensive therapy, patients in Groups I, II and III received losartan 100 mg for 7 days. On Day 6, a trough blood specimen was taken and on Day 7, the patient was admitted to the study clinic for 30 to 60 hours. Blood samples were drawn following oral losartan on Day 7 at 0, 20, 30, 45, 60, 75, and 90 minutes, and 2, 3, 4, 6, 8, 10, 15, 18, 24, 30, 36, 48, and 60 hours. Urine was collected at 0-4, 4-8, 8-12, and 12-24, hours post dose on Day 7. Hemodialysis patients received 100 mg losartan for 7 days, with dose being taken 4 hours before dialysis on dialysis days (Days 2, 4, 6, 9 of the study). Peripheral venous blood samples were taken at times mentioned above. Pre- and postdialyses blood samples were taken from the dialysis shunt circuit at Hours 0, 1, 2, 3, and 4 of dialysis on Day 6 to evaluate the clearance of losartan and E-3174 by dialysis.

ASSAYS: HPLC with UV detection.

PLASMA SAMPLES - LOSARTAN (MK-954) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curves from 5 to 1000 ng/ml.

Accuracy: Satisfactory. 93.4% at 20 ng/ml, 97.1% at 800 ng/ml for MK-954 and 100.0% at 20 ng/ml, 99.4% at 800ng/ml for E-3174.
Precision: Satisfactory. %CV - 7.8% at 20 ng/ml, 5.7% at 800 ng/ml for MK-954; and 7.7% at 20 ng/ml, 3.5% at 800 ng/ml for E-3174.
Sensitivity: LOQ - 5 ng/ml.
Specificity: Satisfactory. Chromatograms submitted.

URINE SAMPLES - LOSARTAN (MK-954) AND ACTIVE METABOLTE (E-3174):

Linearity: Satisfactory. Standard curves from 10 to 2000 ng/ml for E-3174; 20 to 2000 ng/ml for MK-954.
Accuracy: Satisfactory. 97.0% at 40 ng/ml, 102.7% at 1600 ng/ml for MK-954; and 101.8% at 40 ng/ml, 99.8% at 1600 ng/ml for total E-3174.
Precision: Satisfactory. %CV - 8.1% at 40 ng/ml, 1.5% at 1600 ng/ml for MK-954; and 1.9% at 40 ng/ml, 1.6% at 1600 ng/ml for E-3174.
Sensitivity: LOQ - 10 ng/ml for E-3174; 20 ng/ml for MK-954.
Specificity: Satisfactory. Chromatograms submitted.

The assays have been validated over the range of plasma and urine concentrations observed in the study.

DATA ANALYSIS: AUC_{24} , C_{max} , $t_{1/2}$, CL_r , T_{max} , λ and % Dose excreted in urine were calculated.

RESULTS:

MK-954								
Parameter	n	Group I, CL_r ≥ 75 ml/min	n	Group II, CL_r 30-74 ml/min	n	Group III, CL_r 10-29 ml/min	n	Group IV, CL_r <10 ml/min
C_{max} , ng/ml	6	854.2 $\pm$ 315.2	6	1164.6 $\pm$ 743.0	6	801.0 $\pm$ 445.4	6	1615.1 $\pm$ 417.4
T_{max} , hr	6	0.79 $\pm$ 0.37	6	0.68 $\pm$ 0.23	6	0.68 $\pm$ 0.41	6	0.68 $\pm$ 0.32
AUC_{24} , ng hr/ml	6	1106.9 $\pm$ 265.1	6	1212.2 $\pm$ 755.1	6	1790.6 $\pm$ 1369.9	6	2065.6 $\pm$ 551.0
$t_{1/2}$, hr	6	2.13 $\pm$ 0.68	6	2.17 $\pm$ 0.97	5	3.22 $\pm$ 2.19	5	2.64 $\pm$ 1.02
λ , hr ⁻¹	6	0.326 $\pm$ 0.103	6	0.319 $\pm$ 0.142	5	0.215 $\pm$ 0.136	5	0.262 $\pm$ 0.105
CL_r , ml/min	6	50.2 $\pm$ 19.4	6	16.5 $\pm$ 6.5	6	2.3 $\pm$ 0.9		N.A.
Urinary Recovery, % dose	6	3.25 $\pm$ 1.23	6	1.33 $\pm$ 1.03	6	0.27 $\pm$ 0.32		N.A.

E-3174								
Parameter	n	Group I, CL_r ≥ 75 ml/min	n	Group II, CL_r 30-74 ml/min	n	Group III, CL_r 10-29 ml/min	n	Group IV, CL_r <10 ml/min
C_{max} , ng/ml	6	681.3 $\pm$ 210.6	6	623.0 $\pm$ 214.1	6	402.6 $\pm$ 344.2	6	715.3 $\pm$ 579.0
T_{max} , hr	6	2.42 $\pm$ 0.92	6	2.06 $\pm$ 0.49	6	4.17 $\pm$ 1.60	6	2.50 $\pm$ 1.01
AUC_{24} , ng hr/ml	6	4362.2 $\pm$ 1143.2	6	3694.3 $\pm$ 953.1	6	3912.4 $\pm$ 2766.1	6	5011.6 $\pm$ 4037.5
$t_{1/2}$, hr	6	9.55 $\pm$ 3.47	5	11.04 $\pm$ 5.44	6	13.45 $\pm$ 5.76	4	11.25 $\pm$ 9.06
λ , hr ⁻¹	6	0.0726 $\pm$ 0.0256	5	0.0628 $\pm$ 0.0297	6	0.0516 $\pm$ 0.0220	4	0.0616 $\pm$ 0.0300
CL_r , ml/min	6	16.1 $\pm$ 4.1	6	6.9 $\pm$ 2.6	6	1.3 $\pm$ 0.6		N.A.
Urinary Recovery, % dose	6	4.44 $\pm$ 1.34	5	1.65 $\pm$ 0.92	6	0.24 $\pm$ 0.08		N.A.

N.A. - Not applicable.

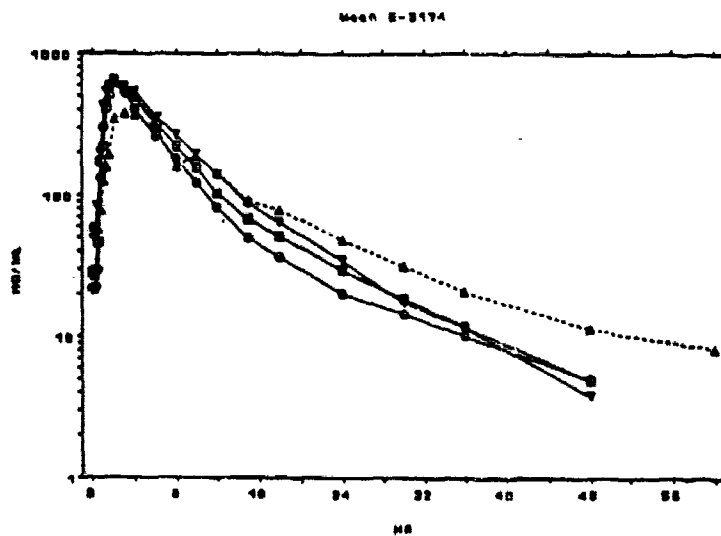
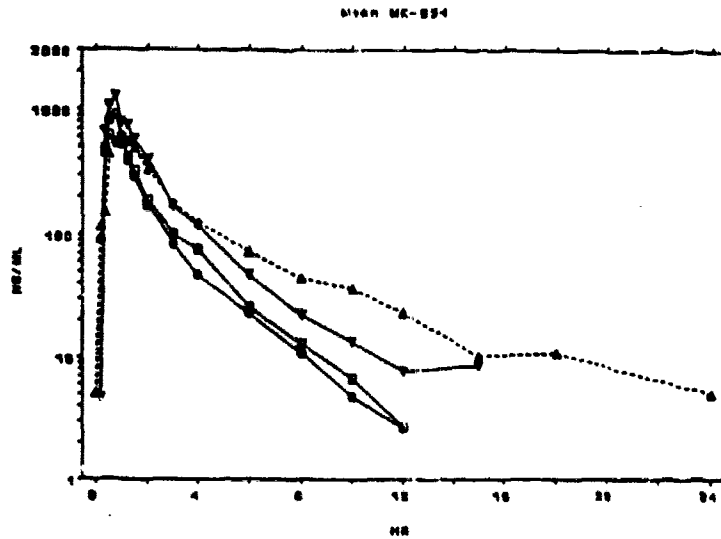


Figure 1. Mean Plasma Concentrations of MK-954 and E-3174 in Patients With Renal Insufficiency: (□) Group I, (○) Group II, (△) Group III and (▽) Group IV.

CONCLUSIONS: (i) The renal clearance of losartan decreases with renal impairment (but renal clearance constitutes only about 12% of total body clearance of losartan); (ii) the renal clearance of E-3174 decreases with renal impairment (renal clearance constitutes about 55% of total body clearance of E-3174) but the AUC does not increase with decreasing renal clearance; (iii) AUC of losartan is higher in hemodialysis patients; (iv) losartan and E-3174 do not appear to be cleared by hemodialysis. These observations should be included in the labeling.

LOSARTAN - PHENOBARBITAL INTERACTION STUDY

STUDY NUMBER: 072

VOLUME: .50

PAGES: 7524 - 7905

INVESTIGATOR AND LOCATION:

OBJECTIVES: To determine whether the pharmacokinetics of a single dose of losartan are altered to a clinically significant degree after administration of phenobarbital for 2 weeks.

FORMULATIONS:

Losartan 100 mg Tablet, Formulation No. C954 FCT004D003

Phenobarbital 100 mg Tablet, Formulation No. CO954 FCT008D002

Phenobarbital Placebo, Formulation No. PO217 OCT001P004

STUDY DESIGN: Single-blind, placebo-controlled, randomized, two-period study in 15 subjects. Each subject received a single dose of losartan (100 mg tablet) orally on Day 1 of Period 1. After a washout period of at least 48 hours, Period 2 commenced, consisting of a 16-day course of either phenobarbital 100 mg or placebo, taken once daily at 10 p.m. ($\pm$ 1 hr). On the morning of Day 15, subjects received another single dose of losartan 100 mg after an overnight fast and fasted until 1 hour post dose. Blood samples were drawn following oral losartan at 0, 15, 30, 45, minutes, and 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, and 36 hours. Urine was collected predose and at 0-3, 3-6, 6-12, and 12-24, 24-36, and 36-48 hours post losartan dose.

ASSAYS: HPLC with UV detection.

PLASMA SAMPLES - LOSARTAN (MK-954) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curves from 5 to 1000 ng/ml.

Accuracy: Satisfactory. 98.5% at 20 ng/ml, 99.5% at 800 ng/ml for MK-954 and 100.0% at 20 ng/ml, 101.9% at 800 ng/ml for E-3174.

Precision: Satisfactory. %CV - 8.0% at 20 ng/ml, 4.3% at 800 ng/ml for MK-954; and 6.7% at 20 ng/ml, 5.7% at 800 ng/ml for E-3174.

Sensitivity: LOQ - 5 ng/ml.

Specificity: Satisfactory. Chromatograms submitted.

URINE SAMPLES - LOSARTAN (MK-954) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curves from 10 to 2000 ng/ml for E-3174; 20 to 2000 ng/ml for MK-954.

Accuracy: Satisfactory. 96.8% at 40 ng/ml, 95.0% at 1600 ng/ml for MK-954; and 98.8% at 40 ng/ml, 98.1% at 1600 ng/ml for total E-3174.

Precision: Satisfactory. %CV - 6.8% at 40 ng/ml, 3.0% at 1600 ng/ml for MK-954; and

4.4% at 40 ng/ml, 2.9% at 1600 ng/ml for E-3174.
 Sensitivity: LOQ - 10 ng/ml for E-3174; 20 ng/ml for MK-954.
 Specificity: Satisfactory. Chromatograms submitted.

The assays have been validated over the range of plasma and urine concentrations observed in the study.

DATA ANALYSIS: AUC_{∞} , C_{max} , $t_{1/2}$, CL_r , T_{max} , λ and % Dose excreted in urine were calculated.

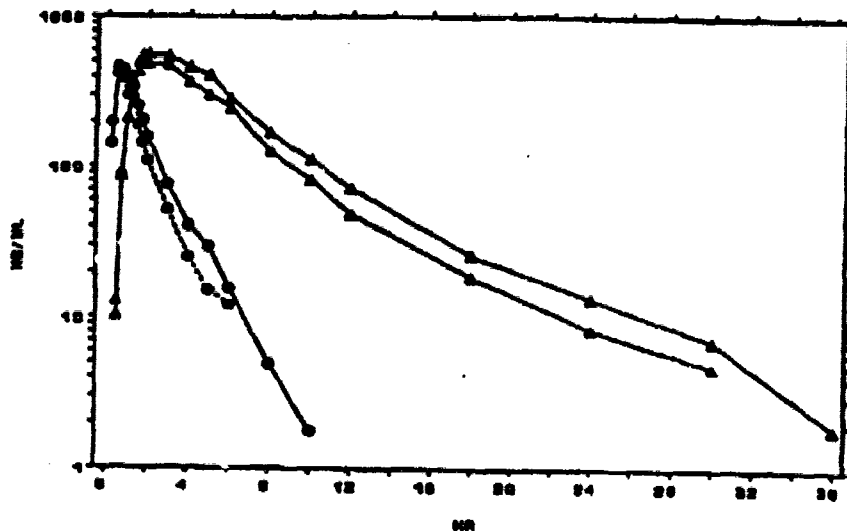
RESULTS:

Losartan L-158,641 Pharmacokinetic Parameters (arithmetic mean $\pm$ S.D.)
 in the Phenobarbital and Placebo Treatment Groups

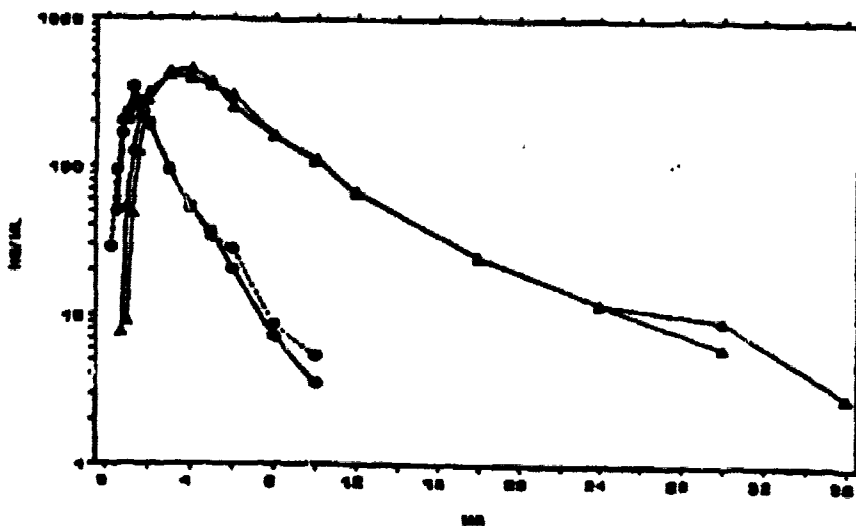
	Period I - 100 mg of MK-954 Given Prior to Phenobarbital or Placebo Administration		Period II - 100 mg of MK-954 Taken on Day 15 of Phenobarbital or Placebo Administration	
	MK-954	L-158,641	MK-954	L-158,641
Phenobarbital Treatment Group (n=10), 100 mg Once a Day for 16 Days				
C_{max} , ng/mL	588.4 $\pm$ 300.1	646.3 $\pm$ 136.8	586.9 $\pm$ 268.8	583.8 $\pm$ 132.9
T_{max} , hr	0.88 $\pm$ 0.29	2.23 $\pm$ 0.70	0.88 $\pm$ 0.46	2.38 $\pm$ 1.14
AUC, ng·hr/mL	854.31 $\pm$ 193.97	3784.92 $\pm$ 468.61	673.84 $\pm$ 124.98	3022.17 $\pm$ 361.38
λ , hr ⁻¹	0.4041 $\pm$ 0.1298	0.1012 $\pm$ 0.0391	0.4049 $\pm$ 0.1100	0.1102 $\pm$ 0.0482
$t_{1/2}$, hr ^a	1.72 $\pm$ 0.55	6.85 $\pm$ 2.76	1.71 $\pm$ 0.45	6.29 $\pm$ 2.88
CL_r , mL/min	69.55 $\pm$ 4.96	22.70 $\pm$ 2.08	68.50 $\pm$ 6.29	22.19 $\pm$ 3.11
Urinary Recovery	mg	3.725 $\pm$ 0.931	5.105 $\pm$ 0.504	2.825 $\pm$ 0.634
	% Dose	3.75 $\pm$ 0.94	5.42 $\pm$ 0.54	2.84 $\pm$ 0.64
Placebo Treatment Group (n=5), Placebo Once a Day for 16 Days ^b				
C_{max} , ng/mL	381.5 $\pm$ 140.7	470.9 $\pm$ 119.3	355.8 $\pm$ 83.8	444.4 $\pm$ 172.2
T_{max} , hr	1.31 $\pm$ 0.13	3.50 $\pm$ 0.58	1.25 $\pm$ 0.41	3.50 $\pm$ 1.29
AUC, ng·hr/mL	684.10 $\pm$ 206.49	3048.38 $\pm$ 909.43	697.93 $\pm$ 189.38	3179.42 $\pm$ 1098.9
λ , hr ⁻¹	0.4098 $\pm$ 0.0622	0.0958 $\pm$ 0.0438	0.3172 $\pm$ 0.083	0.0656 $\pm$ 0.0248
$t_{1/2}$, hr ^a	1.69 $\pm$ 0.25	7.23 $\pm$ 3.13	2.18 $\pm$ 0.59	10.56 $\pm$ 4.02
CL_r , mL/min	78.87 $\pm$ 8.26	26.37 $\pm$ 2.19	77.13 $\pm$ 5.64	24.77 $\pm$ 1.09
Urinary Recovery	mg	3.440 $\pm$ 1.125	4.816 $\pm$ 1.654	3.291 $\pm$ 0.929
	% Dose	3.46 $\pm$ 1.13	5.11 $\pm$ 1.76	3.31 $\pm$ 0.93
^a Harmonic mean and pseudo standard deviation. ^b C_{max} , T_{max} , AUC, λ , $t_{1/2}$, CL_r and urinary recovery. n=4, data for subject #5 excluded.				

Mean Plasma Concentration vs. Time Profiles For Losartan and L-158,641 in the Groups which Received Phenobarbital (TOP) and Placebo (BOTTOM)

Phenobarbital Group(N=10)



Placebo Group(N=4)



O= MK-954 Pre-Rx; ● = MK-954 During Rx; Δ = L-158,641 Pre-Rx;
▲ = L-158,641 During Rx

CONCLUSIONS: (1) Consistent with induction of cytochrome P450 by phenobarbital: (i) the AUC for losartan and E-3174 are reduced by about 20% during phenobarbital administration, (ii) the amount of 6-β-hydroxycortisol excreted in urine is increased during phenobarbital treatment. (2) a subject was identified who did not make appreciable amounts of E-3174 from losartan. These observations should be included in the labeling.

LOSARTAN - CIMETIDINE INTERACTION STUDY

STUDY NUMBER: 024

VOLUME: 1.51

PAGES: 7906 - 8237

INVESTIGATOR AND LOCATION:

OBJECTIVES: (i) To investigate the effect of a clinically relevant dose of cimetidine on the plasma concentration profiles of losartan, (ii) to determine whether any observed effect of cimetidine on the pharmacokinetics of losartan has pharmacodynamics consequences as measured by an effect on losartan-induced increases in plasma renin concentration.

FORMULATIONS:

Losartan 100 mg capsule, Formulation No. E-4359

Cimetidine tablet, 400 mg , Lot No. 10 (Smith Kline French)

STUDY DESIGN: Randomized, open, two-period, cross-over study in 8 subjects with a wash period of at least 7 days. Each subject received a single dose of losartan (100 mg capsule) orally, with and without cimetidine pretreatment (Treatments A and B respectively). Treatment A consists of 100 mg losartan administered orally on Day 1, following an overnight fast. Treatment B consists of cimetidine (400 mg tablet) administered orally every 6 hours on Days 1-7 and 2 hours after the morning cimetidine dose on Day 6 losartan (100 mg) administered orally following an overnight fast. After dosing no food was allowed for four hours. Blood samples were drawn following oral losartan at 0, 10, 20, 30, 40, and 50 minutes, and at 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 30, and 36 hours. Plasma renin activity was determined at 0, 2, 4, 6, 8, 12, and 24 hours post losartan dose.

ASSAYS: HPLC with UV detection.

LOSARTAN (MK-954) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curves from 5 to 1000 ng/ml.

Accuracy: Satisfactory. 96.5% at 20 ng/ml, 98.7% at 800 ng/ml for MK-954; and 93.0% at 20 ng/ml, 93.8% at 800ng/ml for E-3174.

Precision: Satisfactory. %CV - 3.1% at 20 ng/ml, 1.3% at 800 ng/ml for MK-954; and 8.1% at 20 ng/ml, 9.3% at 800 ng/ml for E-3174.

Sensitivity: LOQ - 5 ng/ml.

Specificity: Satisfactory. Chromatograms submitted.

The assays have been validated over the range of plasma concentrations observed in the study.

DATA ANALYSIS: AUC , C_{max}, t_{1/2}, T_{max}, and λ were calculated.

RESULTS:

	Losartan		L-158,641	
	-Cimetidine	+Cimetidine	-Cimetidine	+Cimetidine
C_{max} , ng/mL†	614 ± 366	836 ± 921	504 ± 253	499 ± 218
T_{max} , hr	0.7 ± 0.2	1.2 ± 1.2	2.6 ± 0.8	2.8 ± 1.1
AUC_X , ng·hr/mL†	849 ± 383	1047 ± 647	3359 ± 1329	3430 ± 1553
$t_{1/2}$, hr@	1.7 ± 0.6	1.7 ± 0.5	8.7 ± 3.6	8.1 ± 2.1
λ_z , hr ⁻¹	0.40 ± 0.13	0.42 ± 0.12	0.080 ± 0.031	0.085 ± 0.021
$\frac{AUC_{\infty} (+Cimetidine)}{AUC_{\infty} (-Cimetidine)}$	1.18 (1.10, 1.27)‡		1.00 (0.92, 1.08)‡	
$\frac{C_{max} (+Cimetidine)}{C_{max} (-Cimetidine)}$	1.07 Δ (0.89, 1.38)		1.02 (0.88, 1.15)‡	

@ Harmonic mean and pseudo standard deviation.

† Geometric mean

‡ Geometric mean ratio (90% Confidence Interval).

Δ Hodges-Lehmann Estimate (W/WO) with Moses Co. fidence Interval 88.5% and 94.2%, respectively.

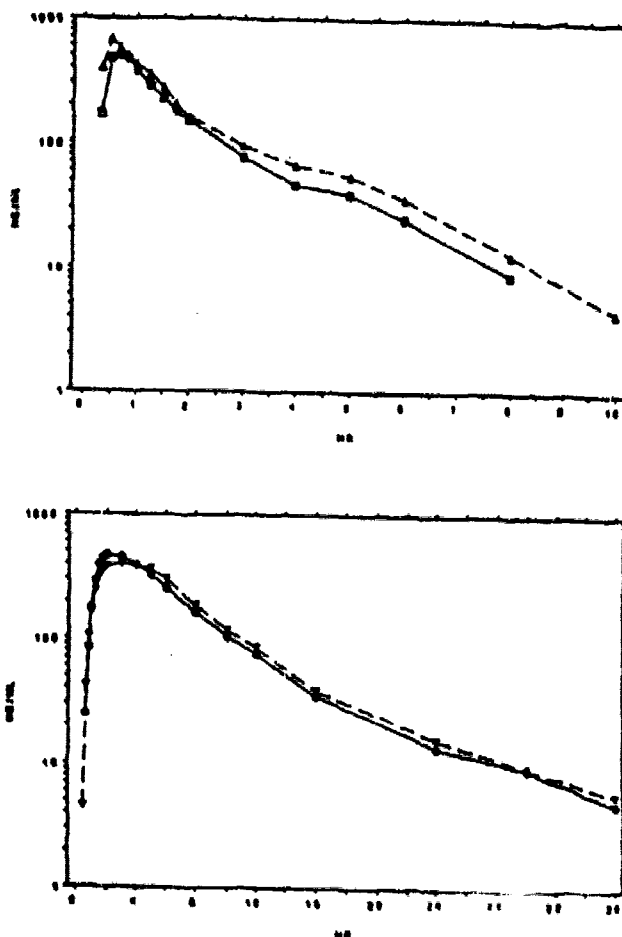


Figure 1. Mean Plasma Concentrations of MK-954 (LA) and L-3174 (O, V) in Eight Subjects Following 100 mg Oral MK-954 With (dash line) and Without (solid line) Cimetidine Pretreatment.

PLASMA RENIN ACTIVITY

PREDOSE

Treatment A Time	AN 01	AN 02	AN 03	AN 04	AN 05	AN 06	AN 07	AN 08	AVG
0 hr	0.69	1.95	0.64	1.18	0.96	1.00	0.92	3.53	1.36
2 hr	0.67	1.82	0.87	0.89	1.01	0.47	0.90	3.72	1.29
4 hr	0.54	1.79	0.56	0.98	0.99	0.65	0.72	3.80	1.25
6 hr	1.07	1.68	0.72	2.16	1.28	0.78	1.03	5.21	1.74
8 hr	0.57	0.89	0.72	1.14	0.66	0.26	0.94	1.89	0.85
12 hr	0.35	0.87	0.54	0.70	0.61	0.56	0.65	1.09	0.67

POSTDOSE

Treatment A Time	AN 01	AN 02	AN 03	AN 04	AN 05	AN 06	AN 07	AN 08	AVG
0 hr	0.73	1.56	1.35	1.08	1.02	1.39	1.28	3.00	1.43
2 hr	0.92	17.96	5.73	5.05	4.02	3.52	8.24	14.96	7.55
4 hr	1.04	24.41	1.64	4.53	5.23	2.44	6.64	30.81	9.59
6 hr	13.81	25.38	6.86	13.33	7.00	4.53	8.78	32.23	13.99
8 hr	6.34	6.77	4.05	8.44	2.46	3.21	2.98	16.54	6.35
12 hr	1.40	6.30	2.97	2.82	2.89	1.90	2.10	6.78	3.40
24 hr	2.52	2.41	3.47	3.51	1.81	4.71	3.18	14.10	4.46

MK-954 Cimetidine Interaction Dr. Hoeglund/Lund Sweden

PREDOSE

Treatment B Time	AN 01	AN 02	AN 03	AN 04	AN 05	AN 06	AN 07	AN 08	AVG
0 hr	0.71	1.03	0.65	1.17	1.27	1.55	0.82	4.04	1.41
2 hr	1.15	1.24	0.60	0.63	1.05	1.03	0.65	5.35	1.49
4 hr	0.54	0.76	0.71	1.29	0.96	0.96	0.61	3.93	1.22
6 hr	0.88	1.20	0.93	1.78	1.29	1.03	0.69	5.28	1.64
8 hr	0.57	0.24	1.24	1.00	0.48	0.79	0.47	1.82	0.83
12 hr	0.44	0.17	0.39	0.87	0.49	0.69	0.35	1.08	0.56

POSTDOSE

Treatment B Time	AN 01	AN 02	AN 03	AN 04	AN 05	AN 06	AN 07	AN 08	AVG
0 hr	0.33	0.92	1.10	1.57	1.27	1.44	1.16	2.63	1.37
2 hr	0.55	0.02	2.80	8.97	4.18	3.66	9.27	24.74	7.36
4 hr	0.13		2.34	8.07	7.31	2.85	4.63	31.44	8.45
6 hr		1.13	2.18	14.19	11.51	2.52	10.31	39.16	13.43
8 hr	0.51	0.95	9.81	6.08	4.92	1.47	4.81	13.30	6.36
12 hr	1.38	1.00	9.05	2.68	4.32	1.11	1.71	8.16	3.41
24 hr	1.89	2.00	4.62	1.23	3.75	2.74	3.92	13.12	4.81

CONCLUSIONS: Co-administration of cimetidine with oral losartan results in an increase of about 23% in the AUC and 36% increase in Cmax of losartan but no alteration in the pharmacokinetics of E-3174 and plasma renin activity. These observations should be included in the labeling.

LOSARTAN - WARFARIN INTERACTION STUDY

STUDY NUMBER: 070

VOLUME: 1.51

PAGES: 8238 - 8681

INVESTIGATOR AND LOCATION:

STUDY PERIOD: JULY 1992 - SEPTEMBER 1992.

OBJECTIVES: (i) to whether the pharmacokinetics of a single dose of warfarin are altered to a clinically significant degree by coadministration with losartan, and (ii) to determine whether the pharmacodynamics of a single dose of warfarin are altered to clinically significant degree by coadministration with losartan.

FORMULATIONS:

100 mg losartan Tablet, Batch No. C-Y064, Formulation No. 0954FCT004D003

Losartan Matching Placebo Tablet, Batch No. C-Y064, Formulation No. PO954FCT005D001

Coumadin (sodium warfarin) 10 mg Tablets, Batch No. C-Y064, Formulation No. DB036B

STUDY DESIGN: Randomized, double-blind, placebo-controlled, two-period, crossover study with 10 subjects and a washout period of two weeks. Subjects received either losartan 100 mg orally (Treatment A) or matched placebo (Treatment B) for 12 days (study days 1-12) according to a random allocation schedule, with a single 30 mg oral dose of warfarin on day 7. Subjects fasted from midnight before and until 1 hour post losartan or placebo dose on study days 1-12 and until 3 hours post warfarin dose on study day 7. Plasma for warfarin levels were drawn at 0, 1, 2, 4, 8, 12, 24, 32, 48, 56, 72, 80, 96, 120, and 144 hours after the oral administration of warfarin and frozen at -20°C until analysis. All subjects had prothrombin time (PT) determinations performed at 0, 1, 2, 4, 8, 12, 24, 32, 48, 56, 72, 80, 96, 120, and 144 hours after the warfarin dose.

ASSAYS: HPLC with UV detection.

Linearity: Satisfactory. Standard curves from 100 to 1250 ng/ml.

Accuracy: Satisfactory. 102.0% at 200 ng/ml, 99.4% at 1000 ng/ml for R-warfarin; and 104.5% at 200 ng/ml, 95.4% at 1000ng/ml for S-warfarin.

Precision: Satisfactory. %CV - 8.6% at 200 ng/ml, 10.2% at 1000 ng/ml for R-warfarin; and 8.1% at 200 ng/ml, 7.9% at 1000 ng/ml for S-warfarin

Sensitivity: LOQ - 100 ng/ml.

Specificity: Satisfactory. Chromatograms submitted.

The assays have been validated over the range of plasma concentrations observed in the study.

DATA ANALYSIS: AUC_{∞} , C_{max} , $t_{1/2}$, T_{max} , and λ were calculated.

Pharmacokinetics (N=9): The description of warfarin pharmacokinetic parameters (arithmetic mean $\pm$ S.D.) following losartan 100 mg or placebo administration.

Parameter	R-Warfarin		S-Warfarin	
	Losartan	Placebo	Losartan	Placebo
AUC(ng•hr/mL) ($\pm$ S.D.)	87861.0 (14941.7)	87195.4 (22525.9)	70266.0 (13956.1)	70194.9 (17945.9)
C_{max} (ng/mL) ($\pm$ S.D.)	1656.3 (382.9)	1496.3 (256.1)	1647.0 (308.8)	1615.6 (258.1)
λ (hr ⁻¹) ($\pm$ S.D.)	0.015 (0.002)	0.016 (0.003)	0.020 (0.003)	0.020 (0.003)
$t_{1/2}$ (hr) ¹ ($\pm$ S.D.)	44.97 (2.49)	44.34 (3.11)	34.97 (2.06)	36.00 (2.20)

The analysis of warfarin (R + S) pharmacokinetic parameters (geometric mean ratios and treatment differences) following losartan 100 mg or placebo administration.

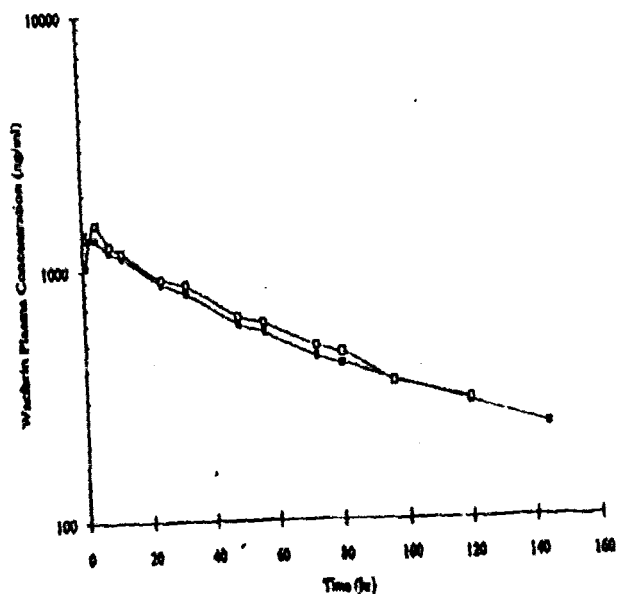
Parameter	Least Square Means		Tr Diff ²	90% CI
	Losartan	Placebo		
R-Warfarin				
AUC(ng•hr/mL) ³	87040.29	84199.81	1.034	(.967, 1.105)
C_{max} (ng/mL) ³	1608.71	1489.29	1.080	(.953, 1.224)
T_{max} (hr)	2.90	2.77	.125	(-1.59, 1.836)
S-Warfarin				
AUC(ng•hr/mL) ³	69461.29	67787.18	1.024	(.945, 1.111)
C_{max} (ng/mL) ³	1616.49	1603.22	1.008	(.928, 1.096)
T_{max} (hr)	1.70	2.08	-.375	(-.999, 0.249)

¹ Harmonic mean and pseudo standard deviation.

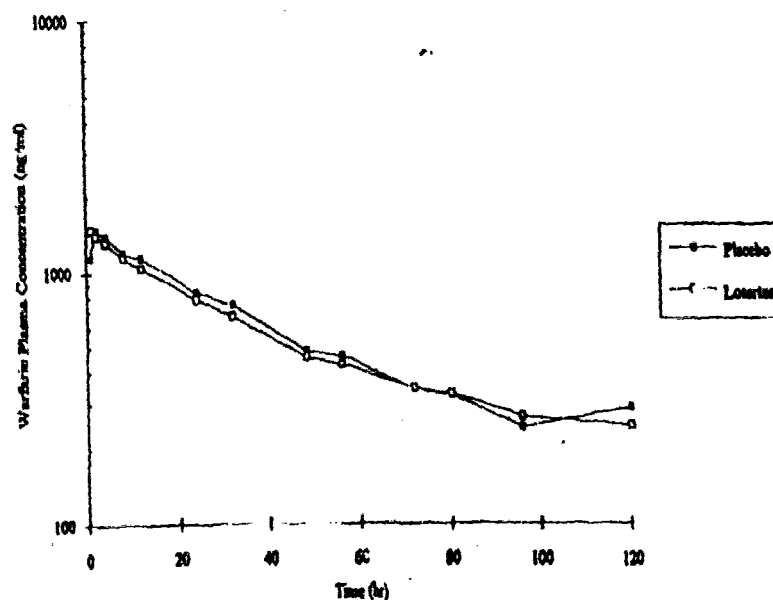
² Treatment effect estimates are geometric mean ratios for log-transformed values, otherwise treatment estimates reflect arithmetic mean differences (losartan - placebo)

³ Log transformed for analysis by ratio.

Mean (Arithmetic) Concentration vs. Time Profiles for the R Enantiomer



Mean (Arithmetic) Concentration vs. Time Profiles for the S Enantiomer

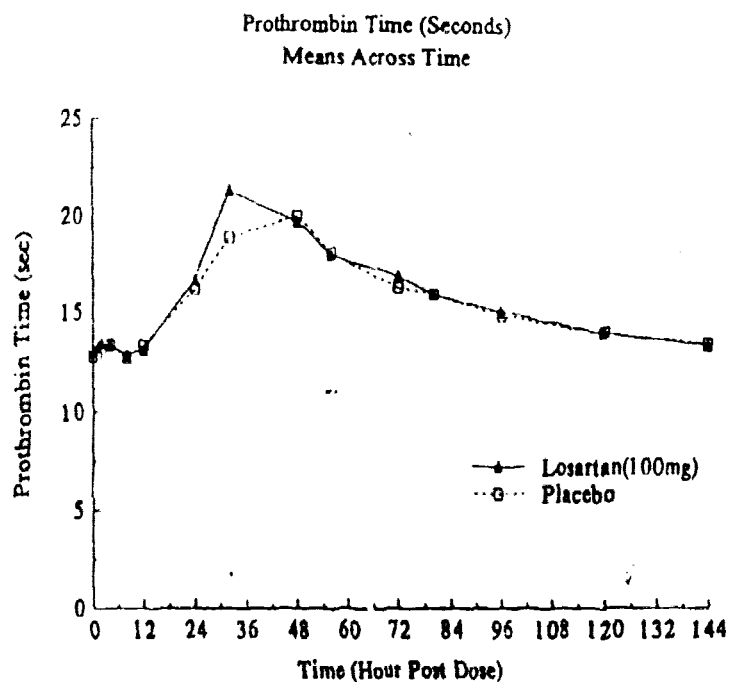
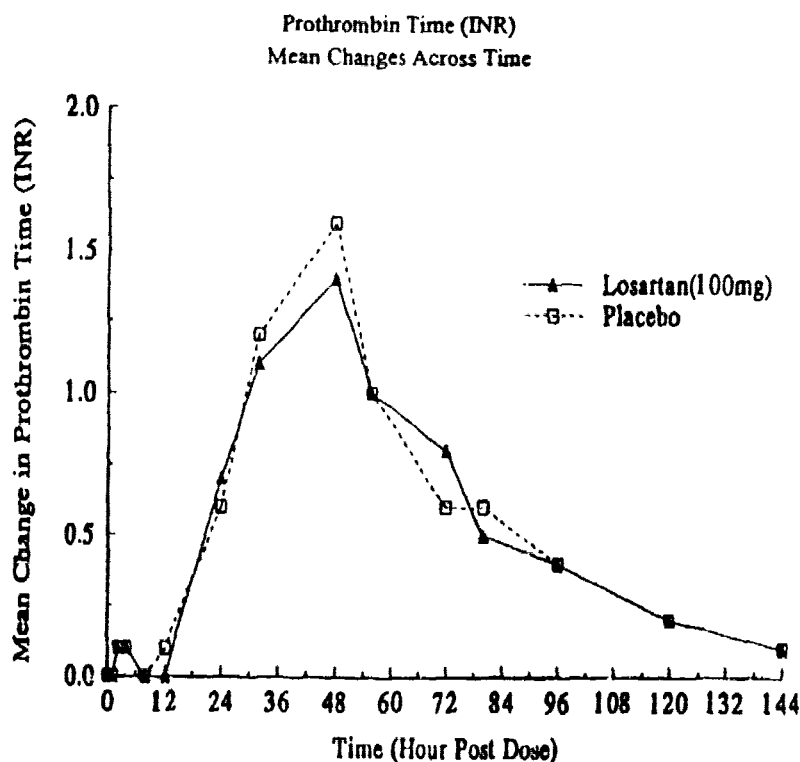


Least Square Mean Areas Under the Curve for Change from Baseline for Prothrombin Time and 90% Confidence Interval on the Difference Between Treatments (Losartan - Placebo)

Prothrombin Time Units	Least Squares Mean AUC (0-144 hr)		Mean Difference	90% CI on Difference
	Losartan	Placebo		
Seconds•hr	433.20	415.42	17.78	(-78.18, 113.74)
INP•hr	76.64	81.10	-4.46	(-17.74, 8.81)

Least Square Mean Maximal Change in Prothrombin Time and 90% Confidence Interval on the Difference Between Treatments (Losartan - Placebo)

Prothrombin Time Units	Least Squares Mean Maximum Change		Mean Difference	90% CI on Difference
	Losartan	Placebo		
Seconds	9.04	7.88	1.163	(-4.176, 6.501)
INR	1.37	1.73	-0.355	(-0.836, 0.126)



CONCLUSION: The study supports the sponsor's labeling claim that losartan does not affect the pharmacokinetics of (R) or (S) warfarin and the pharmacodynamics response to warfarin under the conditions of the study.

LOSARTAN - DIGOXIN INTERACTION STUDY

STUDY NUMBER: 079

VOLUME: 1.52

PAGES: 8692 - 9217

INVESTIGATOR AND LOCATION:

OBJECTIVES: To determine whether the serum concentrations of immunoreactive digoxin after intravenous and oral digoxin are altered by losartan.

FORMULATIONS:

Losartan 50 mg Tablets, Lot # GBC-Y568, Batch # E-4712

Matching Placebo Tablets, Lot # GBC-Y568, Batch # E-4644

Lanoxin Injection (Wellcome), Lot # 052-928

LANOXIN Tablet (Wellcome) Lot # 865-212

STUDY DESIGN: Double-blind, randomized, two-period study in 13 subjects. Each subject received losartan (50 mg tablet) or placebo daily for 15 days in each period. On Days 4 and 11 of each period, subjects received single 0.5 mg intravenous (Day 4) and oral (Day 11) doses of digoxin. Blood samples were drawn following intravenous digoxin on Day 4 at 0, 10, 20, 30, 45 minutes, and at 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, 72, and 96 hours; and following oral digoxin on Day 11 at 0, .5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, and 96 hours. Urine was collected pre-dose (-1-0) and at 0-6, 6-12, 12-24, 24-36, 36-48, 48-72 and 72-96 hours post digoxin dose on Days 4 and 11. Urine and plasma samples were stored at -20°C until analyzed.

ASSAYS: Radioimmunoassay.

PLASMA SAMPLES

Linearity: Satisfactory. Standard curve from 0.18 to 5 ng/ml.

Accuracy: Satisfactory. 110.0% at 0.5 ng/ml, 93.0% at 4.0 ng/ml.

Precision: Satisfactory. %CV - 5.2% at 0.5 ng/ml, 7.5% at 4.0 ng/ml.

Sensitivity: LOQ - 0.18 ng/ml.

Specificity: Satisfactory. Dihydrodigoxin (a metabolite of digoxin) approximately 4.5% cross-reactivity.

URINE SAMPLES

Linearity: Satisfactory. Standard curve from 0.25 to 8 ng/ml.

Accuracy: Satisfactory. 110.0% at 0.5 ng/ml, 110.0% at 4.0 ng/ml.

Precision: Satisfactory. %CV - 7.8% at 0.5 ng/ml, 5.5% at 4.0 ng/ml.

Sensitivity: LOQ - 0.25 ng/ml.

Specificity: Satisfactory. Dihydrodigoxin (a metabolite of digoxin) approximately 5.4% cross-reactivity.

The assays have been validated over the range of plasma and urine concentrations observed in the study.

DATA ANALYSIS: AUC, C_{max}, T_{max}, and % Dose excreted in urine were calculated.

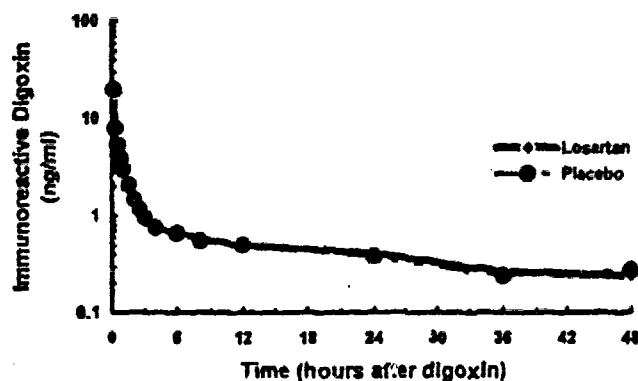
RESULTS:

Pharmacokinetic Parameters for Immunoreactive Digoxin After I.V. and Oral Digoxin During Losartan 50 mg and Placebo

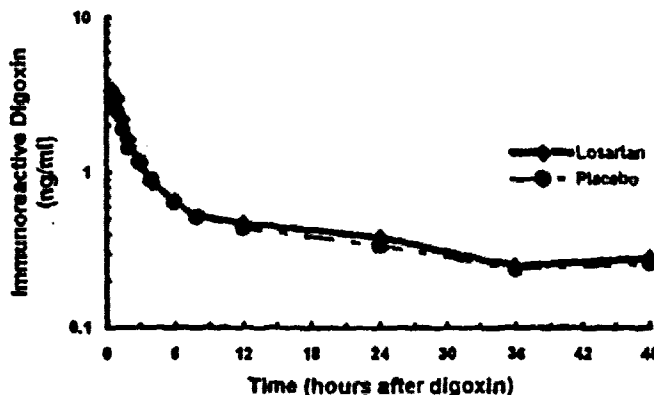
Parameter	With Losartan				Without Losartan			
	Day 4 (I.V.)	N	Day 11 (Oral)	N	Day 4 (I.V.)	N	Day 11 (Oral)	N
C _{max} (ng/mL)	—	—	3.46 (0.70)	11	—	—	3.07 (0.53)	11
AUC ₀₋₄₈ (ng·hr/mL)	28.76 (2.93)	10	23.63 (3.67)	11	28.45 (3.92)	9	22.43 (2.57)	9
AU (% dose)	54.01 (7.20)	7	51.16 (6.30)	8	51.89 (6.48)	7	46.26 (2.44)	8
T _{max} (hr)	—	—	0.64 (0.23)	11	—	—	0.86 (0.74)	11

Mean Plasma Immunoreactive Digoxin Concentrations During Treatment* with Losartan (50 mg/day) and Placebo

Intravenous Digoxin



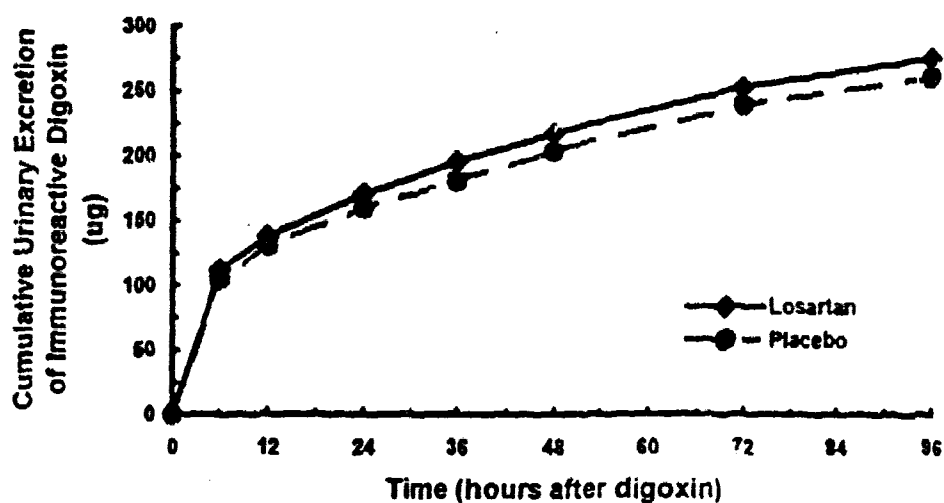
Oral Digoxin



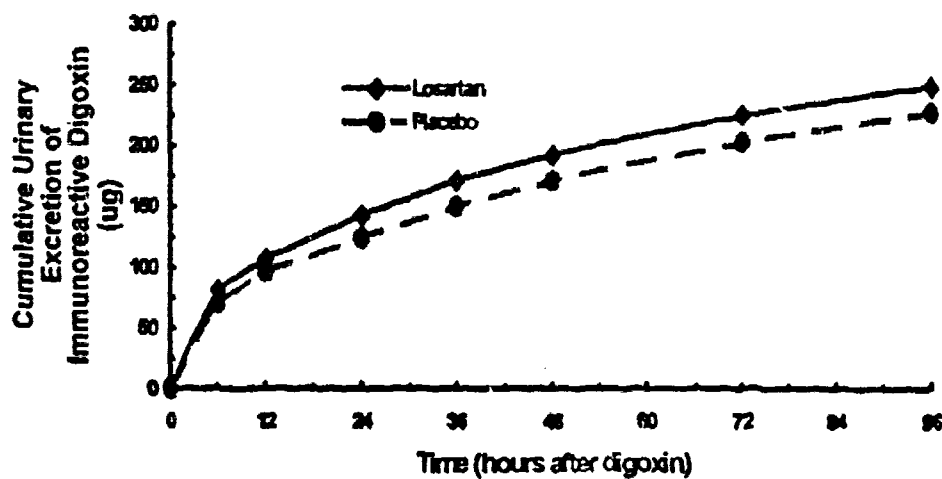
* Intravenous digoxin (0.5 mg/5 min) was administered on Day 4, oral digoxin (0.5 mg) was given on day 11.

Mean Cumulative Urinary Excretion of Immunoreactive Digoxin During Treatment* with Losartan (50 mg/day) and Placebo

Intravenous Digoxin



Oral Digoxin



* Intravenous digoxin (0.5 mg/5 min) was administered on Day 4; oral digoxin (0.5 mg) was given on day 11.

CONCLUSIONS: The study shows that losartan does not alter to a significant degree the pharmacokinetics of immunoreactive digoxin after intravenous or oral digoxin under the conditions of the study.

LOSARTAN - HYDROCHLOROTHIAZIDE (HCTZ) INTERACTION STUDY

STUDY NUMBER: 073 VOLUME: 1.53

PAGES: 9218-9810

INVESTIGATOR AND LOCATION:

OBJECTIVES: (i) To determine whether losartan alters the pharmacokinetics of HCTZ to a clinically significant degree. (ii) To determine whether HCTZ alters the pharmacokinetics of losartan to a clinically significant degree.

FORMULATIONS:

Losartan 50 mg Tablets, Formulation No. 0954FCT005C003, Control No. C-Y244

HCTZ 12.5 mg Tablets, Formulation No. CO954AFCT006C001, Control No. C-Y245

Losartan/HCTZ 50 mg/12.5 mg Tablets, Formulation No. 0954AFCT003B001, Control No. C-Y246

STUDY DESIGN: Open, randomized, three period crossover study in 12 subjects with mild to moderate hypertension and a washout period of seven days. Following a 2 week washout of their hypertension medications, subjects were randomized to receive 3 treatments: (a) one losartan 50 mg tablet daily for 7 days (b) one HCTZ 12.5 mg tablet daily for 7 days and (c) one combination losartan 50 mg/HCTZ 12.5 mg tablet daily for 7 days. Subjects were instructed follow a sodium replete diet 150-200 mEq/24 hours throughout the study. On the night prior to the seventh dose subjects fasted from midnight until 4 hours post the seventh dose. Following the seventh dose, blood samples were collected at 0, 15, 30, and 45 minutes and at 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, and 36 hours for MK-954 and E-3174 plasma concentrations, and at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18 and 24 hours for HCTZ plasma concentrations. Urine samples were collected for assay of MK-954, E-3174 and HCTZ concentrations predose and at 0-2, 2-4, 4-6, 6-8, 8-12, 12-18 and 18-24 hours post dose. Plasma and urine samples were stored at -20°C until analyzed.

ASSAYS: HPLC with UV detection.

PLASMA SAMPLES-LOSARTAN (MK-954) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curves from 5 to 1000 ng/ml

Accuracy: Satisfactory. 95.5% at 20 ng/ml, 95.9% at 800 ng/ml for MK-954; and 98.5% at 20 ng/ml, 96.3% at 800 ng/ml.

Precision: Satisfactory. %CV-6.4% at 20 ng/ml, 4.8% at 800 ng/ml for MK-954; and 5.8% at 20.0 ng/ml, 4.5% at 800 ng/ml.

Sensitivity: LOQ - 5 ng/ml for MK-954 and E-3174.

Specificity: Satisfactory. Chromatograms submitted.

URINE SAMPLES-LOSARTAN (MK-954) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curve: from 20 to 2000 ng/ml for MK-954; and 10 to 2000 ng/ml for E-3174.

Accuracy: Satisfactory. 90.5% at 40 ng/ml, 93.1% for 1600 ng/ml for MK-954; and 93.0% at 40 ng/ml, 95 % at 1600 ng/ml.

Precision: Satisfactory. %CV-7.0% at 40 ng/ml, 2.8% at 1600 ng/ml for E-3174. MK-954; and 3.7% at 40 ng/ml, 3.5% at 1600 ng/ml for E-3174.

Sensitivity: LOQ - 20 ng/ml for MK-954; 10 ng/ml for E-3174.

Specificity: Satisfactory, Chromatograms submitted.

PLASMA SAMPLES-HYDROCHLOROTHIAZIDE (HCTZ):

Linearity: Satisfactory. Standard curves from 2 to 100 ng/ml.

Accuracy: Satisfactory. 101.3% at 3.75 ng/ml, 101.7% at 75 ng/ml.

Precision: Satisfactory. %CV-3.4% at 3.75 ng/ml, 5.5% at 75 ng/ml.

Sensitivity: LOQ - 2.0 ng/ml.

Specificity: Satisfactory, Chromatograms submitted.

URINE SAMPLES-HYDROCHLOROTHIAZIDE (HCTZ):

Linearity: Standard curves from 0.1 to 20 µg/ml.

Accuracy: Satisfactory. 101.3% at 0.75 µg/ml, 95.6% at 15 µg/ml.

Precision: Satisfactory. %CV-3.3% at 0.75 µg/ml, 5.3% at 15 µg/ml.

Sensitivity: LOQ - 0.10 µg/ml.

Specificity: Satisfactory, Chromatograms submitted.

DATA ANALYSIS: AUC_∞, C_{max}, t_{1/2}, CL_r, λ and %Dose excreted in urine were calculated.

RESULTS:

	50-mg MK-954 Tablets Once a Day for 7 days		12.5-mg HCTZ Tablets Once a Day for 7 Days	Combination Tablets of 50 mg MK-954 and 12.5 mg HCTZ Once a Day for 7 Days			
	MK-954	E-3174	HCTZ	MK-954	E-3174	HCTZ	
C _{max} , ng/ml*	223.7 ± 81.9	211.5 ± 72.6	87.5 ± 28.3	240.2 ± 85.3	215.8 ± 68.5	79.0 ± 28.8	
T _{max} , hr	1.0 ± 0.5	3.9 ± 1.4	1.9 ± 0.6	1.2 ± 1.2	3.7 ± 1.1	2.4 ± 0.8	
AUC _{0-∞} , ng-hr/ml*	441.5 ± 173.1	1684.6 ± 451.6	634.0 ± 186.8	449.6 ± 163.8	1724.8 ± 460.9	525.8 ± 134.5	
λ, hr ⁻¹	0.3378 ± 0.1152	0.0943 ± 0.0310	0.0671 ± 0.0113	0.3310 ± 0.0730	0.0943 ± 0.0331	0.0711 ± 0.0158	
t _{1/2} , hr [†]	2.1 ± 0.7	7.4 ± 2.4	10.3 ± 1.8	2.1 ± 0.5	7.3 ± 2.6	9.7 ± 2.1	
CL _r , ml/min	55.8 ± 23.4	20.1 ± 2.7	227.0 ± 54.8	51.5 ± 11.5	18.1 ± 3.4	243.0 ± 56.4	
Urinary Recovery _{0-24 hr}	mg [‡]	1.448 ± 0.467	2.037 ± 0.652	8.245 ± 1.528	1.407 ± 0.461	1.851 ± 0.502	7.513 ± 1.790
	% Dose	2.9 ± 0.9	4.3 ± 1.4	66.0 ± 12.2	2.8 ± 0.9	3.9 ± 1.1	60.1 ± 14.3
AUC Geometric mean ratio (Combo/Single) and confidence interval limits [§]	-	-	-	1.02 (0.952, 1.09)	1.02 (0.964, 1.09)	0.833 (0.771, 0.900)	
C _{max} Geometric mean ratio (Combo/Single) and confidence interval limits [§]	-	-	-	1.07 (0.985, 1.17)	1.03 (0.943, 1.12)	0.889 (0.789, 1.00)	
Urinary recovery geomet- ric mean ratio (Combo/ Single) and confidence interval limits [§]	-	-	-	-	-	0.898 (0.790, 1.02)	

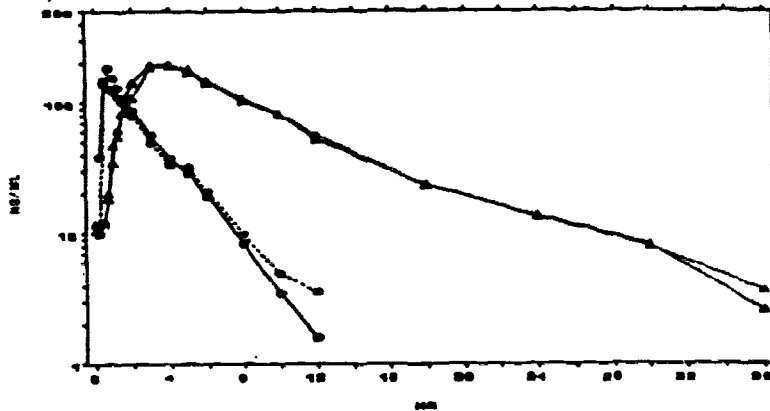
*C_{max}, AUC and urinary recovery normalized to 50.0 mg for MK-954 and E-3174, and to 12.50 mg for HCTZ based on assayed potencies of the formulations.

[†]Harmonic mean and pseudo standard deviation.

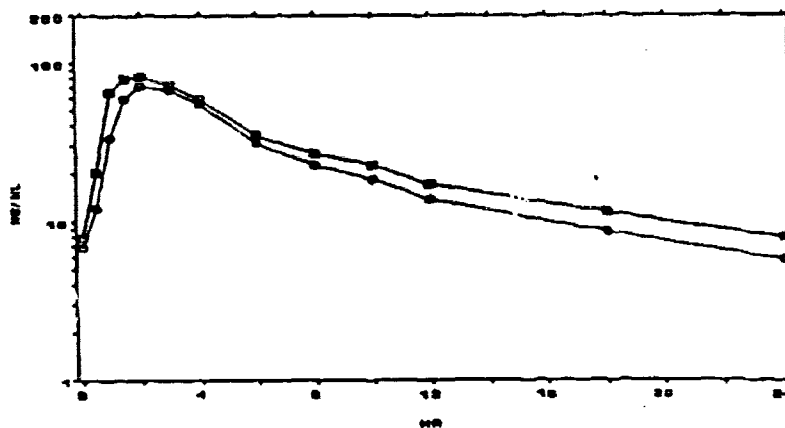
[§]90% Confidence interval limits.

Mean Plasma Concentration vs. Time Profiles in Hypertensive Patients for Losartan, L-158,641, and Hydrochlorothiazide (HCTZ) Following Once-a-Day Administration of Losartan (50 mg), HCTZ (12.5 mg) and a Combination Tablet of Losartan/ HCTZ (50 mg/12.5 mg) for 7 Days

Losartan/ L-158,641



Hydrochlorothiazide



Key: Losartan/ L-158,641-single tablet = ○/ Δ; Losartan/ L-158,641-combination tablet = ●/▲
 Hydrochlorothiazide-single tablet = □; Hydrochlorothiazide-combination tablet = ○

CONCLUSIONS: There is no significant pharmacokinetic between losartan and HCTZ when both drugs are co-administered under the conditions of the study.

PHARMACOKINETIC / PHARMACODYNAMIC RELATIONSHIP

INTRODUCTION: In relating effects of losartan in humans to plasma concentrations of losartan and/or E-3174 (or L-158,641) (the active metabolite), a number of factors must be considered in the analyses: (i) both losartan and E-3174 are active and potent angiotensin II antagonists, (ii) the intrinsic potency of E-3174 is greater (by 5 to 10-fold) than losartan, (iii) only free drug is available for distribution to, and interaction with the receptor, (iv) losartan is a competitive antagonist while E-3174 is a non-competitive antagonist, (v) the elimination of E-3174 is slower ($t_{1/2} = 6-9$ hrs, $CL = 50$ ml/min; concentration can be measured at trough at steady state) than the elimination of losartan ($t_{1/2} = 2$ hrs, $CL = 600$ ml/min, only detectable in plasma through 12 hours after dosing, depending on the dose).

Concentration-effect analyses done by the sponsor have focused only on E-3174, or have utilized a semi-additive approach (for example, $[E-3174] + [losartan]/2$) to account for the presence of both antagonists.

STUDY #006: This study was designed to investigate the capacity of higher single doses (40, 80, 120 mg) of losartan to antagonize pressor responses to bolus injections of angiotensin II which increase systolic blood pressure approximately 20-30 mmHg. The systolic blood pressure responses (% inhibition) to exogenous angiotensin II and concentration of E-3174 were fit to a Hill-Sigmoid-Emax model (Figure 1). Mean model parameters (range) for E-3174 were: $E_{max} - 91\%$ (66-100); $EC_{50} - 32$ ng/ml (1-99 ng/ml); Hill coefficient - 0.9 (0.13-3.0). The time-integrated (i. e. AUC) response to losartan was fit to an E_{max} model (Figure 2) and the model shows that the 80- and 120-mg doses of losartan resulted in similar average levels of inhibition of the pressor response over 9-hour period. Model parameters ($\div 9$ hours) were: $E_{max} - 774\% \cdot hr$ (86); $EC_{50} - 577$ ng*hr/ml (64 ng/ml).

STUDY #035: In this study forearm blood flow responses to brachial artery infusions of angiotensin I, II and bradykinin were determined, with blood collected for measurement of plasma renin concentration (PRC), losartan and E-3174 concentrations at the time of agonist infusions. Treatments included placebo, 20 mg and 100 mg losartan and 10 mg enalapril. Table 1 shows the mean (or median) effects, and losartan and E-3174 concentration obtained from this study. The average pre- and post-angiotensin I (pre-, post-AI) blood flow responses are expressed as a ratio relative to the non-infused arm. ED_{50} is the median angiotensin I infusion rate which was estimated (by interpolation or extrapolation) to result in a blood flow ratio of 0.5. PRC ratio is the PRC measurement just prior to angiotensin I infusion divided by the predose PRC measurement. Figures 3-5 are scatter plots that show that both concentration-effect and dose-effect relationships are apparent and that the results are consistent with the E_{max} model derived above with near-maximal inhibition achieved at concentrations above 250 ng/ml.

STUDY # 013 AND STUDY #017: In these studies the tolerability of 20-minute IV infusions of losartan (40 mg, Study #013) and E-3174 (80 mg, Study #017) was assessed. Figure 6 shows that high losartan and E-3174 concentrations achieved at the end of the infusion were not associated with the greatest changes in blood pressure during the observation period thus indicating that some distribution of losartan/E-3174 is necessary for the expression of this presumed pharmacodynamic effect in healthy subjects.

STUDY #011: Patients with mild to moderate essential hypertension were treated for 8 weeks with losartan doses of 0 (placebo), 10, 25, 50, 100, and 150 mg/day, or 20 mg enalapril. In 181 patients, plasma was collected for measurement of losartan and E-3174 concentrations at trough (predose) and peak (about 6 hours postdose) blood pressure response. The data obtained from this study (Table 2) shows that mean drug concentration (losartan and E-3174) increased with increasing dose of losartan and an apparent dose-response relationship for the antihypertensive effect at peak and trough. The scatter plots of peak and trough E-3174 concentrations versus change at peak and trough in supine diastolic blood pressure (Figure 7) show that individual peak or trough drug concentrations do not correlate with antihypertensive effect in this population.

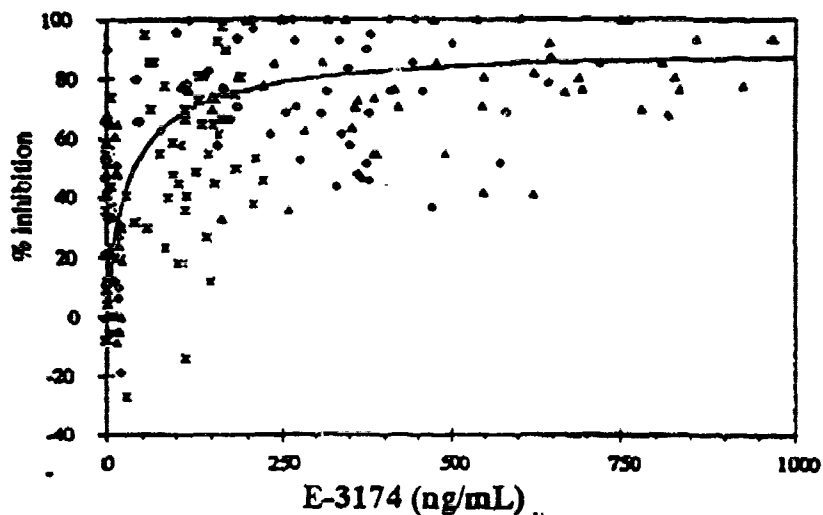
STUDY #043: In this study, plasma drug concentration, blood pressure effects and Renin Angiotensin Aldosterone System (RAAS) mediators (i.e. PRA, and plasma concentrations of angiotensin II and aldosterone) were measured during the 8-12 hours after dosing following the first and last (6 weeks) dose of once-daily placebo and 25 and 100 mg losartan. The effects of losartan on blood pressure and RAAS mediators are summarized in Figures 8-11 (for each individual AUC for effect, an individual AUC for drug concentration ($[\text{losartan}]_{/2} + [\text{E-3174}]$) over the appropriate interval was calculated) from it can be concluded that at 6 weeks, as the concentration AUC of $[\text{losartan}]_{/2} + [\text{E-3174}]$ increased, the observed effect also increased.

STUDY #069: In this study 12 hypertensive patients received a 20 mg dose of E-3174 as an intravenous infusion at a rate of 5 mg/hour and 8 received placebo. Blood pressure was measured for 12 hours following initiation of the infusion. Figure 12 shows that supine diastolic blood pressure declined as the drug concentrations increased and that there was a further decrement in blood pressure after termination of the infusion (even with adjustment for diurnal changes in the placebo group). Plotting supine diastolic blood pressure change vs. E-3174 concentration (Figure 13) resulted in an open hysteresis plot with a somewhat linear portion up to achievement of maximal concentrations, followed by additional decreases in blood pressure as concentration declined.

CONCLUSION: The results of the studies summarized above support the sponsor's labeling claims on the relationship between plasma drug concentration (losartan and E-3174) and pharmacodynamic effect.

Figure 1

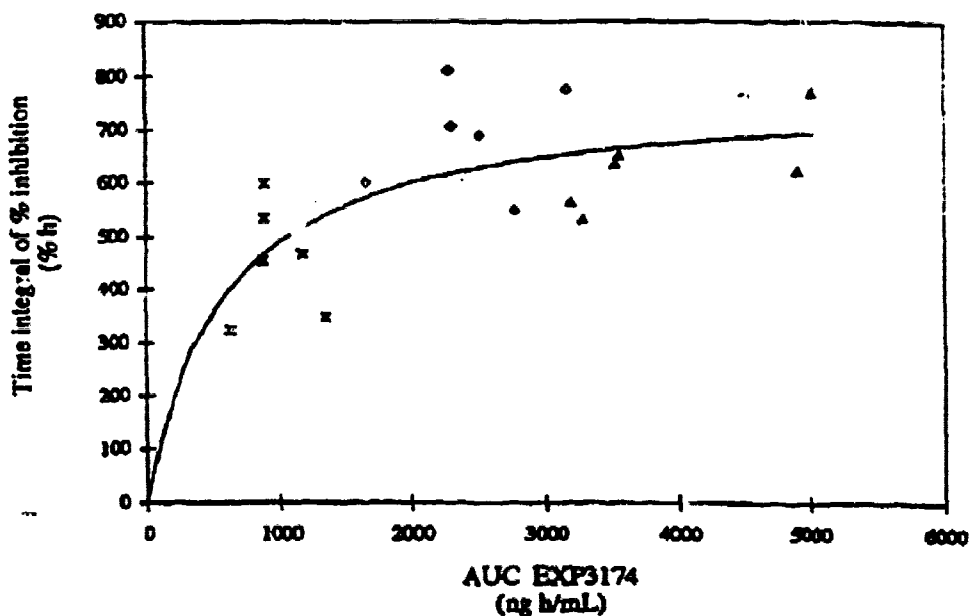
Inhibition of Systolic Pressor Responses to Angiotensin II as a Function of E-3174 (L-158,641) Concentration -- Brunner Protocol #006 [References C-5; C-43]



Solid line is Hill equation fit to the data
* = 40 mg; ◊ = 80 mg; Δ = 120 mg losartan

Figure 2

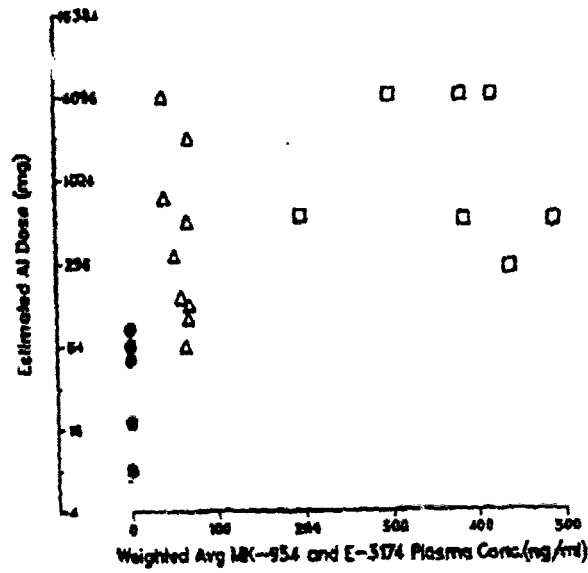
Inhibition of Systolic Pressor Responses to Angiotensin II Injections: AUC for Inhibition vs. AUC for E-3174 (L-158,641) -- Brunner Protocol #006 [References C-5; C-43]



Solid line is Hill equation fit to the data
* = 40 mg; ◊ = 80 mg; Δ = 120 mg losartan

Figure 5

Angiotensin I ED₅₀ vs. Plasma Concentration of Losartan + L-158,641 (Weighted Average) Ritter Protocol #035 [Reference C-13]

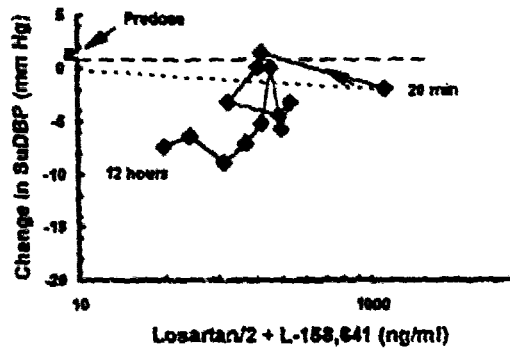


○ = placebo; Δ = 20 mg losartan; □ = 100 mg losartan

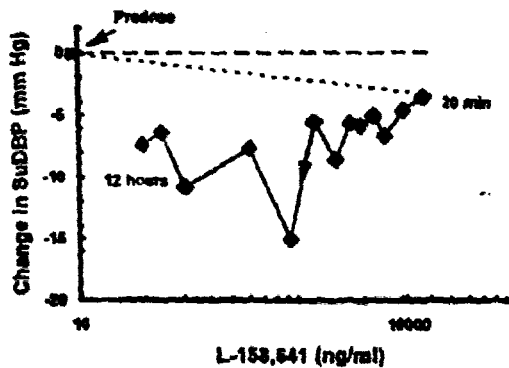
Figure 6

Mean Changes in Supine Diastolic Blood Pressure vs. Plasma Drug Concentration Following 20-minute Intravenous Infusions of Losartan (40 mg) and L-158,641 (80 mg) Protocols # 013 (Losartan) [Reference C-8] and #017 (L-158,641) [Reference C-11]*

Losartan- 40 mg/20 minutes



L-158,641- 80 mg/20 minutes



* Solid lines connect actual data points; dashed lines connect data pre-infusion (i.e., no changes in BP, no drug in blood) with the first measurement after start of infusion. Graphs are redrawn from: Top - [Reference C-8: Appendix 1, Tables 4 and 6; Appendix 3] and, Bottom - [Reference C-11: Appendix 1, Table 5; Appendix 3].

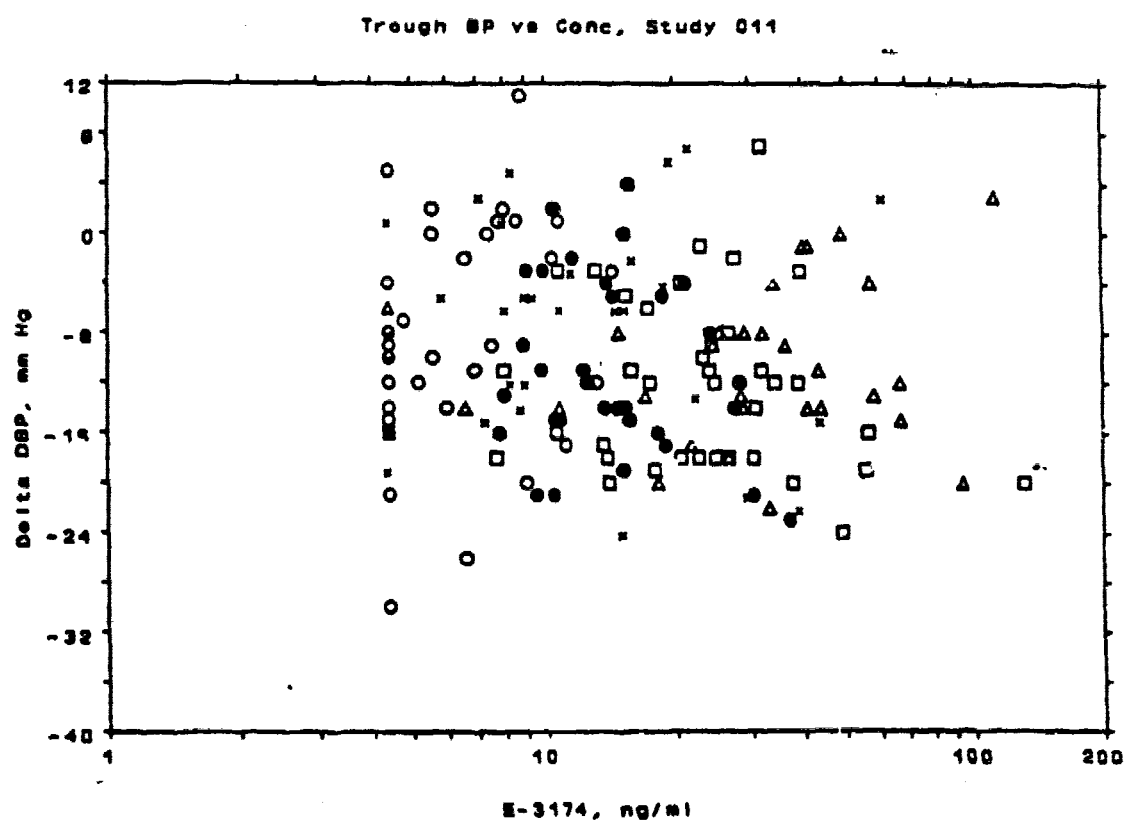
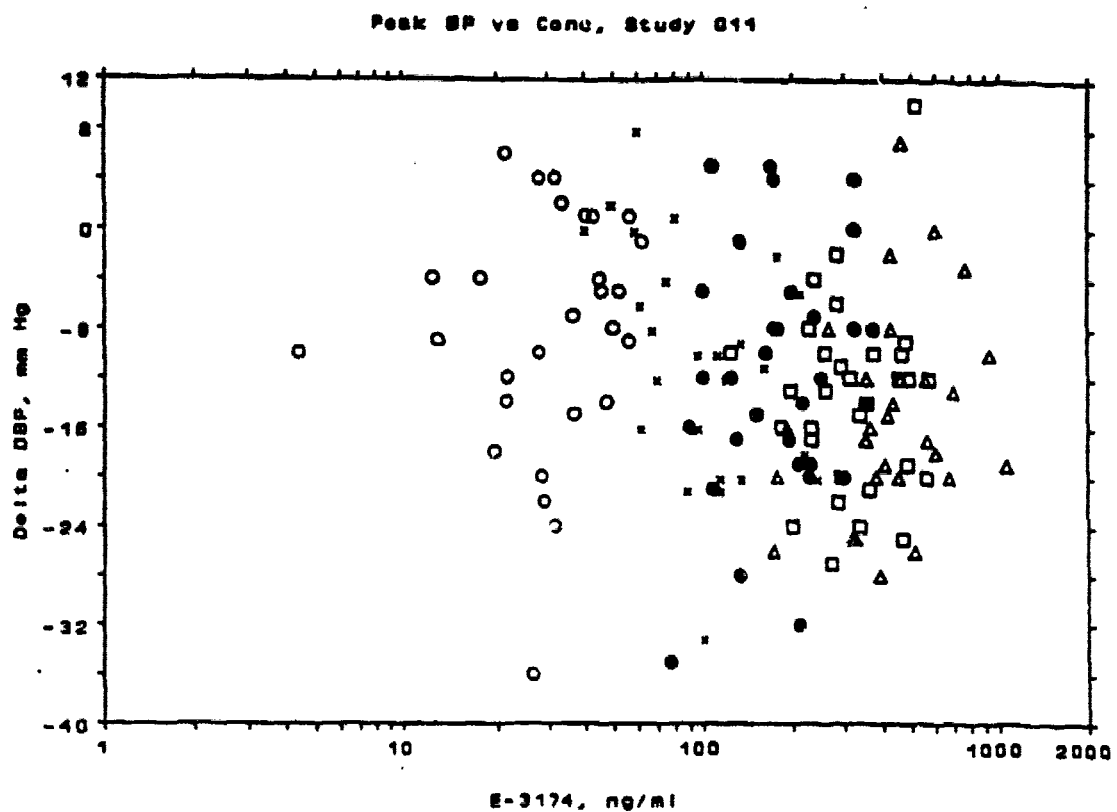


Figure 7 Peak (5-8-hr) and Trough Change in Diastolic Blood Pressure Versus Plasma E-3174 Concentration Relationship in Patients Treated With 10 mg (O), 25 mg (x), 50 mg (●), 100 mg (□) and 150 mg (Δ) of Oral MK-954 Once a Day for Eight Weeks. Concentrations Below the Detection Limit Are Plotted As 4.4 ng/ml.

Figure 8

Change (difference) in Supine Diastolic Blood Pressure vs. Weighted Average Drug Concentration AUC after 6 Weeks Treatment with Placebo (X), 25 mg Losartan (Δ) and 100 mg Losartan ($\bullet$) -- (RAAS Study- Protocol #043) [Reference C-28]

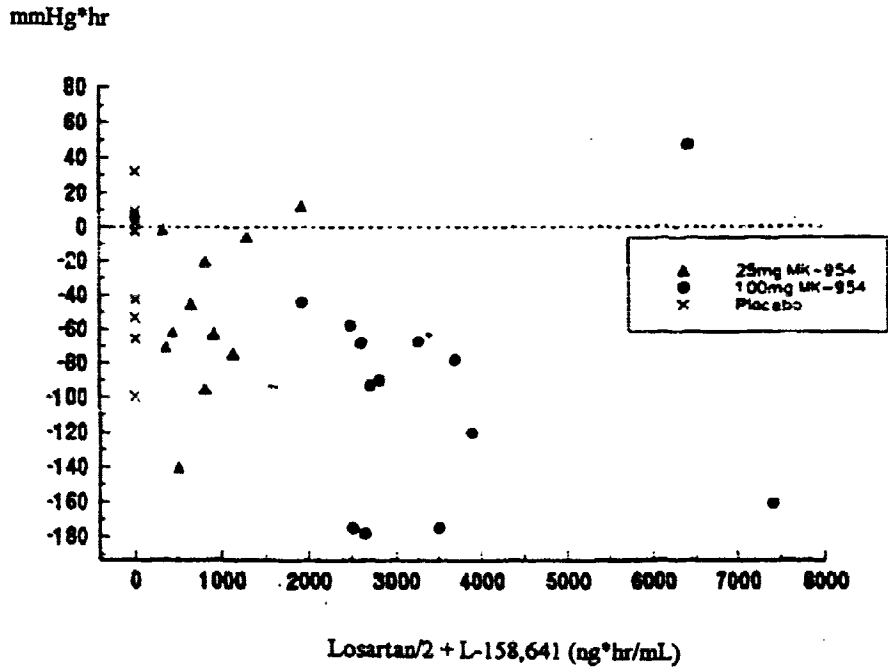


Figure 9

Change (ratio) in Supine Plasma Angiotensin II Concentration (Direct RIA) vs. Weighted Average Drug Concentration AUC after 6 Weeks Treatment with Placebo (X), 25 mg Losartan (Δ) and 100 mg Losartan ($\bullet$) -- (RAAS Study- Protocol # 043) [Reference C-28]

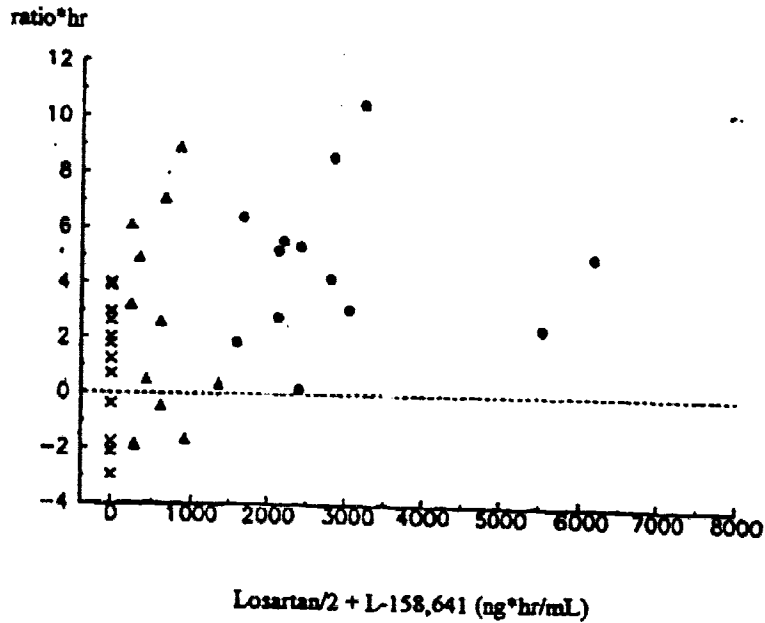


Figure 10

Change (ratio) in Supine Plasma Renin Activity vs. Weighted Average Drug Concentration (AUC) after 6 Weeks Treatment with Placebo (X), 25 mg Losartan ($\blacktriangle$) and 100 mg Losartan ($\bullet$) -- (RAAS Study- Protocol # 043) [Reference C-25]

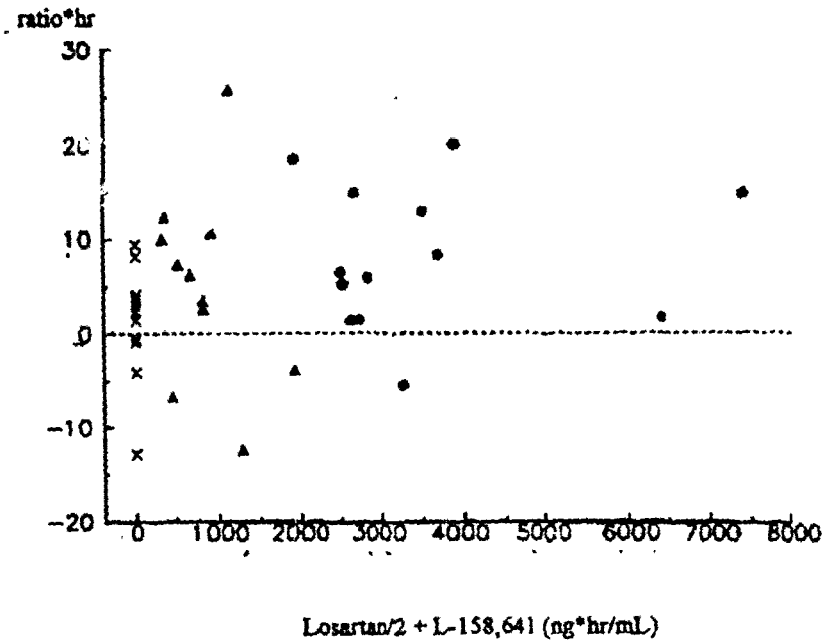


Figure 11

Change (difference) in Supine Plasma Aldosterone Concentration vs. Weighted Average Drug Concentration (AUC) after 6 Weeks Treatment with Placebo (X), 25 mg Losartan ($\blacktriangle$) and 100 mg Losartan ($\bullet$) -- (RAAS Study- Protocol # 043) [Reference C-25]

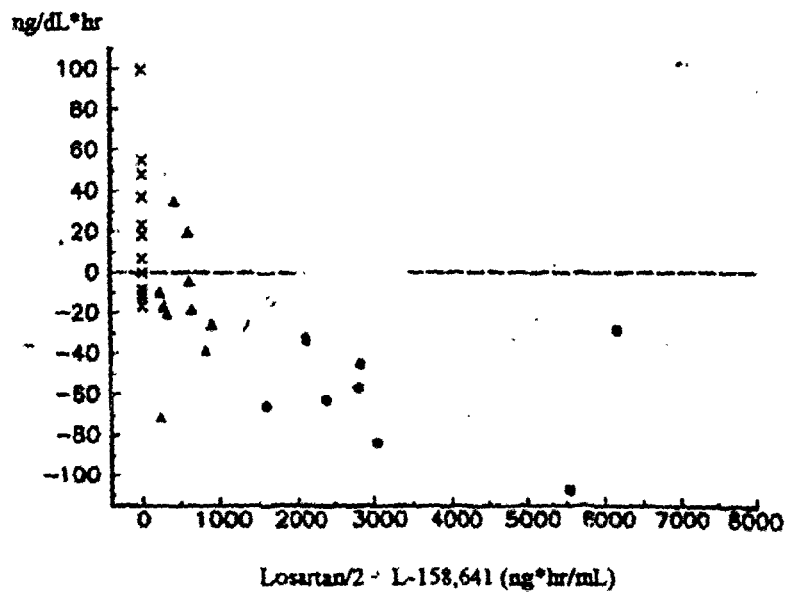
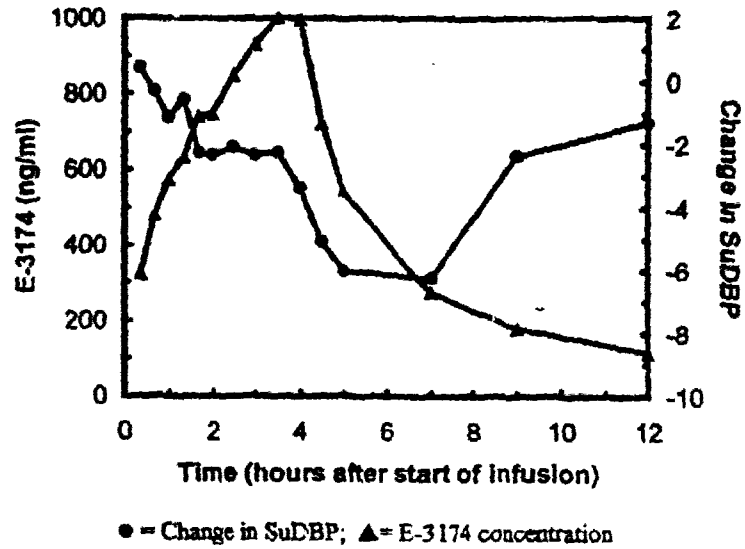


Figure 12

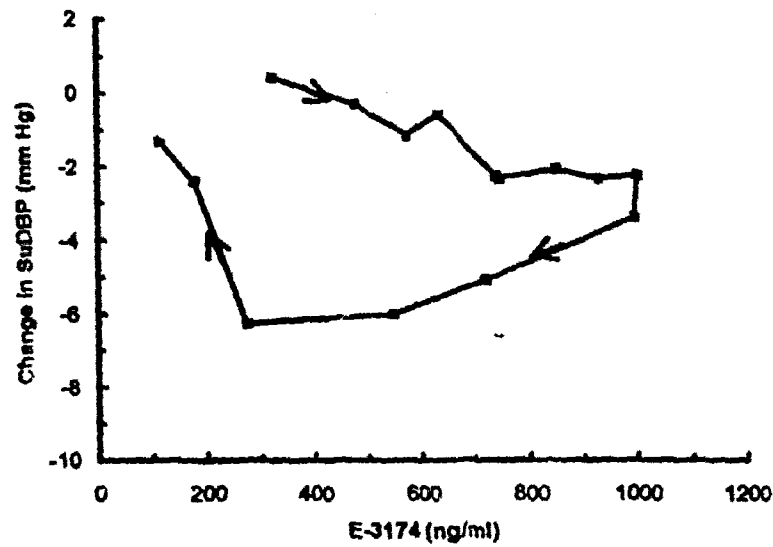
Mean Plasma L-158,641 (E-3174) Concentrations and Changes in Supine Diastolic Blood Pressure (placebo-adjusted) During and After Infusion of L-158,641 at 5 mg/hour for 4 Hours-- (Protocol # 069) [Reference C-27]*



*Drawn from [Reference C-27: p. C-19317, Table 8; Appendix 5]

Figure 13

Mean Plasma L-158,641 Concentrations vs. Changes in Supine Diastolic Blood Pressure (placebo-adjusted) during and after infusion of L-158,641 at 5 mg/hour -- (Protocol # 069) [Reference C-27]*



* Redrawn from data in Figure C-63 [Reference C-27: p. C-19317, Table 8; Appendix 5]

Table 1

Summary of Plasma Concentration and Angiotensin Antagonism Data from Forearm Blood Flow Study – Ritter #035 [Reference C-13]*

	Drug Concentration				Responses to Angiotensin I (AI)			Plasma Renin
	Losartan (ng/mL)		L-158,641 (ng/mL)		Blood Flow Ratio		ED ₅₀ (pmol/min)	
	Pre-AI	Post-AI	Pre-AI	Post-AI	AI: 16 pmol/min	AI: 64 pmol/min		
	PRC Ratio							
PBO					0.5	0.37	8	0.95
20 mg	16.2	10.4	49.9	57.2	0.78	0.63	292	3.09
100 mg	41.5	21.5	413.8	312.7	0.92	0.81	553	7.33

* All values are means except ED₅₀ which is median.

Table 2

Mean Plasma Drug Concentrations and Mean Changes in Supine Diastolic Blood Pressure (SuDBP) in Hypertensive Patients given Losartan for 8 Weeks – Multicenter Study #011 [Reference C-56]

Dose (mg)	N*	Drug Concentrations (ng/mL)				Change in SuDBP (mmHg)	
		Trough		Peak		Trough	Peak
		Losartan	L-158,641	Losartan	L-158,641		
placebo	75	-	-	-	-	-5.8	-4.7
10	79	<5	5.3	6.1	33.5	-7.9	-7.3
25	80	<5	14.9	17	111.0	-7	-9.9
50	77	<5	14.6	29.9	196.7	-10.2	-11.9
100	86	<5	27.2	39.9	337.9	-10.0	-10.5
150	81	<5	38	48.2	475.7	-10.0	-13.1
Enal 20	82	-	-	-	-	-11.2	-16.2

*N is the number of patients with blood pressure data; the number with concentration data ranged from 32 to 40 patients/dose.

HUMAN LIVER MICROSOMAL METABOLISM

VOLUME: 1.50

PAGES: 7849 - 7861

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OBJECTIVE: To investigate the mechanism of the biotransformation of losartan (L-158,086) to its pharmacologically more potent metabolite (l-158,641 or E-3174) and to identify the enzyme(s) responsible for this conversion.

PROCEDURES:

Losartan was incubated with human liver microsomes and microsomes containing recombinant human P-450 isoforms at 2-4 mg/ml protein in 0.1M phosphate buffer, pH 7.4, containing 150 mM KCl and 1 mM EDTA. The incubation was carried out in the presence of NADPH and oxygen as well as in the absence of either cofactor.

Both losartan and its putative aldehyde intermediate (L-158,610) were incubated with human liver microsomes under an atmosphere of $^{18}\text{O}_2$.

L-158,610 was incubated with microsomes isolated from cells containing recombinant isoforms of human cytochrome P-450 (CYP1A1, 1A2, 2B6, 2C8, 2C9, 2D6, 2E1, and 3A4).

Human liver microsomal incubations with losartan were performed in the presence of specific inhibitors of cytochrome P-450. Microsomes were either pretreated for 30 minutes with mechanism based inhibitors (gestodene, 17α -ethynylestradiol, troleandomycin, 1-aminobenzotriazole, and SKF525A) or preincubated for 5 minutes with competitive inhibitors (ketoconazole - CYP2C inhibitor, and sulfaphenazole - CYP3A4 inhibitor). The experiment with sulfaphenazole (1, 5, and 50 μM) was repeated using L-158,610 and L-158,036. Aliquots of the incubation medium were analyzed using HPLC and mass spectrometry.

RESULTS:

**Metabolism of L-158,086 to L-158,641
by Human Liver Microsomes-
Effect of Cytochrome P-450 Inhibitors and Cofactors**

Incubation ^a containing	nmol L-158,641 <u>formed</u>	<u>% of control</u>
- NADPH	0.02	3
+ NADPH regen. system	0.75	100
+ Gestodene (100 μM) ^b	0.35	47
+ Ketoconazole (200 μM)	0.21	28
+ 17α-ethynlestradiol (100 μM) ^b	0.30 ^c	40
+ TAO (100 μM) ^b	0.60 ^c	80
+ TAO (1mM) ^b	0.40	53
+ Sulfaphenazole (1 μM)	0.43 ^c	57 (89) ^d
+ Sulfaphenazole (5 μM)	0.19 ^c	25 (79) ^d
+ Sulfaphenazole (50 μM)	0.10 ^c	14 (48) ^d
+ SKF 525A (100 μM) ^b	0.40 ^c	53
+ 1-Aminobenzotriazole (500 μM) ^b	0.30 ^c	40

^a Incubations consisted of 2 mg/ml microsomal protein (0.38 nmol P-450/mg protein) in 0.1 M phosphate buffer, pH 7.4, containing 150 mM KCl and 1 mM EDTA. Microsomes were typically preincubated with substrate for 5 minutes in a reciprocating-water bath at 37 degrees C. Metabolism was initiated by addition of an NADPH regenerating system consisting of 1.3 mM NADP, 3.3 mM glucose-6-phosphate and MgCl₂, and 0.5-1 u/ml glucose-6-phosphate dehydrogenase. Incubation time varied from 20-40 minutes.

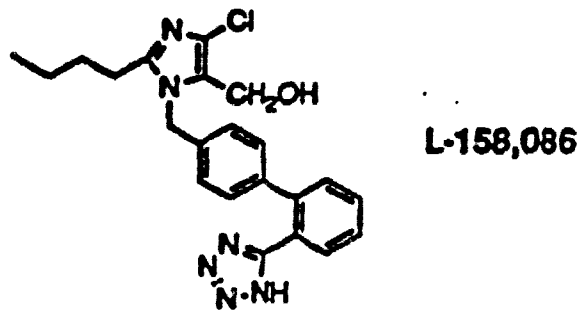
^b Mechanism based inhibitors of cytochrome P-450 were incubated with microsomes and NADPH regenerating system for 30 minutes at 37 degrees C prior to addition of substrate.

^c Data normalized to control value.

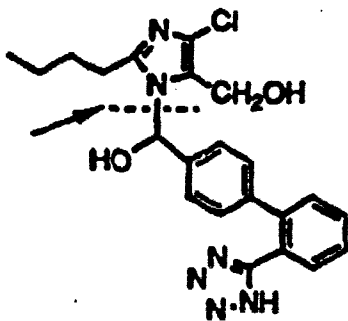
^d Values for incubation of L-158,610 in bracket.

Notebook/Page: 15216/94-99, 142-148 16515/164-169

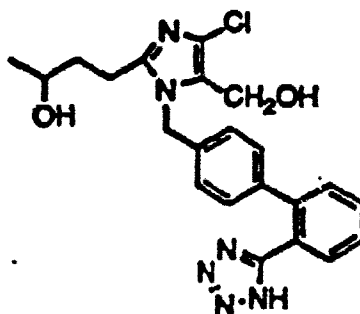
SUMMARY OF METABOLITES FORMED IN LIVER SLICE INCUBATIONS



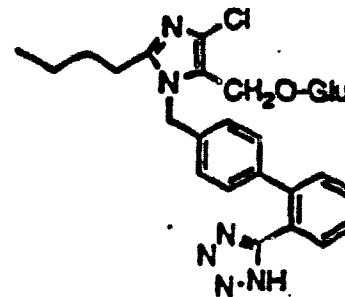
Liver
Slices



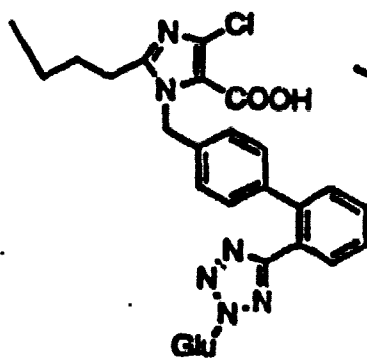
M1
Metabolite is unstable
and fragments (at arrow)
giving L-688,160 and
L-706,591



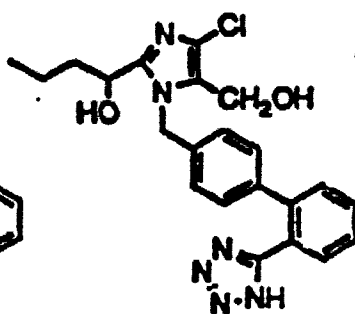
M2
L-158,795



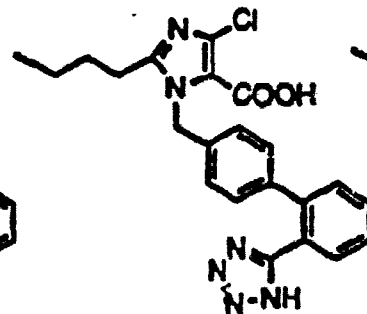
M3
L-158,782



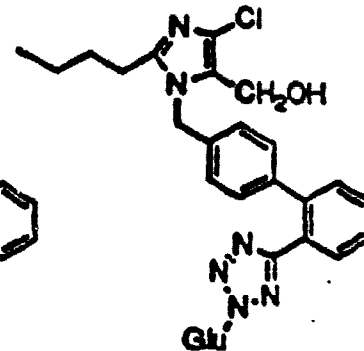
M4
L-158,781



M5
L-158,796



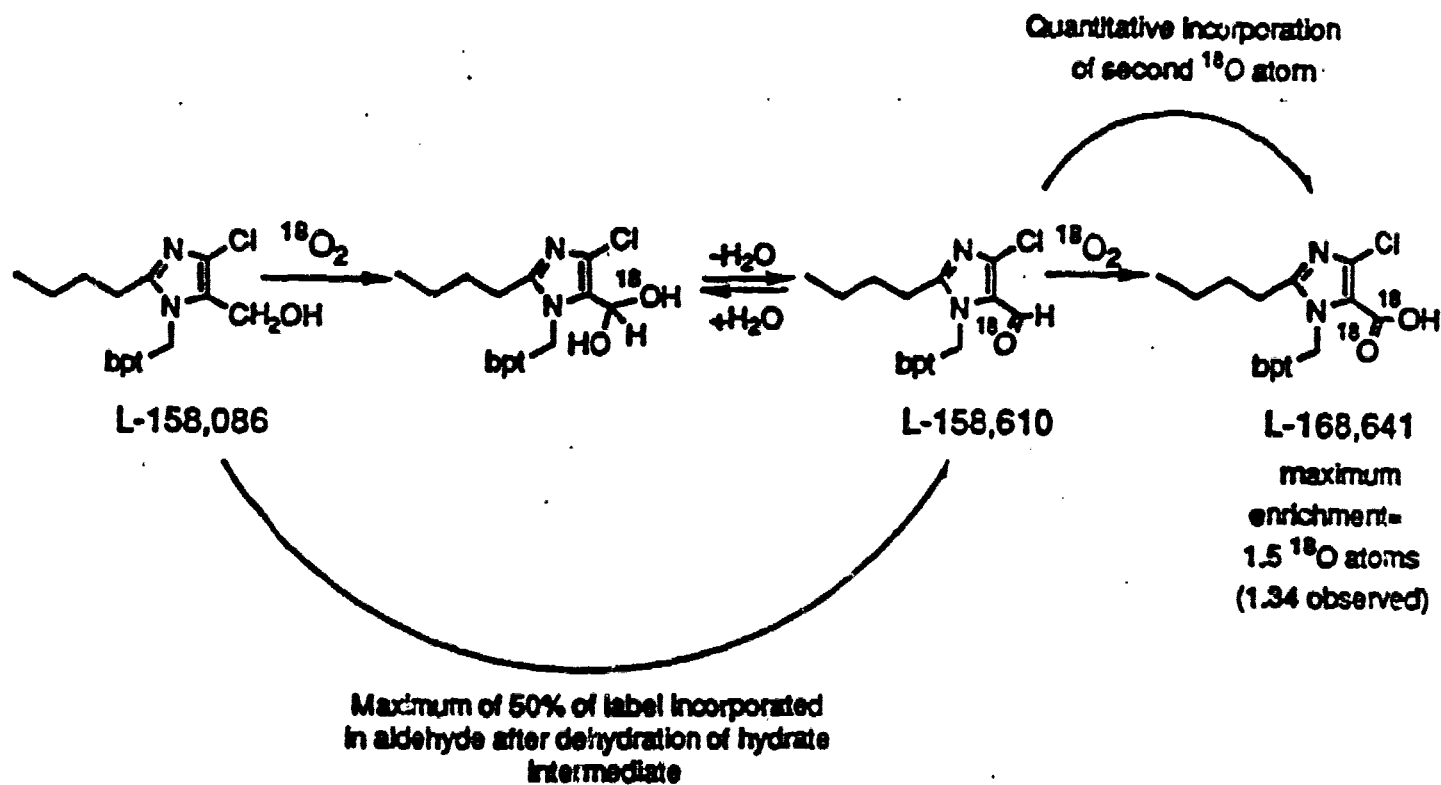
M6
L-158,641



M7
L-158,783

Glu= 2β-glucuronic acid

**Proposed Mechanism for the Biotransformation
of L-158,086 and L-158,610 to L-158,641**



bpt = biphenyl tetrazole

CONCLUSIONS: Conversion of losartan to L-158,641 is catalyzed by cytochrome P-450 and both CYP3A and 2C isozymes are involved in this biotransformation. Both CYP2C9 and 3A4 can metabolize L-158,610 to L-158,641.

IN VITRO PROTEIN BINDING

REPORT NUMBER: DMP 93-008
AMANDA NUMBER: 1009301002

VOLUME: 1.53

PAGES: 9993 - 10014

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PROCEDURES:

Methanolic stock solutions of ^{14}C -losartan or ^3H -E3174 were added to glass test tubes and dried under nitrogen. Plasma from human volunteers (N=4) was added to give final concentrations of 0.050, 0.500, 1.000, 2.00, and 5.00 or 0.100, 1.00, and 10.000 $\mu\text{g/ml}$ of losartan or E-3174 respectively. The samples (in triplicate) were mixed, and incubated for 30 minutes at 37°C and the fraction unbound was determined by ultrafiltration using liquid scintillation counting (LSC).

To determine if the binding varied with pH, aliquots of pooled plasma (N=3 different subjects) were adjusted with 0.14 N HCl or 0.1 N NaOH to values of 6.95, 7.52, 7.95, 8.10, and 8.58 (pH range of the human plasma prior to and after incubation) at 37°C and incubated (in triplicate) with ^{14}C -losartan or ^3H -E3174 ($1 \mu\text{g/ml}$) as described above.

To investigate binding to albumin and α_1 -acid glycoprotein (AAG), stock solutions of purified human albumin or AAG were prepared in isotonic pH 7.4 buffer to yield physiological concentrations of 4.5 g/dL and 1 mg/ml. Incubation and analysis were identical to those described previously.

The displacement of losartan and E-3174 from human plasma proteins by other drugs was investigated using ^{14}C -losartan or ^3H -E3174 ($1 \mu\text{g/ml}$) and diazepam (0.35, 3.50 $\mu\text{g/ml}$); aspirin (300, 3000 $\mu\text{g/ml}$); naproxen (50, 500 $\mu\text{g/ml}$); warfarin (2, 20 $\mu\text{g/ml}$); and ibuprofen (20, 200 $\mu\text{g/ml}$).

The effects of losartan and E-3174 or naproxen on human plasma binding of warfarin was investigated using ^{14}C -warfarin (2 $\mu\text{g/ml}$) and losartan and E-3174 (0.250, 2.500 $\mu\text{g/ml}$) or naproxen (500 $\mu\text{g/ml}$).

The potential effects of unknown metabolites on the binding of losartan and E-3174 were investigated using plasma from volunteers (N=4) dosed orally with either 250 or 300 mg of losartan and ^{14}C -losartan ($1 \mu\text{g/ml}$) or ^3H -E3174 ($1 \mu\text{g/ml}$). The plasma samples were collected from 0-2 or 4-6 hour postdose, reflecting times to peak levels of losartan and E-3174 respectively. The concentrations of losartan and E-3174 present in the samples prior to the addition of the radiolabelled tracers were determined by HPLC.

RESULTS:

SPECIES-DEPENDENT PLASMA PROTEIN BINDING OF LOSARTAN AND E3174

Concentration µg/mL	Percent Free (f _u)				
	Losartan			E3174	
	Man	Dog	Rat	Man	Rat
0.100	ND	ND	ND	0.2 ± 0.0	0.1 ± 0.0
0.500	1.4 ± 0.2	3.1 ± 0.3 ^a	0.7 ± 0.2 ^{a,b}	ND	ND
1.000	1.3 ± 0.1	2.7 ± 0.5 ^a	0.8 ± 0.0 ^{a,b}	0.2 ± 0.0 ^c	0.2 ± 0.0 ^c
2.000	ND	2.9 ± 0.5	1.0 ± 0.0 ^b	ND	ND
5.000	1.2 ± 0.1	ND	ND	ND	ND
10.000	ND	ND	ND	0.2 ± 0.0	0.1 ± 0.0

Mean ± S.D., N=3-4 analyzed in triplicate.

ND, Not Determined.

^a p<0.05 vs human.

^b p<0.05 vs dog.

^c p<0.05 vs losartan.

EFFECTS OF VARYING pH ON THE HUMAN PLASMA PROTEIN BINDING OF 1 µg/mL OF LOSARTAN AND E3174

pH	Percent Free (f _u)	
	Losartan	E3174
6.95	2.2 ± 0.2	1.1 ± 0.1
7.52	1.7 ± 0.3	1.0 ± 0.1
7.95	1.5 ± 0.2	0.8 ± 0.0 ^a
8.10	1.3 ± 0.2	0.7 ± 0.1
8.58	1.5 ± 0.3	0.8 ± 0.1
Unadjusted	1.3 ± 0.2	0.7 ± 0.1

Mean ± S.D., triplicate analyses.

^a duplicate analyses.

BINDING OF 1 µg/mL OF LOSARTAN AND E 3174 TO PURIFIED RAT OR HUMAN ALBUMIN AND ALPHA₁-ACID GLYCOPROTEIN (AAG)

Protein	Percent Free (f _u)			
	Losartan		E3174	
	Human	Rat	Human	Rat
Albumin	4.0 ± 0.4	1.4 ± 3.0 ^a	1.5 ± 0.4	0.8 ± 0.0
AAG	60.2 ± 0.8	14.9 ± 1.4	76.4 ± 4.5	76.0 ± 4.5

Mean ± S.D., triplicate analyses.

^a duplicate.

HUMAN PLASMA PROTEIN BINDING OF 1 µg/mL OF LOSARTAN AND E3174 IN THE PRESENCE OF OTHER COMMONLY ADMINISTERED DRUGS.

Drug	Conc. µg/mL	Percent Free (f _u)			
		Losartan		E3174	
		Subject 1	Subject 2	Subject 1	Subject 2
None	-	1.2 ± 0.1	1.3 ± 0.1	0.8 ± 0.0	0.7 ± 0.0
ASA	300	2.7 ± 0.1 ^a	2.8 ± 0.2 ^a	1.4 ± 0.1 ^a	1.4 ± 0.2 ^a
	3000	9.0 ± 1.0 ^a	9.0 ± 0.6 ^a	5.4 ± 0.2 ^a	5.5 ± 1.1 ^a
Naproxen	50	1.4 ± 0.0	1.3 ± 0.1	0.8 ± 0.0	0.8 ± 0.1
	500	2.9 ± 0.5 ^a	3.7 ± 0.2 ^a	2.9 ± 0.0 ^a	2.6 ± 0.5 ^a
Ibuprofen	20	1.2 ± 0.0	1.2 ± 0.1	0.8 ± 0.0	0.8 ± 0.0
	200	1.8 ± 0.3 ^a	1.9 ± 0.1 ^a	1.1 ± 0.0 ^a	1.0 ± 0.1 ^a
Diazepam	0.35	1.3 ± 0.1	1.1 ± 0.1	0.8 ± 0.0	0.8 ± 0.0
	3.50	1.1 ± 0.2	1.5 ± 0.0	0.8 ± 0.0	0.6 ± 0.0
Warfarin	2	1.3 ± 0.1	1.2 ± 0.2	0.7 ± 0.0	0.8 ± 0.1
	20	1.0 ± 0.1	1.5 ± 0.1	0.8 ± 0.0	0.6 ± 0.1

Mean ± S.D. of triplicate analyses.

^a Greater than control (none), p < 0.05.

HUMAN PLASMA PROTEIN BINDING OF WARFARIN (2.0 µg/mL) IN THE PRESENCE OF LOSARTAN AND E3174.

Drug	Conc µg/mL	Percent Free (f _u)
None		1.3 ± 0.1
Losartan	0.250	1.2 ± 0.1
	2.500	1.3 ± 0.1
E3174	0.250	1.4 ± 0.1
	2.500	1.4 ± 0.2
Losartan + E3174	0.250	1.4 ± 0.1
Naproxen	500	2.4 ± 0.2 ^a

Mean ± S.D., triplicate analyses

^a p < 0.05 vs control (none)

PLASMA BINDING IN VOLUNTEERS DOSED WITH LOSARTAN

Sample	Losartan		E-3174	
	Conc $\mu\text{g/ml}$	f_u %	Conc $\mu\text{g/ml}$	f_u %
Volunteers (0-2 hr)	0.93 ± 0.028	1.5 ± 0.3	1.342 ± 0.06	0.5 ± 0.0
Volunteers (4-6 hr)	0.432 ± 0.065	1.5 ± 0.3	0.535 ± 0.0	0.5 ± 0.0
Naive human plasma	-	1.4 ± 0.1	-	0.4 ± 0.0

CONCLUSIONS: The data obtained from the studies support the sponsor's labeling claims for the plasma protein binding of both losartan and E-3174.

COMMENTS: The lower end of the therapeutic concentrations for losartan (< 500 ng/ml) and E-3174 (< 100 ng/ml) were not used in the binding studies.

DRUG PRODUCT DISSOLUTION TESTING

Summary of Losartan Potassium Tablets Results for Initial Dissolution⁽¹⁾

<u>Dose Strength</u>	<u>Lot No.</u>	<u>Test No.</u>	<u>No. of Tablets</u>	<u>Dissolution 30 minutes (% label)</u>	<u>Mean Dissolution 30 minutes</u>	<u>Dissolution 45 minutes (% label)</u>	<u>Mean Dissolution 45 minutes</u>
25 mg	002B001	1	6		100		101
	002B002	1	6		102		104
	003B001	1	6		101		101
		2	12		102		103

⁽¹⁾ Dissolution results reported to ones place for Merck data and to tenths place for DuPont Merck data.

**Summary of Losartan Potassium Tablets
Results for Initial Dissolution**

<u>Dose Strength</u>	<u>Lot No.</u>	<u>Test No.</u>	<u>No. of Tablets</u>	<u>Dissolution 30 minutes (% label)</u>	<u>Mean Dissolution 30 minutes</u>	<u>Dissolution 45 minutes (% label)</u>	<u>Mean Dissolution 45 minutes</u>
25 mg	003B001	3	12		97		97

	007B001	1	5,6		100		101

	4220-88	1	6		97.8		99.0

	E-4639	1	6		100		100

Summary of Losartan Potassium Tablets
Results for Initial Dissolution

<u>Dose Strength</u>	<u>Lot No.</u>	<u>Test No.</u>	<u>No. of Tablets</u>	<u>Dissolution 30 minutes (% label)</u>	<u>Mean Dissolution 30 minutes</u>	<u>Dissolution 45 minutes (% label)</u>	<u>Mean Dissolution 45 minutes</u>
25 mg	E-4957	1	6		104		104
	E-7725	1	6		100		99
	E-7726	1	6		101		101

**Summary of Losartan Potassium Tablets
Results for Initial Dissolution**

<u>Dose Strength</u>	<u>Lot No.</u>	<u>Test No.</u>	<u>No. of Tablets</u>	<u>Dissolution 30 minutes (% label)</u>	<u>Mean Dissolution 30 minutes</u>	<u>Dissolution 45 minutes (% label)</u>	<u>Mean Dissolution 45 minutes</u>
50 mg	005C001	1	6		99		100
	005C002	1	6		98		102
	005C003	1	6		100		103
		2	12		100		102

**Summary of Losartan Potassium Tablets
Results for Initial Dissolution**

<u>Dose Strength</u>	<u>Lot No.</u>	<u>Test No.</u>	<u>No. of Tablets</u>	<u>Dissolution 30 minutes (% label)</u>	<u>Mean Dissolution 30 minutes</u>	<u>Dissolution 45 minutes (% label)</u>	<u>Mean Dissolution 45 minutes</u>
50 mg	G05C004	1	6		96		99
	G05C005	1	6		99		101
	016C001	1	6		97		100
	017C001	1	6		99		101
		2	6		99		101

**Summary of Losartan Potassium Tablets
Results for Initial Dissolution**

<u>Dose Strength</u>	<u>Lot No.</u>	<u>Test No.</u>	<u>No. of Tablets</u>	<u>Dissolution 30 minutes (% label)</u>	<u>Mean Dissolution 30 minutes</u>	<u>Dissolution 45 minutes (% label)</u>	<u>Mean Dissolution 45 minutes</u>
50 mg	017C001	3	6		95		99
		4	12		95		99
	4220-92	1	6		90.6		98.3
	018C001	1	6		90.5		97.3

**Summary of Losartan Potassium Tablets
Results for Initial Dissolution**

<u>Dose Strength</u>	<u>Lot No.</u>	<u>Test No.</u>	<u>No. of Tablets</u>	<u>Dissolution 30 minutes (% label)</u>	<u>Mean Dissolution 30 minutes</u>	<u>Dissolution 45 minutes (% label)</u>	<u>Mean Dissolution 45 minutes</u>
50 mg	018C001	2	6		95.3		99.2
		3	12		93.3		96.2
	E-4640	1	6		98		101
	E-4712	1	6		100		102

**Summary of Losartan Potassium Tablets
Results for Initial Dissolution**

<u>Dose Strength</u>	<u>Lot No.</u>	<u>Test No.</u>	<u>No. of Tablets</u>	<u>Dissolution 30 minutes (% label)</u>	<u>Mean Dissolution 30 minutes</u>	<u>Dissolution 45 minutes (% label)</u>	<u>Mean Dissolution 45 minutes</u>
50 mg	E-4757	1	6		94		97
	E-4774	1	6		98		99
	E-4808	1	6		96		99
	E-4811	1	6		100		102

**Summary of Losartan Potassium Tablets
Results for Initial Dissolution**

<u>Dose Strength</u>	<u>Lot No.</u>	<u>Test No.</u>	<u>No. of Tablets</u>	<u>Dissolution 30 minutes (% label)</u>	<u>Mean Dissolution 30 minutes</u>	<u>Dissolution 45 minutes (% label)</u>	<u>Mean Dissolution 45 minutes</u>
100 mg	004D001	1	6		92		99
		2	6		97		101
	004D003	1	6		90		98
	004D004	1	6		95		98
	004D005	1	6		95		100

**Summary of Losartan Potassium Tablets
Results for Initial Dissolution**

<u>Dose Strength</u>	<u>Lot No.</u>	<u>Test No.</u>	<u>No. of Tablets</u>	<u>Dissolution 30 minutes (% label)</u>	<u>Mean Dissolution 30 minutes</u>	<u>Dissolution 45 minutes (% label)</u>	<u>Mean Dissolution 45 minutes</u>
100 mg	006D001	1	6		94		100
		2	12		91		100

**Summary of Losartan Potassium Tablets
Results for Initial Dissolution**

<u>Dose Strength</u>	<u>Lot No.</u>	<u>Test No.</u>	<u>No. of Tablets</u>	<u>Dissolution 30 minutes (% label)</u>	<u>Mean Dissolution 30 minutes</u>	<u>Dissolution 45 minutes (% label)</u>	<u>Mean Dissolution 45 minutes</u>
100 mg	006D001	3	24		86		95

4220-90 1 6 84.0 92.3

NDA 020386

FIRM: MERCK

8 OF 10

TRADE NAME: COZAAR (LOSARTAN POTASSIUM) 25/50 MG TAB

GENERIC NAME: LOSARTAN POTASSIUM

**Summary of Losartan Potassium Tablets
Results for Initial Dissolution**

<u>Dose Strength</u>	<u>Lot No.</u>	<u>Test No.</u>	<u>No. of Tablets</u>	<u>Dissolution 30 minutes (% label)</u>	<u>Mean Dissolution 30 minutes</u>	<u>Dissolution 45 minutes (% label)</u>	<u>Mean Dissolution 45 minutes</u>
100 mg	E-4713	1	6		92		98
	E-4775	1	6		90		96
100 mg	E-4888	1	6		94		97

Based on the above results the sponsor is proposing the following method and specifications:

Dosage Form, Strength: Film-coated tablets, 25, 50 and 100 mg

Dissolution Apparatus: USP, Apparatus II (paddle)

Dissolution Medium: Water (at $37^{\circ} \pm 0.5^{\circ}\text{C}$)

Volume 900 ml

Speed of Rotation: 50 rpm

Sampling Time: 45 min

Procedure: Determine the amount of losartan potassium dissolved from UV absorbance at 256 nm, of clear dissolution sample (obtained by filtration or centrifugation).

Recommended Specification: of the labelled amount of losartan potassium dissolved in 45 min.

COMMENTS: The dissolution specification should be changed to not less than at 30 min.

**B. PROPOSED TEXT
OF LABELING**

Synopsis of Application

I. Synopsis

B. Proposed Text of Labeling

B. Annotated Package Circular

This section contains the annotated package circular. Each annotation has at least two references. The first reference is to Item 2 — Synopsis of Application contained in this volume. The page number indicates where a brief description of the information supporting the labeling statement can be found. The other references are to the specific technical section and give the volume and page number where a more detailed description of the supporting data can be found.

COZAAR®

(LOSARTAN POTASSIUM TABLETS)

USE IN PREGNANCY¹

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death in the developing fetus. When pregnancy is detected, COZAAR should be discontinued as soon as possible. See WARNINGS: *Fetal/Neonatal Morbidity and Mortality.*

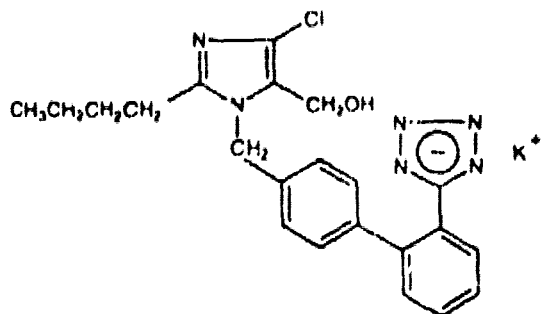
1. Per FDA letter of August 16, 1993

DESCRIPTION

COZAAR* (losartan potassium), the first of a new class of antihypertensives, is an angiotensin II receptor (type AT₁) antagonist.²

Losartan potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)][1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol monopotassium salt.³

Its empirical formula is C₂₂H₂₂ClKN₆O, and its structural formula is:⁴



Losartan potassium is a white to off-white free-flowing crystalline powder⁵ with a molecular weight of 461.01.⁶ It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone.⁷

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5. Synopsis, I.E.2.a.2. [p. E-2]	Vol. 1.1
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6. Synopsis, I.E.2.a.1 [p. E-1]	Vol. 1.1
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Synopsis = Synopsis of Application (Item 2)
C & M = Chemical and Pharmaceutical Manufacturing and Control Documentation (Item 3)
Nonclinical = Nonclinical Pharmacology and Toxicology Documentation (Item 5)
Biopharm = Human Pharmacokinetics and Bioavailability Documentation (Item 6)
Clinical = Clinical Documentation (Item 8)

Oxidation of the 5-hydroxymethyl group on the imidazole ring results in the active metabolite of losartan.⁸

COZAAR is available for oral administration containing either 25 mg, 50 mg, or 100 mg of losartan potassium⁹ and the following inactive ingredients: microcrystalline cellulose, lactose hydrous, pregelatinized starch, magnesium stearate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, titanium dioxide, D&C yellow No. 10 aluminum lake and FD&C blue No. 2 aluminum lake.¹⁰

COZAAR 25 mg, 50 mg, and 100 mg contain potassium in the following amounts: 2.12 mg (0.054 mEq), 4.24 mg (0.108 mEq), and 8.48 mg (0.217 mEq), respectively.¹¹

CLINICAL PHARMACOLOGY

Mechanism of Action

Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin-angiotensin system, and a major determinant of the pathophysiology of hypertension.¹² Angiotensin II binds to the AT₁ receptor found in many tissues (e.g., vascular smooth muscle, adrenal gland, kidneys, and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth muscle cell proliferation.¹³ A second angiotensin II receptor has been identified as the AT₂ receptor subtype, but it plays no known role in cardiovascular homeostasis.¹⁴

Losartan is a potent, synthetic, orally active compound. Based on binding and pharmacological bioassays, it binds selectively to the AT₁ receptor.¹⁵ *In vitro* and *in vivo*, both losartan and its pharmacologically active carboxylic acid metabolite block all physiologically relevant actions of angiotensin II, regardless of the source or route of synthesis.¹⁶ In contrast to some peptide antagonists of angiotensin II, losartan has no agonist effects.¹⁷

Losartan binds selectively to the AT₁ receptor and does not bind to or block other hormone receptors or ion channels important in cardiovascular regulation.¹⁸ Furthermore, losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin.¹⁹ Consequently, effects not directly related to blocking the AT₁ receptor, such as the potentiation of bradykinin-mediated effects or the generation of edema (losartan 1.7%, placebo 1.9%), are not associated with losartan.^{20,21}

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Pharmacokinetics

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites.^{22,23} The systemic bioavailability of losartan tablets is approximately 33%.²⁴ Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively.^{25,26} There was no clinically significant effect on the plasma concentration profile of losartan when the drug was administered with a standardized meal.²⁷

Both losartan and its active metabolite are ≥99% bound to plasma proteins, primarily albumin.²⁸ The volume of distribution of losartan is 34 liters.²⁹ Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.³⁰

About 14% of an intravenously- or orally-administered dose of losartan is converted to the active metabolite.^{31,32} Following oral and intravenous administration of ¹⁴C-labeled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and the active metabolite.³³ Minimal conversion of losartan to the active metabolite was seen in about one percent of individuals studied.³⁴

In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N-2 tetrazole glucuronide.³⁵

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COZAAR® (Losartan Potassium)

Plasma clearance of losartan and its active metabolite is about 600 mL/min and 50 mL/min, respectively.^{36,37} Renal clearance of losartan and its active metabolite is about 74 mL/min and 26 mL/min, respectively.^{38,39} When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite.^{40,41} The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.⁴²

Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6-9 hours, respectively.^{43,44} During once-daily dosing at 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.⁴⁵

Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose of ¹⁴C-labeled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the feces. Following an intravenous dose of ¹⁴C-labeled losartan in man, about 43% of radioactivity is recovered in the urine and 50% in the feces.⁴⁶

The plasma concentrations of losartan and its active metabolite observed in elderly male hypertensives are not significantly different from those observed in young male hypertensives.^{47,48}

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Plasma concentrations of losartan were up to 2-fold higher in female hypertensives as compared to male hypertensives.^{49,50} Concentrations of the active metabolite were not different in males and females.⁵¹ This apparent pharmacokinetic difference is not judged to be of clinical significance.⁵²

Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-fold and 1.7-fold greater than those seen in young male volunteers.^{53,54}

Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 mL/min.^{55,56} Compared to patients with normal renal function, the AUC for losartan is approximately 2-fold greater in hemodialysis patients.⁵⁷ Plasma concentrations of the active metabolite are not altered in patients with renal impairment or in hemodialysis patients.⁵⁸ Neither losartan nor the active metabolite can be removed by hemodialysis.⁵⁹

Pharmacodynamics

Losartan inhibits systolic and diastolic pressor responses to angiotensin II infusions.⁶⁰ At peak, 100 mg of losartan potassium inhibits these responses by approximately 85%; 24 hours after single and multiple-dose administration, inhibition is about 26-39%.⁶¹

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During losartan administration, removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity.⁶² Increases in plasma renin activity lead to increases in angiotensin II in plasma. During chronic (6 weeks) treatment of hypertensive patients with 100 mg/day losartan, approximately 2-3 fold increases of plasma angiotensin II were observed at time of peak plasma drug concentrations. In some patients, greater increases were observed, particularly during short term (2 weeks) treatment.⁶³ However, antihypertensive activity and suppression of plasma aldosterone concentration were apparent at 2 and 6 weeks, indicating effective angiotensin II receptor blockade.^{64,65} After discontinuation of losartan, plasma renin activity and angiotensin II levels declined to untreated levels within 3 days.⁶⁶

Since losartan is a specific antagonist of the angiotensin II receptor type AT₁, it does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. In a study which compared the effects of 20 mg and 100 mg of losartan potassium and an ACE inhibitor on responses to angiotensin I, angiotensin II and bradykinin, losartan was shown to block responses to angiotensin I and angiotensin II without affecting responses to bradykinin. This finding is consistent with losartan's specific mechanism of action. In contrast, the ACE inhibitor was shown to block responses to angiotensin I and enhance responses to bradykinin without altering the response to angiotensin II, thus providing a pharmacodynamic distinction between losartan and ACE inhibitors.^{67,68}

Plasma concentrations of losartan and its active metabolite and the antihypertensive effect of losartan increase with increasing dose.^{69,70} Since losartan and its active metabolite are both angiotensin II receptor antagonists, they both contribute to the antihypertensive effect.⁷¹

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In a single-dose study in normal males, the administration of 100 mg of losartan potassium, under dietary high- and low-salt conditions,⁷² did not alter glomerular filtration rate,⁷³ effective renal plasma flow or⁷⁴ filtration fraction.⁷⁵ Losartan had a natriuretic effect which was more pronounced on a low-salt diet⁷⁶ and did not appear to be related to inhibition of early proximal reabsorption of sodium.⁷⁷ Losartan also caused a transient increase in urinary uric acid excretion.⁷⁸

In nondiabetic hypertensive patients with proteinuria (≥ 2 g/24 hours) treated for 8 weeks, the administration of losartan potassium 50 mg titrated to 100 mg⁷⁹ significantly reduced proteinuria by 42%.⁸⁰ Fractional excretion of albumin⁸¹ and IgG⁸² also was significantly reduced. In these patients losartan maintained glomerular filtration rate⁸³ and reduced filtration fraction.⁸⁴

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In postmenopausal hypertensive women treated for 4 weeks, 50 mg of losartan potassium⁸⁵ had no effect on renal or systemic prostaglandin levels.^{86a}

Losartan has no effect on autonomic reflexes⁸⁷ and no sustained effect on plasma norepinephrine.⁸⁸

Losartan potassium, administered in doses of up to 150 mg once daily, did not cause clinically important changes in fasting triglycerides, total cholesterol or HDL-cholesterol in patients with hypertension. The same doses of losartan had no effect on fasting glucose levels.⁸⁹

Generally losartan caused a decrease in serum uric acid (usually <0.4 mg/dL) which was persistent in chronic therapy.⁹⁰⁻⁹⁴ In controlled clinical trials in hypertensive patients, no patients were discontinued due to increases in serum creatinine or serum potassium.^{95,96}

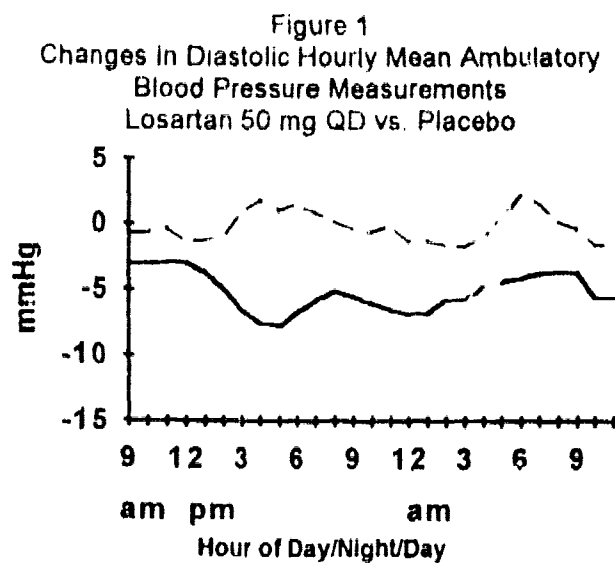
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In a 12-week, parallel-design study in patients with left ventricular failure (New York Heart Association Functional Classes II-IV), most of whom were receiving diuretics and/or digitalis, losartan potassium administered in once-daily doses of 2.5, 10, 25 and 50 mg was compared to placebo.^{97,98} The 25-mg and 50-mg doses produced positive hemodynamic and neurohormonal effects which were maintained for the length of the study. Hemodynamic responses were characterized by an increase in cardiac index⁹⁹ and decreases in pulmonary capillary wedge pressure,¹⁰⁰ systemic vascular resistance,¹⁰¹ mean systemic arterial pressure¹⁰² and heart rate.¹⁰³ The occurrence of hypotension was dose related in these heart failure patients.¹⁰⁴ Neurohormonal results were characterized by a reduction in circulating levels of aldosterone and norepinephrine.^{105,106}

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Clinical Studies

The antihypertensive efficacy of COZAAR was demonstrated in 11 controlled studies involving 1679 patients on COZAAR, 471 patients on placebo and 488 patients receiving a variety of comparator agents.¹⁰⁷ Once-daily administration of COZAAR to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure;¹⁰⁸ the antihypertensive effect was maintained in clinical studies for up to one year.¹⁰⁹ Measurement of blood pressure at trough (24 hours postdose) relative to peak (5-6 hours postdose) demonstrated relatively smooth blood pressure reduction over 24 hours¹¹⁰ (see Figure 1).¹¹¹ The antihypertensive effect paralleled the natural diurnal rhythms.¹¹² Blood pressure reduction at the end of the dosing interval was approximately 70-80% of the effect seen 5-6 hours postdose.¹¹³ The maximal antihypertensive effect was attained 3-6 weeks after initiation of therapy.¹¹⁴ Despite the significant decrease in blood pressure, administration of COZAAR had no clinically significant effect on heart rate.¹¹⁵ Discontinuation of losartan in hypertensive patients did not result in an abrupt rebound of blood pressure.¹¹⁶



NOTE: Average time of dosing 9 a.m.

————— Losartan 50 mg
- - - - - Placebo

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The administration of COZAAR 50-100 mg once daily produced a significantly greater antihypertensive effect than captopril 50-100 mg given once daily.¹¹⁷ The antihypertensive effect of once-daily administration of COZAAR 50 mg was shown to be similar to once-daily administration of enalapril 20 mg.¹¹⁸ The antihypertensive effect of once-daily administration of COZAAR 50-100 mg was shown to be comparable to once-daily administration of atenolol 50-100 mg.¹¹⁹ The effect of administration of COZAAR 50-100 mg once daily also was equivalent to felodipine 5-10 mg in older hypertensives (≥ 65 years) after 12 weeks of therapy.¹²⁰

COZAAR is equally effective in males and females¹²¹ and in younger (<65 years) and older (≥65 years) hypertensives.¹²² Although COZAAR was antihypertensive in all races studied, as with other drugs that affect the renin-angiotensin system, black hypertensive patients had a smaller average response to losartan monotherapy than nonblack patients.¹²³

When given together with thiazide-type diuretics, the blood pressure lowering effects of COZAAR are approximately additive.¹²⁴

Because COZAAR selectively blocks the AII receptor site, it is expected that patients taking COZAAR will not develop cough.¹²⁵ In an 8-week controlled study of the incidence of cough in hypertensive patients with a history of cough during ACE inhibitor therapy, the incidence of cough reported by patients receiving COZAAR or an agent not associated with ACE inhibitor-induced cough (hydrochlorothiazide) was similar and was significantly less than in patients rechallenged with an ACE inhibitor.¹²⁶ In addition, in an overall analysis of 16 double-blind clinical trials in 4131 patients, the incidence of spontaneously reported cough in patients treated with COZAAR was similar (3.1%) to that of patients treated with placebo (2.6%) or hydrochlorothiazide (4.1%), whereas the incidence with ACE inhibitors was 8.8%.¹²⁷

INDICATIONS AND USAGE

COZAAR is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.¹²⁸

CONTRAINDICATIONS

COZAAR is contraindicated in patients who are hypersensitive to any component of this product.

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COZAAR® (Losartan Potassium)

WARNINGS:

129. Per FDA letter of August 16, 1993

Fetal/Neonatal Morbidity and Mortality¹²⁹

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, COZAAR should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester.

Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of losartan potassium as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, losartan potassium should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

COZAAR® (Losartan Potassium)

Losartan potassium has been shown to produce adverse effects in rat fetuses and neonates. The effects include decreased body weight, mortality and/or renal toxicity.¹³⁰ In addition, significant levels of losartan and its active metabolite were shown to be present in rat milk.¹³¹ Based on pharmacokinetic assessments, these findings are attributed to drug exposure in late gestation and during lactation.¹³²

PRECAUTIONS

General

In patients who are intravascularly volume-depleted (e.g., those treated with high-dose diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of COZAAR, or a lower starting dose should be used (see DOSAGE AND ADMINISTRATION).¹³³

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with a history of hepatic impairment (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY, *Pharmacokinetics*).¹³⁴

Other drugs that affect the renin-angiotensin system may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. While not confirmed, this potentially may occur with angiotensin II receptor antagonists.¹³⁵

Information for Patients

Pregnancy. Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.¹³⁶

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136. Per FDA letter of August 16, 1993

Drug Interactions

No drug interactions of clinical significance have been identified.¹³⁷ Compounds which have been studied in clinical pharmacokinetic trials include hydrochlorothiazide,¹³⁸ digoxin,¹³⁹ warfarin,¹⁴⁰ cimetidine¹⁴¹ and phenobarbital.¹⁴²

Carcinogenesis, Mutagenesis, Impairment of Fertility

Losartan potassium was not carcinogenic when administered at maximum tolerated dosage levels to rats and mice for 105 and 92 weeks, respectively.^{143,144} These maximum tolerated dosage levels provided respective margins of systemic exposure for losartan and its pharmacologically active metabolite over that achieved in humans treated with 50 mg of losartan of approximately 270- and 150-fold in rats¹⁴⁵ and 45- and 27-fold in mice.¹⁴⁶

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Losartan potassium was negative in the microbial mutagenesis and V-79 mammalian cell mutagenesis assays.¹⁴⁷ In addition, there was no evidence of direct genotoxicity in the *in vitro* alkaline elution and *in vitro* chromosomal aberration assays at concentrations that were approximately 1700 times greater than the maximum plasma level achieved in man at the recommended therapeutic dosage level.^{148,149} Similarly, there was no induction of chromosomal aberrations in bone marrow cells of male or female mice after the administration of toxic oral doses of up to 1500 mg/kg (4500 mg/m²) (750 times** the maximum recommended daily human dose).^{150,151} In addition, the active metabolite showed no evidence of genotoxicity in the microbial mutagenesis, *in vitro* alkaline elution, and *in vitro* chromosomal aberration assays.^{152,153,154}

Fertility and reproductive performance were not affected in studies with male and female rats given oral doses of losartan potassium up to approximately 150 and 300 mg/kg/day, respectively.^{155,156} These dosages provide respective margins of systemic exposure for losartan and its pharmacologically active metabolite of approximately 150/125-fold in male rats and 300/170-fold in female rats over that achieved in man at the recommended daily dose.¹⁵⁷

Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters).

See WARNINGS, *Fetal/Neonatal Morbidity and Mortality*¹⁵⁸

Nursing Mothers

It is not known whether losartan is excreted in human milk. However, significant levels of losartan and its active metabolite were shown to be present in rat milk.¹⁵⁹ Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children have not been established.

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Nonclinical, D.I.C.11 [p. D-49]	Vol. 1.23
154. Synopsis, I.H.6 [p. H-52]	Vol. 1.1
Nonclinical, D.I.C.16 [p. D-69]	Vol. 1.23
155. Synopsis, I.H.5.a [p. H-47]	Vol. 1.1
Nonclinical, C.I.C.1 [p. C-8]	Vol. 1.18
156. Synopsis, I.H.5.a [p. H-47]	Vol. 1.1
Nonclinical, C.I.C.2 [p. C-15]	Vol. 1.18
157. Synopsis, I.H.9 [p. H-69]	Vol. 1.1
Nonclinical, Q.I.D [p. Q-69]	Vol. 1.37
158. Per FDA letter of August 16, 1993	
159. Synopsis, I.H.5.b [p. H-50]	Vol. 1.1
Nonclinical, Q.I.C.9 [p. Q-28]	Vol. 1.37

** Based on a patient weight of 50 kg.

Use in the Elderly

Of the total number of patients receiving COZAAR in controlled clinical studies, 391 patients (19%) were 65 years and over, while 37 patients (2%) were 75 years and over.¹⁶⁰ No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.^{161,162}

ADVERSE REACTIONS

COZAAR has been evaluated for safety in more than 2500 patients treated for essential hypertension.¹⁶² In general, treatment with COZAAR was well tolerated. The overall incidence of adverse experiences reported with COZAAR was comparable to placebo.¹⁶³ For the most part, adverse experiences have been mild and transient in nature and have not required discontinuation of therapy.¹⁶⁴ In controlled clinical trials, discontinuation of therapy due to clinical adverse experiences was required in only 2.3 percent and 3.7 percent of patients, treated with COZAAR and placebo, respectively.¹⁶⁵

In controlled clinical trials for essential hypertension, dizziness was the only adverse experience reported as drug related that occurred with an incidence greater than placebo in one percent or more of patients treated with COZAAR.¹⁶⁶ In addition, dose-related orthostatic effects were seen in less than one percent of patients.¹⁶⁷ Rarely, rash was reported, although the incidence in controlled clinical trials was less than placebo.¹⁶⁸

160. Synopsis, I.J.5.a.14 [p. J-124]	Vol. 1.1
Clinical, D.I.B.3.n.1.a [p. D-290]	Vol. 1.101
161. Synopsis, I.J.4.a [p. J-48]	Vol. 1.1
Clinical, D.I.A.3.d.1 [p. D-120]	Vol. 1.101
162. Synopsis, I.J.5.a.14 [p. J-124]	Vol. 1.1
Clinical, D.I.B.3.n.1.a [p. 291]	Vol. 1.101
162. Synopsis, I.J.5.a.1 [p. J-57]	Vol. 1.1
Clinical, D.I.B.3.a [p. D-157]	Vol. 1.101
163. Synopsis, I.J.5.a.3.a.1 [p. J-64]	Vol. 1.1
Clinical, D.I.B.3.c.1 [p. D-170]	Vol. 1.101
164. Synopsis, I.J.5.a.3.a.3 [p. J-77]	Vol. 1.1
Clinical, D.I.B.3.c.1 [p. D-183]	Vol. 1.101
165. Synopsis, I.J.5.a.3.a.3 [p. J-75]	Vol. 1.1
Clinical, D.I.B.3.c.1 [p. D-182]	Vol. 1.101
166. Synopsis, I.J.5.a.3.a.1 [p. J-70]	Vol. 1.1
Clinical, D.I.B.3.c.1 [p. D-175]	Vol. 1.101
167. Synopsis, I.J.5.a.12.a [p. J-121]	Vol. 1.1
Clinical, D.I.B.3.1.1.a [p. D-282]	Vol. 1.101
168. Synopsis, I.J.5.a.3.a [p. J-70]	Vol. 1.1
Clinical, D.I.B.3.c.1 [p. D-175]	Vol. 1.101

In these double-blind controlled clinical trials, the following adverse experiences reported with COZAAR occurred in ≥1 percent of patients, regardless of drug relationship:¹⁶⁹

169. Synopsis, I.J.5.a.3.a.1 [p. J-66] Vol. 1.1
Clinical, D.I.B.3.c.1 [p. D-171] Vol. 1.101

	COZAAR (n=2085)	Placebo (n=535)	Angiotensin Converting Enzyme Inhibitors (n=239)	Beta Blocking Agent (n=68)	Calcium Channel Blocker (n=43)	Hctz* (n=271)
<i>Body as a Whole</i>						
Abdominal pain	1.7	1.7	0.8	2.9	2.3	1.5
Asthenia/fatigue	3.8	3.9	6.7	5.9	0.0	5.5
Chest pain	1.1	2.6	2.1	1.5	2.3	0.4
Edema/swelling	1.7	1.9	1.7	1.5	14.0	1.8
<i>Cardiovascular</i>						
Palpitation	1.0	0.4	0.8	2.9	0.0	0.7
Tachycardia	1.0	1.7	0.8	1.5	2.3	0.0
<i>Digestive</i>						
Djarrhea	1.9	1.9	2.9	0.0	4.7	0.4
Dyspepsia	1.1	1.5	0.4	0.0	2.3	0.7
Nausea	1.8	2.8	2.9	5.9	4.7	0.4
<i>Musculoskeletal</i>						
Back pain	1.6	1.1	1.3	4.4	4.7	0.4
Muscle cramps	1.0	1.1	0.4	2.9	0.0	0.4
<i>Nervous/Psychiatric</i>						
Dizziness	4.1	2.4	6.3	7.4	2.3	4.1
Headache	14.1	17.2	10.9	19.1	14.0	14.0
Insomnia	1.1	0.7	0.8	4.4	2.3	1.1
<i>Respiratory</i>						
Cough	3.1	2.6	8.8	0.0	2.3	4.1
Nasal congestion	1.3	1.1	0.8	0.0	0.0	1.8
Pharyngitis	1.5	2.6	3.3	1.5	2.3	3.0
Sinus disorder	1.0	1.3	0.0	0.0	0.0	2.2
Upper respiratory infection	6.5	5.6	5.4	1.5	7.0	5.5

*Hydrochlorothiazide

Laboratory Test Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of COZAAR.¹⁷⁰ Hyperkalemia (serum potassium >5.5 mEq/L) occurred in 1.5% of patients,¹⁷¹ but in these trials, discontinuation of losartan therapy due to hyperkalemia was not necessary.¹⁷² Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy.¹⁷³

170. Synopsis, I.J.5.a.8.b [p. J-113] Vol. 1.1
Clinical, D.I.B.3.h.2 [p. D-268] Vol. 1.101

171. Synopsis, I.J.5.a.8.b [p. J-113] Vol. 1.1
Clinical, D.I.B.3.h.2 [p. D-268] Vol. 1.101

172. Synopsis, I.J.5.a.3.b.3 [p. J-90] Vol. 1.1
Clinical, D.I.B.3.c.2 [p. D-199] Vol. 1.101

173. Synopsis, I.J.5.a.8.b [p. J-114] Vol. 1.1
Clinical, D.I.B.3.h.2 [p. D-269] Vol. 1.101

OVERDOSAGE

Significant lethality was observed in mice and rats after oral administration of 1000 mg/kg (3000 mg/m²) and 2000 mg/kg (11,800 mg/m²), respectively.^{174,175}

Limited data are available in regard to overdosage in humans.¹⁷⁶ The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.¹⁷⁷

Neither losartan nor its active metabolite can be removed by hemodialysis.¹⁷⁸

DOSAGE AND ADMINISTRATION

The usual starting and maintenance dose is 50 mg once daily in most patients.¹⁷⁹ The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy.¹⁸⁰ Some patients may receive an additional benefit by increasing the dose to 100 mg once daily.¹⁸¹

For patients with intravascular volume-depletion (e.g., those treated with high-dose diuretics), a starting dose of 25 mg once daily should be considered (see PRECAUTIONS, *General*).¹⁸²

No initial dosage adjustment is necessary for elderly patients¹⁸³ or for patients with renal impairment, including patients on dialysis.¹⁸⁴ A lower dose should be considered for patients with a history of hepatic impairment (see PRECAUTIONS, *General*).¹⁸⁵

COZAAR may be administered with other antihypertensive agents.¹⁸⁶

COZAAR may be administered with or without food.¹⁸⁷

HOW SUPPLIED^{188,189}

No. 3612 — Tablets COZAAR, 25 mg, are light green, teardrop-shaped, film-coated tablets with code MRK 951 on one side and COZAAR on the other. They are supplied as follows:

- NDC 0006-0951-31 unit of use bottles of 30
- NDC 0006-0951-54 unit of use bottles of 90
- NDC 0006-0951-58 unit of use bottles of 100
- NDC 0006-0951-28 unit dose packages of 100
- NDC 0006-0951-82 bottles of 1000.

174. Synopsis, I.H.3 [p. H-26]	Vol. 1.1
Nonclinical, A.I.C.2 [p. A-9]	Vol. 1.8
175. Synopsis, I.H.3 [p. H-26]	Vol. 1.1
Nonclinical, A.I.C.3 [p. A-10]	Vol. 1.8
176. Synopsis, I.J.5 [p. J-55]	Vol. 1.1
Clinical, D.I.F.2 [p. D-636]	Vol. 1.101
177. Synopsis, I.J.5 [p. J-55]	Vol. 1.1
Clinical, D.I.E.3 [p. D-638]	Vol. 1.101
178. Synopsis, I.I.3.i.3 [p. I-34]	Vol. 1.1
Clinical, C.I.C.4.h.4 [p. C-149]	Vol. 1.54
179. Synopsis, I.J.4.a [p. J-53]	Vol. 1.1
Clinical, D.I.E.2.a [p. D-615]	Vol. 1.101
180. Synopsis, I.J.4 [p. J-40]	Vol. 1.1
Clinical, D.I.E.2.a [p. D-613]	Vol. 1.101
181. Synopsis, I.J.4.a [p. J-53]	Vol. 1.1
Clinical, D.I.E.2.c [p. D-626]	Vol. 1.101
182. Synopsis, I.K.3 [p. K-7]	Vol. 1.1
Clinical, D.I.E.4 [p. D-630]	Vol. 1.101
183. Synopsis, I.I.3.i.1.c [p. I-31]	Vol. 1.1
Clinical, D.I.E.3 [p. D-626]	Vol. 1.101
184. Synopsis, I.I.3.i.3 [p. I-34]	Vol. 1.1
Clinical, D.I.E.3 [p. D-628]	Vol. 1.101
185. Synopsis, I.I.3.i.2 [p. I-32]	Vol. 1.1
Clinical, D.I.E.3 [p. D-628]	Vol. 1.101
186. Synopsis, I.J.4.a [p. J-53]	Vol. 1.1
Clinical, D.I.E.6 [p. D-632]	Vol. 1.101
187. Synopsis, I.I.3.g [p. I-27]	Vol. 1.1
Clinical, D.I.E.5 [p. D-631]	Vol. 1.101
188. Synopsis, I.E.3.a [p. E-7]	Vol. 1.1
C&M, I.C.4.a [p. 280]	Vol. 1.2
189. Synopsis, I.E.3.c [p. E-10]	Vol. 1.1
C&M, I.C.6.a [p. 389]	Vol. 1.2

No. 3613 -- Tablets COZAAR, 50 mg, are green, teardrop-shaped, film-coated tablets with code MRK 952 on one side and COZAAR on the other. They are supplied as follows:

- NDC 0006-0952-31 unit of use bottles of 30
- NDC 0006-0952-54 unit of use bottles of 90
- NDC 0006-0952-58 unit of use bottles of 100
- NDC 0006-0952-28 unit dose packages of 100
- NDC 0006-0952-82 bottles of 1000.

No. 3614 -- Tablets COZAAR, 100 mg, are dark green, teardrop-shaped, film-coated tablets with code MRK 960 on one side and COZAAR on the other. They are supplied as follows:

- NDC 0006-0960-31 unit of use bottles of 30
- NDC 0006-0960-54 unit of use bottles of 90
- NDC 0006-0960-58 unit of use bottles of 100
- NDC 0006-0960-28 unit dose packages of 100
- NDC 0006-0960-82 bottles of 1000.

*Storage*¹⁹⁰

Store at temperatures below 30°C (86°F). Keep container tightly closed. Protect from light.

190. Synopsis, I.E.3.e [p. E-10]
C&M, I.C.7.d [p. 440]

Vol. 1.1
Vol. 1.2

Manuf by:

 **MERCK & CO., INC.**, West Point, PA 19486, USA

by:



Wilmington, DE 19880, USA

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STATISTICAL

REVIEW

R.B.

STATISTICAL REVIEW AND EVALUATION

NOV 23 1994

NDA#: 20-386

Date:

Applicant: Merck Sharp & Dohme Research Labs.

Name of Drug: Losartan (Cozaar)

Indication: Hypertension

Document Reviewed: Studies Reports on the submitted CANDA.

Volumes 1.1, 1.208, 1.209, 1.212, 1.213,
1.219, 1.220, 1.223, and 1.224,
received 12/06/93.

1. Introduction

This application includes 8 randomized multi-center studies: 011, 021, 044, 045, 050, 055, 056, and 065. Studies 011, 021, 050, and 065 are placebo-controlled and studies 044, 045, 055, and 056 were active-controlled comparing losartan with captopril, atenolol, felodipine, and lisinopril or hydrochlorothiazide (HCTZ), respectively.

Except for the cough study #056, the primary efficacy variable was the change from baseline in sitting or supine diastolic blood pressure (SDBP, SuDBP, respectively).

For the efficacy analyses of these studies, the sponsor conducted an "all-patients-treated" and a "per-protocol" approach. In the "all-patients-treated" approach, patients with at least one treatment period measurement were included. The last measurements of withdrawn patients were carried forward to subsequent time points. For patients with data missing from a visit, the missing data was estimated by carrying forward data from the last visit at which it was available (excluding the baseline visit).

In the "per-protocol" approach, patients with specific protocol violations were excluded. Patients who withdrew prior to an analyzed time point were not included. No data was estimated for this approach.

For the purpose of evaluating treatment x center interaction, investigators who had less than two patients in any treatment group were combined.

The sponsor's analyses of the four placebo-controlled studies show that treatment x center interaction was not significant.

This review will only cover study 056 and the placebo-controlled studies: studies 011, 021, 050, and 065.

2. Study 011

This was a multicenter, randomized, parallel, placebo-controlled,

double-blind study to compare the antihypertensive efficacy of different doses of losartan (LOS) compared to placebo and 20 mg enalapril (ENAL) in patients with supine diastolic blood pressures of 100-115 mmHg. The study included 41 centers with a planned enrollment of 574 patients.

Patients were stratified by race (Black and non-Black) into two groups. After a 4-week single-blind baseline placebo period patients were randomly allocated within each center to once-daily for 8 weeks into one of seven double-blind treatment groups: placebo, LOS 10 mg, LOS 25 mg, LOS 50 mg, LOS 100 mg, LOS 150 mg, and ENAL 20 mg.

2. Study 021

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group pilot study in patients with mild to moderate essential hypertension. It was intended to evaluate the magnitude and duration of the antihypertensive effect of losartan (50 mg given once (qd) or twice (bid) daily, or 100 mg given once daily (qd)) compared to placebo using ambulatory blood pressure monitoring. Also, the safety and efficacy of losartan (50 mg (bid) vs. 100 mg (qd)) was evaluated. Ambulatory blood pressure monitoring (ABPM) was performed twice during the study, once at the end of the placebo washout period and again at the end of four (4) weeks of double-blind monotherapy treatment.

One hundred and twenty-two (122) patients from nine (9) centers were randomized into the study. Of these, 112 patients had data suitable for analysis of ABPM and 117 patients had data suitable for analysis of conventional clinic blood pressures. For clinic BP the sponsor considered only the "per-protocol" approach for the efficacy analysis. For ABPM, patients must have completed both baseline and end-of-treatment monitoring.

Both the clinic blood pressure measurements and the ABPM measurements were used for the efficacy evaluation. For the ABPM measurements, the 24-hour ABPM average of all subjects and for each treatment was used in analysis.

3. Study 050

This was a randomized, double-blind, multicenter study to test the hypothesis that losartan is more effective than placebo in lowering sitting diastolic blood pressure (SDBP) in patients with mild to moderate hypertension (95-115 mmHg) following 12 weeks of therapy with either losartan 50 mg once daily or 50 mg once daily titrated to 100 mg once daily for nonresponders (SDBP $\geq$ 90 mmHg) after 6 weeks. The study included 22 centers with an enrollment of 366 patients.

Patients were stratified by race (black and non-black) and degree

of hypertension [mild (95-105 mmHg) and moderate (106-115 mmHg)]. All patients successfully completing the single-blind baseline period were randomly allocated within each center to once-daily treatment into one of three double-blind treatment groups: Placebo, losartan 50 mg for 12 weeks, and losartan 50 mg titrated to 100 mg after 6 weeks if a patient was nonresponder (i.e. the SDBP $\geq$ 90 mmHg).

Patients were seen in the clinic at 3-week intervals during the double-blind period. Patients whose blood pressure was uncontrolled (SSBP $>$ 210 mmHg, SDBP $>$ 120 mmHg, SDBP increased $>$ 15 mmHg from baseline, or at the investigator's discretion) during the 12-week double-blind period of the study were dropped.

4. Study 065

This was a randomized, parallel, double-blind, multicenter, placebo-controlled study of 16 weeks' duration. A 4-week, single-blind, placebo baseline period was followed by 12 weeks of double-blind treatment. The study included 41 centers with a planned enrollment of 344 patients completing double-blind treatment.

Hypertensive patients whose mean SDBP was 95-115 at the end of Week 2 and Week 4 of the placebo baseline period and whose mean SiDBP values at Week 2 and Week 4 did not differ by $>$ 7 mmHg were stratified by degree of hypertension (mild or moderate) and by race (black or non-black) and were randomly assigned to 1 of 4 treatment groups. An equal number of patients were randomized to each of the following 4 groups: placebo (qd), losartan 50 mg (qd), losartan 25 mg (bid) and losartan 25 mg (qd). Patients took double-blind therapy for 12 weeks.

5. Study 056 (Cough study)

This is a multicenter, double-blind, randomized, parallel-group study to investigate the incidence of cough in patients receiving losartan 50 mg (qd), lisinopril 20 mg (qd) or hydrochlorothiazide 25 mg (qd) who have reported cough with an ACEI. The study consisted of three Phases: I, II, and III as described below.

1. Phase I (Positive Challenge Filter)

During this period, all patients received lisinopril (20 mg qd) for a maximum of 6 weeks to establish that they were susceptible for developing the "dry cough" characteristic of ACE inhibitors. To be eligible for moving into Phase II (Placebo Washout), patients had to respond positively for cough, i.e., "moderately", "quite a bit" or "extremely" on the questionnaire on two (2) consecutive visits.

2. Phase II (Placebo Washout Period):

During this phase, the "dry cough" had to resolve. Within 4

weeks, but after a minimum of 2 weeks after starting Phase II (to allow for adequate "washout" of lisinopril), patients had to respond negatively for cough (i.e., "not at all" on the questionnaire), on 2 consecutive visits which were >1 day apart.

3. Phase III (Randomized, Double-blind Treatment Period): Qualifying patients were randomized on a double-blind basis, to receive losartan (50 mg), or lisinopril (20 mg) or HCTZ (25 mg) once daily (qd) for 8 weeks. The literature suggested that cough is more common (i.e., develops and/or is reported more) in women than in men; therefore, stratification was according to gender.

Clinic visits were scheduled every two weeks, but could occur more frequently, if clinically indicated. That is, the patient could return to the clinic following the development of a persistent cough for ≥ 1 day; the presence of cough had to be documented on a subsequent visit >1 day later. Patients who were withdrawn because of a severe cough were considered to have completed the study; they are not counted as a discontinued patient.

A planned interim analysis of this study consisting of positive cough response summarizations was performed on approximately 50% of the final patient total. The purpose of this analysis was to assess the accuracy of the positive cough definition that was defined in the protocol. This analysis did not affect the conduct of the study. The study remained blinded (patient-treatment assignments were not reported) until validation of the data was complete. No adjustments to final statistical p-values were made since no statistical analyses were performed.

The Sponsor's Efficacy Analyses Approaches

The following is a description of analyses that the sponsor had conducted or planned to conduct. Later on, this reviewer will make some comments about these analyses.

The primary analysis of this study included all-patients-treated in the eight-week double-blind phase of the study. A secondary analysis included only those patients that followed the protocol (per-protocol analysis) for measurements during the double-blind phase of the study. The protocol specified that a patient must have responded positively for dry cough on two consecutive visits at any time during the double-blind treatment period in order to be considered positive for dry cough. A positive response in the double-blind period was defined as a response of 'a little', "moderately", "quite a bit" or "extremely" by a patient on the self-administered questionnaire. A negative response was a response of "not at all". A patient was negative for dry cough if the patient completed the double-blind treatment period and did not respond positively for dry cough on two consecutive visits. Patients who followed the protocol as described were

evaluated for cough the same way in both analyses; patients who did not follow the protocol were evaluated for cough in the following manner.

a. All-Patients-Treated Analysis

In the all-patients-treated analysis, patients who did not complete the double-blind period and who reported dry cough at the last double-blind visit were classified as having a positive response for dry cough. Patients who completed the four-week double-blind period according to protocol but reported a positive response for cough at the last visit were classified as having a positive response for dry cough in the all-patients-treated analysis (as this was a more conservative approach in defining a positive cough response).

b. Per-Protocol Analysis

In the per-protocol analysis, patients who did not complete the double-blind period (i.e., had fewer than the protocol-specified four visits but did not have two consecutive positive responses) were removed from the analysis of dry cough because they violated the protocol definition of negative for dry cough. Patients who completed the four-week double-blind period according to protocol but reported a positive response for cough at the last visit were classified as having a negative response for dry cough in the per-protocol analysis (as they did not have two consecutive positive responses).

The percentage of patients with dry cough was compared between treatments using Fisher's exact test.

REVIEWER' COMMENTS

In studies 011, 021, 050, and 065 the sponsor had investigated the effectiveness of losartan 10, 25, 50, 100 and 150 mg in reducing blood pressure versus placebo in patients with mild to moderate essential hypertension. The sponsor also had conducted study 056 (cough study) to investigate the incidence of cough in patients receiving losartan 50 mg (qd), lisinopril 20 mg (qd) or hydrochlorothiazide 25 mg (qd) who have reported cough with an ACEI.

This reviewer has constructed Tables 1 and 2 for the summary of some of the sponsor's results at the end of studies 011, 021, 050, and 065; Table 1 for the All-Patients-Treated analysis and Table 2 for the Per-Protocol analysis. In the sponsor's All-Treated-Patients analysis, the missing BP measurements at some weeks were estimated from previous weeks and consequently, at the end of a study, the missing data for patients who previously dropped out or failed to contribute BP measurements are replaced by measurements from some previous time points. Certainly, this

process of generating data is not acceptable and this reviewer will consider the sponsor's Per-Protocol analysis as the appropriate analysis. Thus, in the following discussion the reference will primarily be made to the results shown in Table 2. Table 5 was constructed for the 24-hour average diastolic ABPM.

In this review drug effect in mmHg, abbreviated as DE, will be defined as the adjusted mean change for drug - adjusted mean change for placebo and will be reported as a positive value without the mmHg.

Q.D. Regimen

Table 2 shows that at the end of study 011 LOS 10 mg had resulted in a significantly ($p=0.018$, $DE=2.8$) greater reduction in BP over that of placebo. In this same study LOS 25 mg (qd) resulted in a non-significantly ($p=0.257$, $DE=1.4$) greater reduction in BP over that of placebo but, the result of study 065 for the same dose did result in a significantly ($p=0.001$, $DE=3.5$) greater reduction in BP over that of placebo. This nonsignificant result for LOS 25 mg in study 011 was probably due to the small change from baseline in BP (-2.7 mmHg) among blacks (see Table 3). For all the four studies, LOS 50 mg (qd) had resulted in significantly (p -values range from 0.000 to 0.019 and DE values range from 3.4 to 4.6) greater reductions in BP over that for placebo.

Losartan 100 mg in studies 011, 021, and 050 had resulted in significantly (p -values ≤ 0.002 and DE values range from 2.9 to 7.6) greater BP reductions over that of placebo. In study 011, losartan 150 mg had resulted in a significantly ($p=0.000$, $DE=4.9$) greater BP reduction over that of placebo.

BID regimen

Table 2 shows that in study 065 LOS 25 (bid) and in study 021 LOS 50 mg (bid) had resulted in significantly ($p \leq 0.001$ and DE values are 5.3 and 6.5, respectively) greater reductions in BP over that of placebo. The significance in the reduction of BP of LOS 50 (bid) over that of placebo is also supported by the 24-hour average diastolic ABPM in study 021, which is shown in Table 5 ($p=0.000$, $DE=8.2$).

In both of these two studies there were no significant (p -values range between 0.095 and 0.580) differences in the reduction in BP between the qd and the bid regimens (see Tables 2 and 5). However, in study 065 LOS 25 mg (bid) resulted in a numerically greater BP reduction over that for LOS 50 mg (qd) (DE values are 5.3 and 3.5, respectively). Also, LOS 50 mg (bid), as shown by the average diastolic ABPM of study 021 (Table 5), resulted in a greater BP reduction over that for LOS 100 mg (qd) (DE values are 8.2 and 6.3, respectively).

24-Hour ABPM Measurements

For study 021 the sponsor presented a number of evaluations of the ABPM data including 3-point smoothing of BP measurements during the 24-hour period. The graphs of the unsmoothed and the smoothed data are shown in Figures 4 and 5, respectively.

For this study neither the sponsor nor this reviewer has attempted to perform a statistical analysis for the time course of losartan's effect during the 24-hour period using the ABPM data. However, by examining the 24-hour profiles of the ABPM data (shown in Figures 4 and 5) one can see that, throughout most of the 24-hour period, patients in the (bid) regimen had greater reductions in BP compared to those who were on the (qd) regimen.

Dose Response

Data from study 011 were analysed to fit dose response models for the average reduction in BP for the 7 treatment groups. The quadratic, E_{MAX} , and the logistic models were fitted and graphs showing the fitted models and the observed average reductions are found in Figures 1 to 3, respectively. The logistic model with RMSE=0.8698 seems to provide the best fit among the three models.

By considering the results of this study, Figures 1 to 3, and the results of other studies one can see that plateau is reached somewhere between 50 and 100 mg, which means that losartan has a very narrow usable dose range.

Losartan's Effect in Black Versus Non-black Patients

This reviewer has constructed Table 3 to summarize the results for BP changes from baseline for black and non-black patients in the three studies, 011, 050, and 065. This table shows that in general the average changes in BP for all losartan groups are less among blacks than non-blacks. In fact in most of the cases no clinically significant drug effect was observed, and even there were cases of negative drug effect, among the black population. However, the sample sizes are too small to be definitive.

Losartan's Effect by Gender

The four placebo-controlled studies were not designed on the basis of a stratification by gender to obtain appropriate sample sizes, under a fairly high power, so that one would be able to apply some statistical method for inference. In this case one can only resort to a descriptive exposition of the results to investigate the effect of losartan by gender. This reviewer has constructed Table 4 which shows that in studies 011 and 050 higher doses, 100 mg and 150 mg, of losartan resulted in smaller drug effect among females than males. There does not seem to be

any significant difference in BP changes from baseline between females and males in other doses of losartan.

These findings suggest that there may be a difference in dose response profiles between males and females. If this is indeed true, then losartan may be a 1-dose drug for females.

The Cough Study (Study 056)

The protocol of this study stated that *"The primary parameter that will be considered is the percentage of patients with two consecutive positive responses ("a little", "moderately", quite a bit", or "extremely") at any time in the double-blind phase of the study. The actual response during the double-blind phase will be used to investigate differences in the distribution of responses between the treatment groups."* Thus, from the description of the sponsor's analyses approaches described above, the per-protocol analysis should be the primary analysis.

Also, Dr. Charles Ganley (the medical reviewer) noticed that the sponsor had included in the efficacy analysis patients who had confirmatory visits that occurred only one day after experiencing persistent cough; such cases were in violation of the protocol. On the basis of these findings this reviewer has conducted a per-protocol analysis (which was not provided by the sponsor) by excluding those patients who had visits only one day apart. The results of this analysis are given in Table 6, which shows a significantly ($p < 0.001$) smaller number of patients who experienced cough in the losartan group compared to those who received lisinopril but, no such significance is found when compared with the HCTZ group.

However, since losartan 100 mg is a possible regimen, as indicated by the sponsor's proposed labeling, the comparisons in the incidence of cough of this dose with lisinopril should have been investigated.

SUMMARY AND CONCLUSION (WHICH MAY BE CONVEYED TO THE SPONSOR)

Studies 011, 021, 050, and 065 were conducted by the sponsor to investigate the effectiveness of losartan 10, 25, 50, 100 and 150 mg in reducing blood pressure versus placebo in patients with mild to moderate essential hypertension. The results of these four studies (see Table 2) show that the following losartan doses had resulted in significantly greater reductions in BP over that for placebo: losartan 50 mg (qd) with p-values ≤ 0.019 and DE (drug effect as defined earlier) values range from 3.4 to 4.6, losartan 100 mg (qd) with p-values ≤ 0.002 and DE values range from 2.9 to 7.6, and losartan 150 mg with $p=0.000$ and $DE=4.9$. Study 065 also shows that losartan 25 mg had resulted in a significantly ($p=0.001$, $DE=4.9$) greater reduction in BP over that of placebo but, the results of study 011 did not show such a significant reduction ($p=0.257$, $DE=1.4$).

From the dose response models that this reviewer had investigated, using the results of study 011, the logistic model seems to provide a good fit. The results of this study show that plateau is reached somewhere between 50 and 100 mg, indicating a very narrow usable dose range.

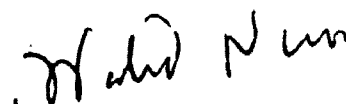
The results of study 065 suggest that losartan 25 mg (qd) may be a minimum effective dose. This needs to be confirmed by another study. The results of study 011 do not support this effectiveness of losartan 25 mg (qd); they show a non-significant ($p=0.257$, $DE=1.4$) drug effect.

Considering the effects of losartan 25 mg (bid) and 50 mg (bid), the results of studies 065 and 021 (see Table 2) show that there were no significant differences in the reduction in BP between the qd and the bid regimens. However, in study 065 LOS 25 mg (bid) resulted in a numerically greater BP reduction over that for LOS 50 mg (qd) (DE values are 5.3 and 3.5, respectively). Also, LOS 50 mg (bid), as shown by ABPM data of study 021 (Table 5), resulted in a greater BP reduction over that for LOS 100 mg (qd) (DE values are 8.2 and 6.3, respectively). Furthermore, Figures 4 and 5 show that, throughout most of the 24-hour period, patients in the (bid) regimen had greater reductions in BP compared to those who were on the (qd) regimen.

Table 4 shows that in studies 011 and 050 higher doses, 100 mg and 150 mg, of losartan resulted in smaller drug effect among females than males which suggests that there may be a difference in dose response profiles between males and females and that losartan may be a 1-dose drug for females.

Table 3 shows that in general the average changes in BP for all losartan groups are less among blacks than non-blacks.

In investigating the incidence of cough in patients who had reported cough with ACEI, study 056 shows that there were significantly fewer patients who had developed cough using losartan 50 mg than those who used lisinopril 20 mg and there was no such significance between those patients who were taking losartan 50 mg and those who were taking HCTZ 25 mg. However, the sponsor did not consider losartan 100 mg, which is a possible regimen, in the above comparison.



Walid A. Nuri, Ph.D.
Mathematical Statistician

This review consists of 10 pages, 6 tables, and 5 figures.

Concur:

Dr. Chi *Chi*
11/23/94
for Dr. Dubey *SDM 11-25-94*

cc: Orig. NDA 20-386
HFD-110/Dr. Ganley
HFD-110/Mrs. Morgenstern
HFD-344/Dr. Lisook
HFD-713/Dr. Dubey [File: DRU 1.3.2 NDA]
HFD-713/Dr. Chi
HFD-713/Dr. Nuri
Chron:
W A Nuri: x45303 SERB: 11-22-94: DISC7/cozaar2.

Table 1. Mean change from baseline in SDBP or SuDBP at the end of studies 011, 050, and 065. (All-Patients-Treated analysis).

<u>Study#</u>	<u>Week</u>	<u>Treatment</u>	<u>N</u>	<u>Baseline</u>	<u>Adj. Mean Change</u>	<u>Drug Effect*</u>	<u>p-value*</u>
		(All qd)					
		Placebo	78	103.3	-5.3		
		LOS 10 mg	80	104.3	-7.6	2.3	0.024
		LOS 25 mg	82	103.3	-6.4	1.1	0.327
011	8	LOS 50 mg	78	104.1	-10.1	4.8	0.000
		LOS 100 mg	89	104.1	-9.9	4.6	0.000
		LOS 150 mg	84	103.4	-9.5	4.2	0.000
		ENAL 20 mg	82	103.1	-10.8	5.5	0.000
		(All qd)					
		Placebo	114	101.3	-4.5		
050	12	LOS 50 mg	125	102.1	-7.9	3.4	0.000
		LOS 50/100 mg	118	102.2	-8.6	4.1	0.000
		(All qd)					
		Placebo	102	101.3	-2.1		
065	12	LOS 25 mg qd	105	101.8	-5.9	3.8	0.000
		LOS 50 mg qd	101	102.3	-6.6	4.5	0.000
		LOS 25 mg bid	101	102.0	-8.3	6.2	0.001
							(0.103) [@]

&Drug effect=(Adj. mean change for drug - Adj. mean change for placebo), reported as a positive value.

*p-value for comparison versus placebo

@p-value for comparison of LOS 50 mg (qd) versus LOS 25 mg (bid)

Table 2. Mean change from baseline in SDBP or SuDBP at the end of studies 011, 021, 050, and 065. (Per-Protocol analysis).

<u>Study#</u>	<u>Week</u>	<u>Treatment</u>	<u>N</u>	<u>Baseline</u>	<u>Adj. Mean Change</u>	<u>Drug Effect*</u>	<u>p-value*</u>
		(All qd)					
011	8	Placebo	70	103.0	-5.3		
		LOS 10 mg	74	104.2	-8.1	2.8	0.018
		LOS 25 mg	68	103.3	-6.7	1.4	0.257
		LOS 50 mg	71	104.2	-10.4	5.1	0.000
		LOS 100 mg	76	103.8	-10.3	5.0	0.000
		LOS 150 mg	72	103.4	-10.2	4.9	0.000
		ENAL 20 mg	74	103.1	-11.0	5.7	0.000
021	4	Placebo	30	100.3	-2.1		
		LOS 50 mg qd	29	100.0	-6.7	4.6	0.019
		LOS 100 mg qd	28	101.1	-9.7	7.6	0.000
		LOS 50 mg bid	30	101.4	-8.6	6.5	0.001
						(0.580) ⁺	
		(All qd)					
050	12	Placebo	92	100.7	-5.3		
		LOS 50 mg	104	102.1	-8.7	3.4	0.000
		LOS 50/100 mg	102	102.2	-8.2	2.9	0.002
065	12	Placebo	79	100.4	-3.1		
		LOS 25 mg qd	83	100.4	-6.6	3.5	0.001
		LOS 50 mg qd	83	101.8	-6.6	3.5	0.001
		LOS 25 mg bid	82	101.2	-8.4	5.3	0.000
						(0.095) [@]	

&Drug effect=(Adj. mean change for drug - Adj. mean change for placebo), reported as a positive value.

*p-value for comparison versus placebo

+p-value for comparison of LOS 100 mg (qd) versus LOS 50 mg (bid)

@p-value for comparison of LOS 50 mg (qd) versus LOS 25 mg (bid)

Table 3. Mean change from baseline in SDBP or SuDBP at the end of studies 011, 050, and 065. (All-Patients-Treated By Race).

Study#	Week	Treatment	<u>Black</u>			<u>Non-Black</u>				
			<u>N</u>	<u>Mean Baseline</u>	<u>Change</u>	<u>Drug Effect^a</u>	<u>N</u>	<u>Mean Baseline</u>	<u>Change</u>	<u>Drug Effect^a</u>
		(All qd)								
		Placebo	5	107.4	-5.2		73	103.1	-5.6	
		LOS 10 mg	10	105.5	-4.7	-0.5	70	104.1	-8.4	2.8
		LOS 25 mg	14	104.4	-2.7	-2.5	68	103.1	-7.6	2.0
011	8	LOS 50 mg	10	105.0	-8.4	3.2	68	103.9	-10.3	4.7
		LOS 100 mg	17	105.1	-8.0	2.8	72	103.8	-10.3	4.7
		LOS 150 mg	11	103.6	-7.5	2.3	73	103.4	-10.1	4.5
		ENAL 20 mg	7	103.0	-4.4	-0.8	75	103.1	-11.8	6.2
		(All qd)								
		Placebo	17	102.1	-4.0		97	101.2	-4.3	
050	12	LOS 50 mg	14	103.9	-3.7	-0.3	111	101.9	-8.4	4.1
		LOS 50/100 mg	16	103.3	-5.6	1.6	102	102.0	-9.2	4.9
		Placebo	21	104.7	-2.5		81	100.4	-1.9	
065	12	LOS 25 mg qd	21	101.9	-4.0	1.5	84	101.8	-6.3	4.4
		LOS 50 mg qd	16	104.3	-1.5	-1.0	85	101.9	-7.2	5.3
		LOS 25 mg bid	10	103.6	-2.8	0.3	91	101.8	-8.6	6.7

^aDrug effect=(Mean change for drug - Mean change for placebo), values reported after multiplying by .-1.

Table 4. Mean change from baseline in SDBP or SuDBP
at the end of studies 011, 050, and 065.
(All-Patients-Treated By Gender).

Study#	Week	Treatment	<u>Female</u>			<u>Male</u>				
			<u>N</u>	<u>Mean</u> <u>Baseline</u>	<u>Change</u>	<u>Drug</u> <u>Effect*</u>	<u>N</u>	<u>Mean</u> <u>Baseline</u>	<u>Change</u>	<u>Drug</u> <u>Effect*</u>
		(All qd)								
		Placebo	31	102.4	-6.5		47	104.0	-5.0	
		LOS 10 mg	29	104.7	-6.8	0.3	51	104.0	-8.6	3.6
011	8	LOS 25 mg	27	102.8	-8.5	2.0	55	103.6	-6.0	1.0
		LOS 50 mg	25	103.2	-11.5	5.0	53	104.5	-9.4	4.4
		LOS 100 mg	31	103.1	-8.9	2.4	58	104.6	-10.4	5.4
		LOS 150 mg	22	103.0	-9.4	2.9	62	103.5	-9.8	4.8
		ENAL 20 mg	27	102.8	-13.0	6.5	55	103.3	-10.3	5.3
		(All qd)								
		Placebo	41	100.1	-5.6		73	102.1	-3.5	
050	12	LOS 50 mg	44	102.1	-9.6	4.0	81	102.2	-7.0	3.5
		LOS 50/100 mg	41	100.1	-6.6	1.0	77	103.3	-9.5	6.1
		(All qd)								
		Placebo	34	100.2	-2.4		68	101.9	-1.8	
065	12	LOS 25 mg qd	40	102.2	-6.0	3.6	65	101.5	-5.7	3.9
		LOS 50 mg qd	33	102.2	-6.2	3.8	68	102.3	-6.4	4.6
		LOS 25 mg bid	34	100.7	-7.3	4.9	67	102.6	-8.4	6.6

*Drug effect=(Mean change for drug - Mean change for placebo), values reported after multiplying by -1.

Table 5. Mean change from baseline in the 24-hour average diastolic ABPM. (Study 021).

<u>Treatment</u>	<u>N</u>	<u>Baseline</u>	<u>Adj. Mean Change</u>	<u>Drug Effect*</u>	<u>p-value*</u>
Placebo	26	94.8	-0.8		
LOS 50 mg qd	28	94.0	-5.6	4.8	0.002
LOS 100 mg qd	28	93.8	-7.1	6.3	0.000
LOS 50 mg bid	30	94.4	-9.0	8.2	0.000
					(0.199) ⁺

*Drug effect=(Adj. mean change for drug - Adj. mean change for placebo), reported as a positive value.

*p-value for comparison versus placebo

+p-value for comparison of LOS 100 mg (qd) versus LOS 50 mg (bid)

Table 6. Per-Protocol Analysis* of the Incidence of Dry Cough by Treatment. (Study 056)

	No. of Patients <u>Answered YES</u>	No. of Patients <u>Answered NO</u>	<u>Total</u>
Losartan 50 mg	7	33	40
Lisinopril 20 mg	22	10 ¹	32
HCTZ 25 mg	10	22 ²	32

* Conducted by the reviewer by excluding those patients who had two consecutive visits that were only one day apart.

(1) p<0.001 for the comparison with losartan 50 mg.

(2) p=0.264 for the comparison with losartan 50 mg.

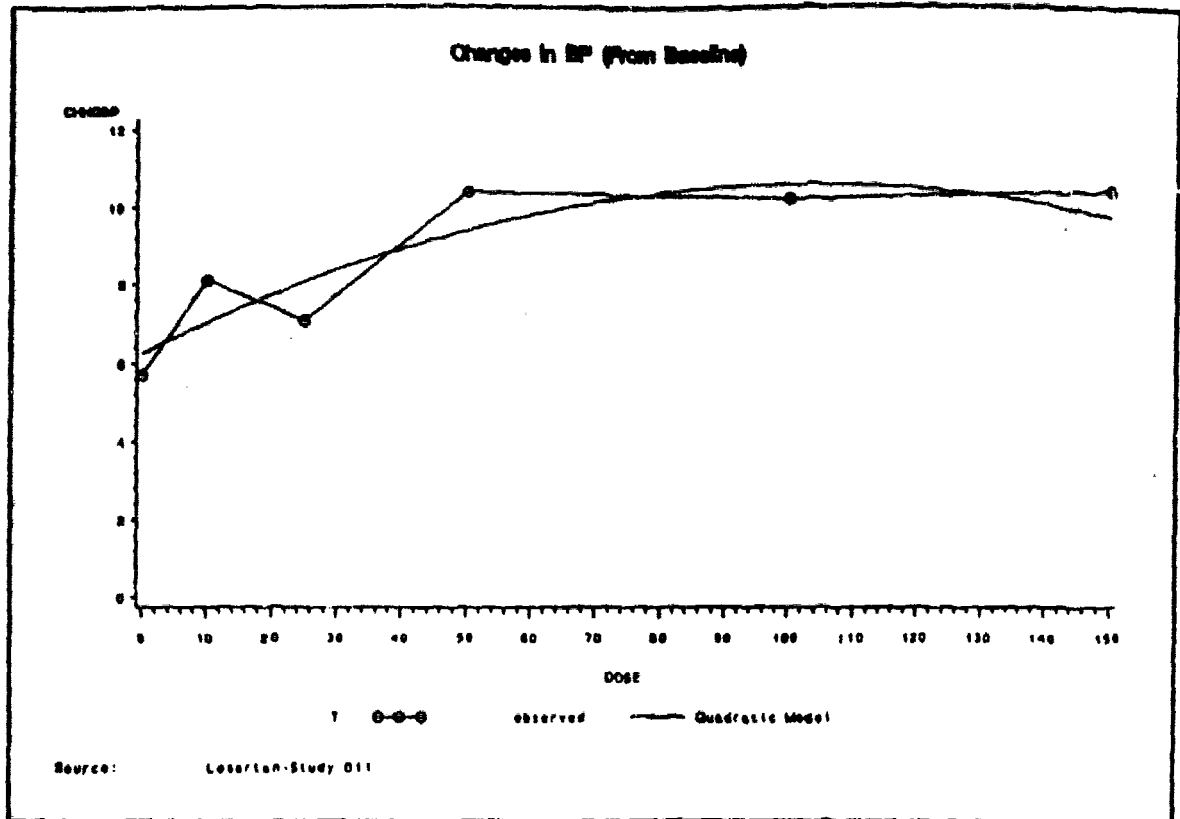


Figure 1. Quadratic model for the mean change from baseline in SDBP at week 8. (Study 011)

Estimated Model:

$$\text{Change} = 6.26 + 0.083(\text{dose}) - 0.0004(\text{dose})^2$$

$$\text{RMSE} = 1.104$$

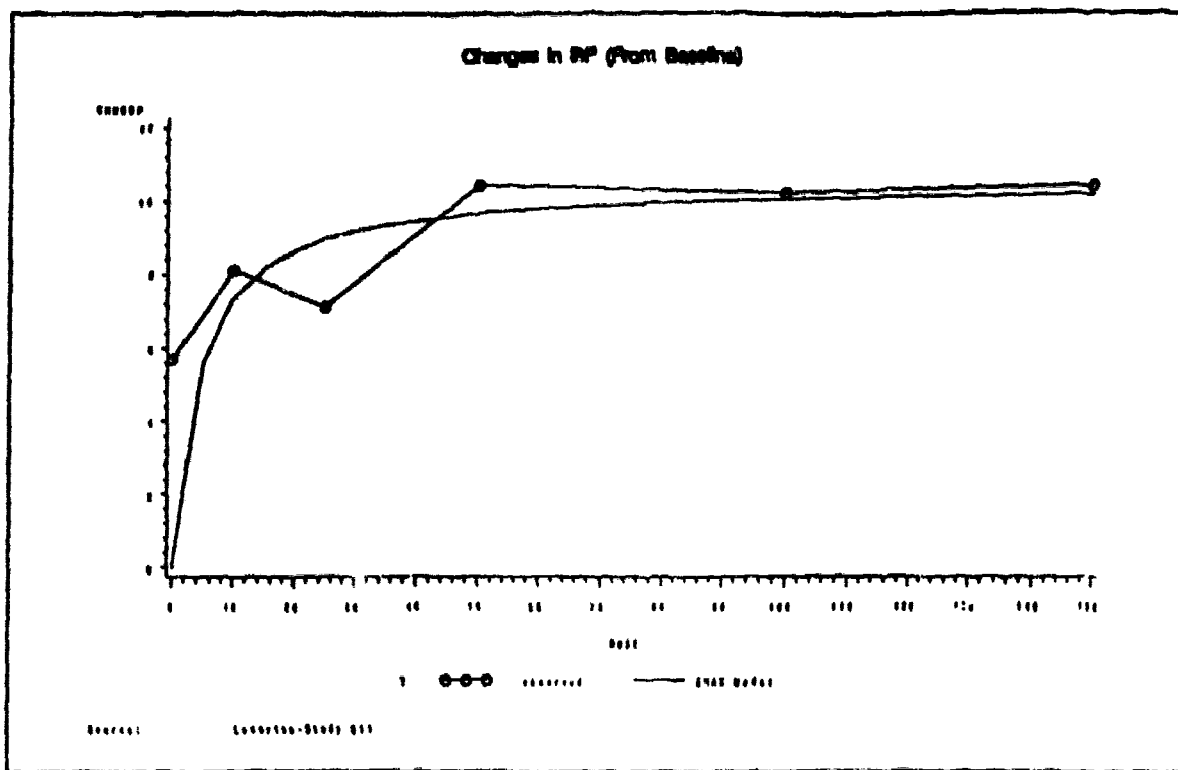


Figure 2. E_{max} model for the mean change from baseline in SBP at week 8. (Study 011)

Estimated Model:

$$\text{Change} = 10.44 * \text{dose} / (4.21 + \text{dose})$$

$$\text{RMSE} = 3.046$$

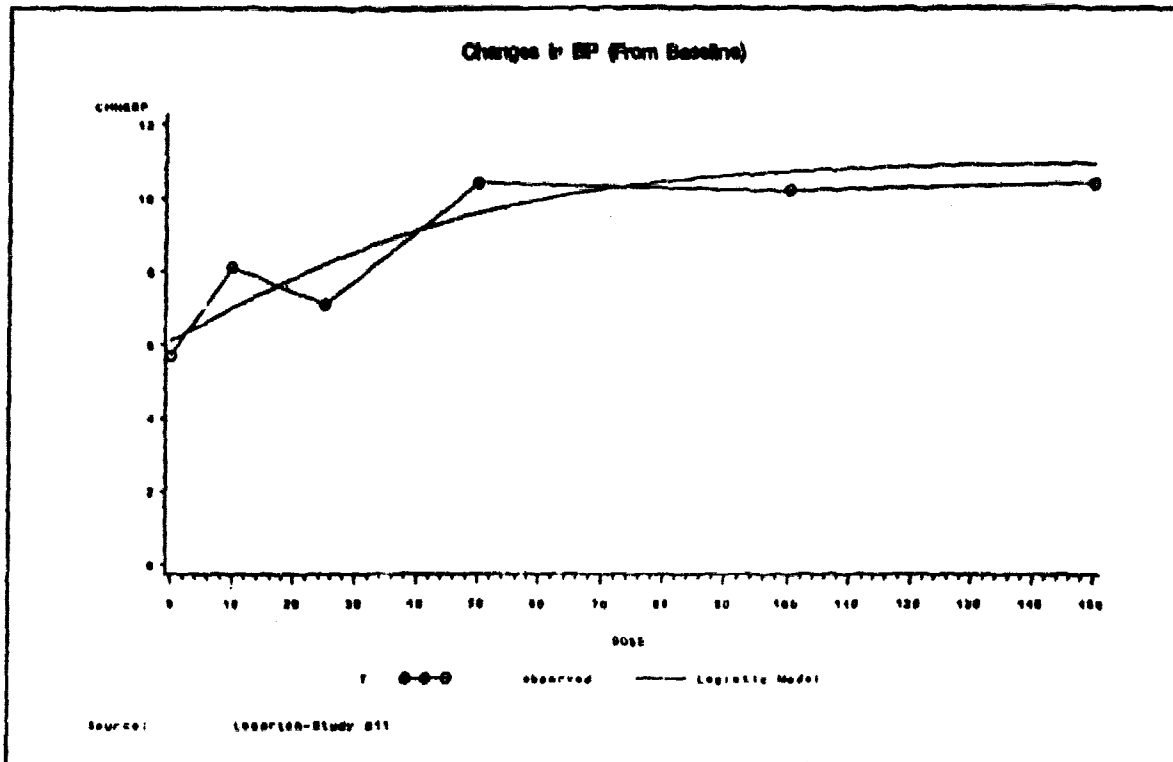


Figure 3. Logistic model for the mean change from baseline in SDBP at week 8. (Study 011)

Estimated Model:

$$\text{Change} = 11 / (1 + 0.8 * \exp(-0.034 * \text{dose}))$$

$$\text{RMSE} = 0.8698$$

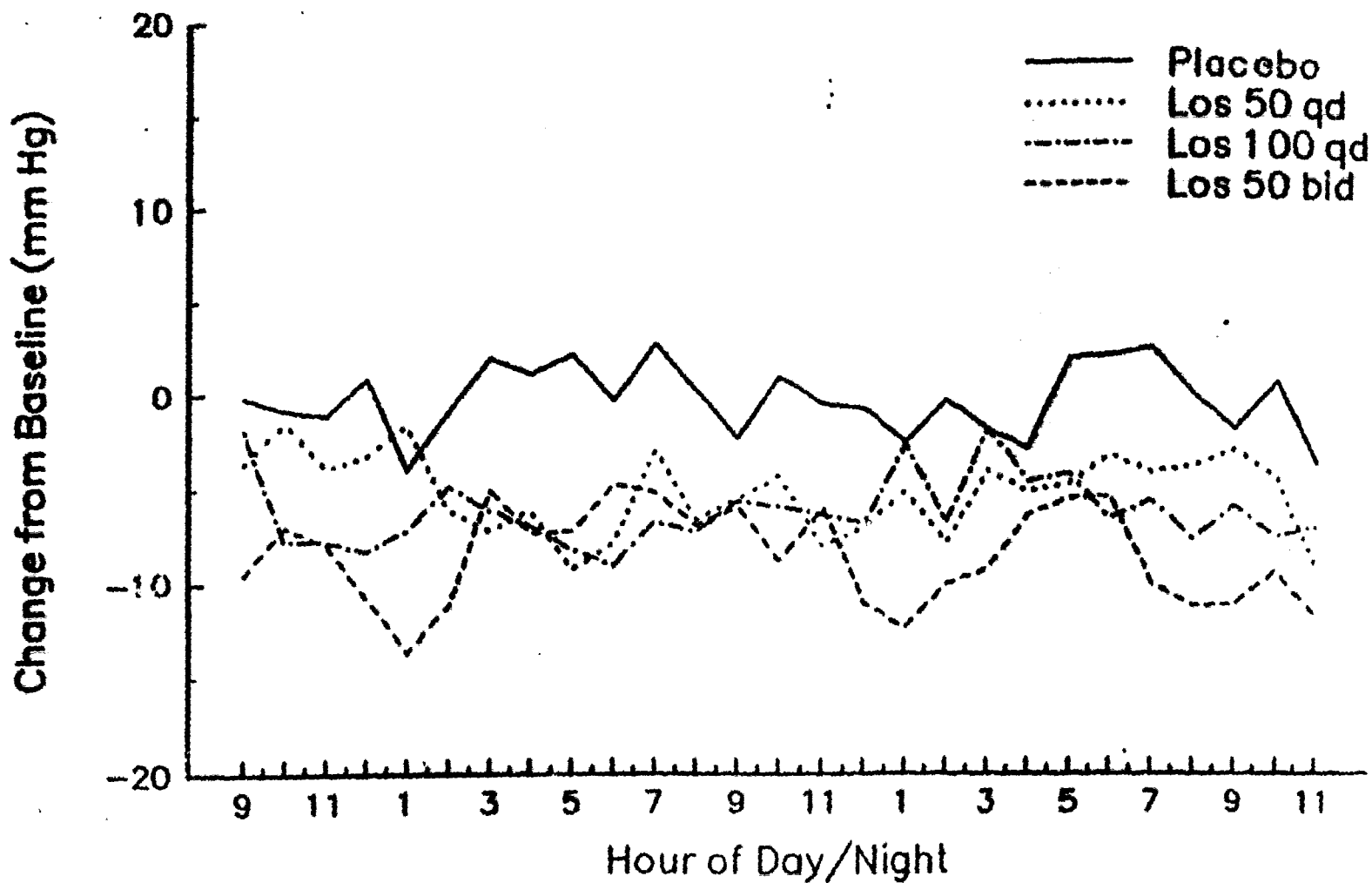


Figure 4. Change from baseline in diastolic hourly mean ABPM. (Study 021).

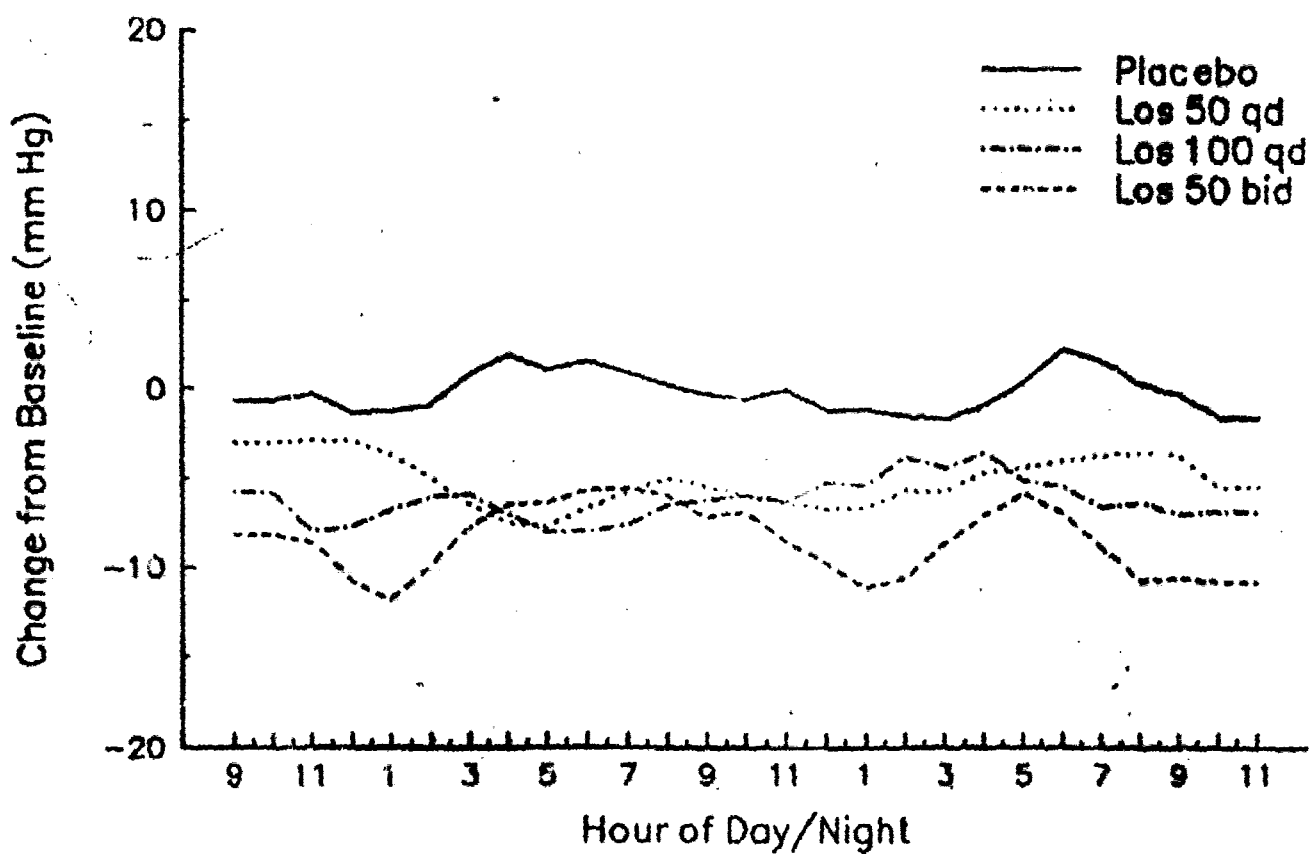


Figure 5. Smoothed data for the change from baseline in diastolic hourly mean ABPM. (Study 021).

HFD-110
OCT - 7 1994
K. Bongiorno

Statistical Review and Evaluation

(Addendum)

NDA: 20-386

Date: SEP 23 1994

Applicant: Merck Research Laboratories

Name of Drug: Cozaar (Losartan Potassium Tablets)

Documents Reviewed: Original NDA submission volumes 1.29 and 1.30. Data on floppy diskette supplied by the sponsor.

I. Background

A report of statistical review and evaluation on the mouse and the rat carcinogenicity studies of this NDA was issued by the Division of Biometrics on July 25, 1994. In that report the reviewer's analysis showed a statistically significant positive linear trend in the incidence of pancreas acinus adenoma in female rats. However, the sponsor's analysis did not show such a significant trend. In reply to a FDA comment in the meeting with the sponsor, the sponsor sent a reply explaining the statistical methods they used and some remarks on the methods used by the FDA statistician. This addendum contains some comments on sponsor's response.

II. Sponsor's response

Comment #5: "... When present, (in the historical control) the respective incidence of acinar cell hyperplasia and adenoma in a given group has been approximately 2% and .8% to 2%. The incidence of pancreatic acinar adenomas in high-dose Losartan-treated females (4%) was statistically positive by trend analysis. However, when adjusted for multiplicity the increased incidence was not statistically significant". "... The method used in our laboratory was developed in consultation with Professor John Tukey and Nathan Mantel, has been published (Mantel 1980: Mantel, Tukey, Ciminera, and Heyse 1982, and has been in routine use at our laboratory for over a decade. In contrast, the "Haseman .05/.01" rule is a rule-of-thumb that does not take into account the number of tumor sites examined, survival, or sample size".

III. Reviewer's discussion

The multiple testing adjustment method used by the sponsor is precisely the procedure described in the paper of Heyse and Rom (Adjusting for multiplicity of statistical tests in the analysis of carcinogenicity studies, J. F. Heyse and D. Rom, Biom. J (1988) 8, 883-896).

In the sponsor's analysis the incidence rates of pancreas acinus adenoma in female rats were found to be 0/130, 0/75, 0/75, and 3/75 in the control, low, medium, and high dose group with a calculated P-value of .0084 by the reviewer and .009 by the sponsor. Also P-values for the pairwise comparison of the high dose group with the control were found to be .0434 by the reviewer and .042 by the sponsor. Therefore, the calculated P-values by the reviewer and by the sponsor are essentially the same. However, due to the multiplicity of testings these P-values need to be adjusted before they could be interpreted as statistically significant.

There are various adjustment methods proposed in the literature for this adjustment. Some of these methods had been developed purely from the theoretical point of view, while some others from empirical studies of the historical data. In the present context Tukey's and Mantel's method, and Rom and Heyse's method fall in the first category and Haseman's method [Haseman, (1983), A re-examination of false-positive rates for carcinogenesis studies, Fundamental and Applied Toxicology, 3: 334-339] falls in the second category, which was based on the NTP data base.

Briefly, in Heyse and Rom's method the minimum $p_{(1)}$ of the calculated P-values of all tested tumor types is considered and the adjusted P-value for this is calculated using the formula $1 - (1 - p_{(1)})^k$, where k is equal to the number of tested tumor types for which the minimum P-value for all possible permutations of the observed number of tumor bearing animals is at least as low as $p_{(1)}$. In Haseman's method the calculated P-values for tumor types with incidence rates less than 1% is compared with $\alpha = .05$ and P-values for tumor types with incidence rates more than 1% is compared with $\alpha = .01$.

To compare the two methods regarding mortality, sample size, and number of observed tumor types we note the following:

Adjustment of mortality: None of the above mentioned adjustment methods takes care of the mortality differences among the treatment groups by themselves. In normal case mortality is adjusted by dividing the entire study period into a few number of small intervals and by calculating the test statistic from each individual interval. The test statistic was calculated in a similar fashion by both the sponsor and the reviewer. Therefore, in both sponsor's and reviewer's methods mortality had been adjusted and was adjusted similarly.

Effect of sample size: In Heyse and Rom's method k depends on number of tumor types tested. As the number of observed tumor types increases, k is expected to increase. Also as the sample size increases it is believed that the observed tumor types will also increase. It is therefore seen that Heyse and Rom's method is indirectly effected by the sample size (number of animals per treatment group). The reviewer likes to make the following two

comments on this issue:

1. The sample size for typical carcinogenicity studies in drug safety experiments is more or less standardized, that is, between 50 to 60 animals per treatment/sex group. Therefore, in practice in drug safety experiments the effect of sample size will be the same for all studies. The Haseman's procedure was based on historical data of studies with 50-60 animals per treatment/sex group. Hence, in reviewer's opinion for any drug safety carcinogenicity experiment the effect of sample size (i.e. the number of tumor types observed) will be about the same in both Haseman's, and Heyse and Rom's methods.

2. The few additional tumor types which may be observed because of the increase in sample size will probably be of rare kind. As Haseman (Ref.) pointed out that this kind of rare tumors do not have any significant effect on the experimentwise false positive rate.

Number of observed tumor types: As mentioned above, the Haseman's method was proposed based on the empirical studies of historical data from NTP data base. Therefore, the number of observed tumor types considered in his study is close to what is expected in any typical 2 year carcinogenicity study with two species and two sexes.

IV. Reviewer's comments

1. From the above discussions it is evident that for this particular study the effects of mortality, sample size, and number of observed tumor types on Heyse and Rom's method, and on Haseman's method are in effect the same.

2. In a simulation performed by the Division of Biometrics it was shown that the power of Heyse and Rom's method is extremely low. In other words this method is overly conservative.

3. Haseman's method was originally proposed for pairwise comparisons of control with a treated group (generally the high dose group). A simulation performed by the Division of Biometrics showed that the use of Haseman's method in case of trend test may result in a over all false positive rate much higher than 5%. The same simulation showed that Haseman's verbally proposed modification to his original method to use for the trend test, namely use $\alpha = .025$ for rare tumor types and $\alpha = .005$ for common tumor types has overall false positive rate of about 10-15% for four experiments (two species, two sexes).

4. The calculated P-value of pancreas acinus adenoma in female rats has a P-value of .009, which according to the above mentioned modified Haseman's method is statistically significant.

v. Conclusion

From the above discussions the reviewer concludes that the positive linear trend and the pairwise comparison of the high dose group with the control in the incidence of pancreas acinus adenoma in female rats are statistically significant.

Mohammad Aliar Rahman
Mohammad A. Rahman, Ph.D.
Mathematical Statistician

Karl K. Lin 9/22/94

Concur: Karl K. Lin, Ph.D., Group Leader

cc: Original NDA 20-386
HFD-110/Dr. Lipicky
HFD-110/Dr. Resnic
HFD-110/Dr. Bongiovanni
HFD-110/Dr. Proakis
HFD-110/Dr. Jagadeesh
HFD-710/Chron
HFD-715/Dr. K. Lin
HFD-715/Dr. Rahman
HFD-715/SARB Chron
HFD-715/DRU 2.1.1 NDA 20-386 Cozaar Mouse and Rat
carcinogenicity studies
HFD-502/Dr. Taylor
HFD-715/Diskette Rahman-2/COZAAR.ADN

HFD-110
Bongiovanni

Statistical Review and Evaluation

NDA: 20-386

Date: JUL 25 1994

Applicant: Merck Research Laboratories

Name of Drug: Cozaar (Losartan Potassium Tablets)

Documents Reviewed: Original NDA Submission volumes 1.29 and 1.30
Data on floppy diskette supplied by the sponsor.

I. Background: In this NDA submission two animal carcinogenicity studies, one in mice and one in rats, were included. These two studies were intended to assess the carcinogenicity potential of Cozaar tablets in mice and rats when administered orally by gavage once daily at some selected dose levels. The length of the mouse study was 92 weeks and that of the rat study was 105 weeks. Ms. Katherine Bongiovanni, HFD-110, requested the Division of Biometrics to perform the statistical review and evaluation of these studies. The results of the review have been discussed with the reviewing pharmacologists Dr. Anthony G. Proakis and the supervisory pharmacologist Dr. Charles A. Resnick.

II. The mouse study

IIa. Design: Two separate experiments, one in male and one in female mice, were conducted. In these two experiments there were three treated groups known as low, medium, and high dose groups, and two control groups known as control 1 and control 2. Two hundred and fifty male and two hundred and fifty female Crl:CD-1(ICR)BR mice were randomly divided into 5 groups of 50 animals each. The dose levels for the treated male groups were 20, 100, and 300/200¹ mg/kg/day, and for the female groups were 20, 100, and 500/300/200¹ mg/kg/day. The animals in the control group received the drug vehicle, deionized water, by gavage once daily.

The animals were checked daily for mortality and morbidity and were examined for the presence of any palpable masses every 4 weeks beginning in drug week 26. A complete histopathological examination was performed on all animals found dead, killed moribund during the experiment or sacrificed at the end of the experiment.

¹ Due to treatment related decreases in body weight gain and increases in mortality, the dosage level for the high dose females was lowered from 500 to 300 mg/kg/day in drug week 28 and from 300 to 200 mg/kg/day in drug week 42. Also due to the same reasons the dosage level for the high dose males was lowered from 300 to 200 mg/kg/day on drug week 42.

IIb. Sponsor's analysis

Survival data analysis: The survival data were analyzed using the extended Mantel-Haenszel test procedure (Tukey, J.W., Ciminera, J.L., Heyse, J.F. "Testing the statistical certainty of a response to increasing doses of a drug", Biometrics, Vol. 41, 1985, 295-301.). This approach compares the entire 'life-table' incidence patterns by summarizing the mortality data at, and cumulating over each week. Testing for trend proceeds sequentially starting with an evaluation through the highest dose of the test compound and stepping downward to the next highest dose each time a statistically significant ($P \leq .05$) trend is observed. Testing for trend stops at the highest dose of the test compound through which a statistically significant positive trend is not observed. Cumulative percent mortality or 'life-table' plots were also constructed using the methods described in the paper of Cutler and Adherer (Cutler, S.J., Adherer, F., "Maximum utilization of the life table method in analyzing survival" Journal of Chronic Disease, Vol. 8, 1958, 699-712).

The test showed that for the female mice, over the entire length of the study, there was statistically significant evidence of an increased mortality with increasing dosage. This increased mortality in female mice can be attributed, primarily, to the early deaths in the high dose level. During the second year of the study, this mortality was comparable with the concurrent controls. No such positive dose-response was found in the mortality of male mice.

Tumor data analysis: The tumor data were also analyzed using the extended Mantel-Haenszel test procedure (1985) using ordinal, arithmetic (real dose levels), and arithmetic-logarithmic score. Mortality adjustment was done using intervals 1-52, 53-65, 66-78, 79-end of study, and terminal sacrifice. The smallest P-value found from the three scoring was used to test the trend. Data of tumor types with fewer than 10 tumor bearing animals were analyzed using the exact test procedure described in the paper of Ciminera (Ciminera, J.L., "Some issues in the design, evaluation, and interpretation of tumorigenicity studies in animals", Proceedings of the symposium on long term animal carcinogenicity studies: A statistical perspective, American Statistical Association, Washington, D.C., 1985, 26-35). This method incorporates (i) time-to-tumor detection, (ii) time-to-death without tumor, and (iii) context of observation.

Adjustment for multiple testing was performed using the procedure described in the paper of Heyse and Rom (Heyse J.F., Rom, D. "Adjusting for multiplicity of statistical tests in the analysis of carcinogenicity studies", Biometrical Journal, Vol. 30, 1988, 883-896), and Harter (Harter, H.L. "Error rates and sample sizes for range tests in multiple comparisons", Biometrics, Vol. 13, 1957, 511-536).

The test showed a statistically significant positive dose-response in the incidence of lung-adenocarcinoma ($P=.004$) in male mice. Also in male mice the P-value for trend test in lymphoma for primary site undetermined was found to be .022. However, after the adjustment for multiple testing using the above stated procedures it was not considered to be statistically significant. No positive linear trend was found in the tumor types tested in the female mice.

IIc. Reviewer's analysis

The reviewer independently performed analyses on the survival and the tumor data. For survival data analysis the methods described in the papers of Cox (Regression models and life tables, Journal of the Royal Statistical Society, B, 34 187-220, 1972), and of Gehan (A generalized Wilcoxon test for comparing arbitrarily singly censored samples, Biometrika, 52 203-223, 1965) were used. The tumor data were analyzed using the methods described in the paper of Peto et al. (Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments, Long term and short term screening assays for carcinogens: A critical appraisal, International agency for research against cancer monographs, Annex to supplement, World Health Organization, Geneva, 311-426, 1980) and the method of exact permutation trend test, developed by the Division of Biometrics. All data used in the reviewer's analysis were provided by the sponsor on a floppy diskette.

Survival analysis: The intercurrent mortality data of mouse study are given in table 1. The plots of Kaplan-Meier estimates of the survival distributions of male and female mice are given in Figures 1a and 1b, respectively. The homogeneity of survival distributions of four groups (Control, Low, Medium, High) were tested separately for male and female mice using the Cox test and the Generalized Wilcoxon test. The tests did not show any statistically significant (at .05 level) positive linear trend or difference in the mortality among treatment groups in male mice. Mortality of female mice showed a statistically significant (at $\alpha=.01$) positive linear trend across the dose levels. Pairwise comparisons showed statistically significant (at $\alpha=.01$) increment in mortality in the high dose group when compared with the low and the medium dose group. The pairwise comparison of the high dose group with the control however, was not statistically significant.

The p-values of the positive linear trend and the pairwise tests are given in Tables 2a and 2b, respectively.

Tumor data analysis: The reviewer performed the trend test on data of all tumor types and the pairwise comparisons of the treated groups with the control for some selected tumor types. Since the sponsor classified the tumor types as 'cause of death' or 'not a cause of death', following Peto et al. (1980), the reviewer applied

the 'death rate method' and the 'prevalence method' for testing positive linear trend in these two categories of tumor types, respectively. For tumor types occurring in both categories (i.e. same tumor found as cause of death for some animals and not cause of death for some other animals) a combined test was performed. The exact permutation trend test was used to calculate the p-values of all trend tests, except when the tumors were found in the both categories, in those cases the continuity corrected normal test was used. The scores used were 0, 20, 100, and 300 for control, low, medium, and high dose groups, respectively. The tests were repeated using score 200 for the high dose group in case of any positive finding. Since the two control groups were treated in the same way, in the reviewer's analysis they were combined to form a single control group. The time intervals used were 0-52, 53-78, 79-91 weeks, and terminal sacrifice.

The incidence rates of tumor type with p-value less than .05 are listed below.

<u>Male mice</u> <u>Organ/Tumor</u>	<u>Tumor rate</u>				<u>P-value</u>	
	<u>C</u>	<u>L</u>	<u>M</u>	<u>H</u>	<u>Trend</u>	<u>Pairwise</u>
Lung/Adenocarcinoma	100	50	50	50	.0040 ²	.0233 ² (C,H)

Multiple testing adjustment: The rule proposed by Haseman was used to adjust the effect of multiple testings. Haseman's rule states that in order to keep the false-positive rate at the nominal level of approximately five percent, tumor types with a spontaneous tumor rate of no more than one percent should be tested at .05 level, otherwise the level should be set at .01 (Haseman, (1983), A re-examination of false-positive rates for carcinogenesis studies, Fundamental and Applied Toxicology, 3: 334-339).

On the basis of the above Haseman's rule the positive linear trend in lung adenocarcinoma in male mice is considered to be statistically significant. None of the tested tumor types in female mice showed statistically significant positive linear trend. Again on the basis of Haseman's rule the P-value of the pairwise comparison of incidences of lung adenocarcinoma in male mice in the high dose group with those in the control group is not considered to be statistically significant.

For Lung adenocarcinoma the positive linear trend test using weight 200 for the high dose group has a P-value equal to .0071², which is considered to be statistically significant.

On the request of the supervisory pharmacologist Dr. Resnick, the reviewer performed the following analysis on the combined data of lung adenoma and adenocarcinoma in male mice.

² Continuity corrected normal test P-values

<u>Male mice</u> <u>Organ/Tumor</u>	<u>Tumor rate</u>				<u>P-value</u>	
	<u>C</u>	<u>L</u>	<u>M</u>	<u>H</u>	<u>Trend</u>	<u>Pairwise</u>
Lung/Adenoma+Adenocarcinoma	18	12	12	14	.0436 ²	.0548 ² (C,H)

Using weight 200 for the high dose group the P-value of the trend test for this combined tumor type is equal to .0475². On the basis of the Haseman's rule none of the trend P-values or the P-value for the pairwise comparison is considered to be significant.

The incidence rates and p-values of all tumor types tested for positive linear trend are given in Tables 3.

III. The rat study

IIIa. Design: Two separate experiments, one in male and one in female rats, were conducted. In these two experiments there were three treated groups known as low, medium, and high dose groups, and a control group. Three hundred and fifty five male, and three hundred and fifty five female sprague-dawley Cr1. CD(SD) BR rats were randomly divided into selected sizes of 130, 75, 75, and 75 for control, low, medium, and high dose group, respectively. The dose levels for the treated groups were 15, 45, and 135/270 mg/kg/day for low, medium, and high dose groups, respectively. The animals in the control group received the drug vehicle, deionized water, by gavage once daily.

The animals were checked daily for mortality and morbidity and were examined for the presence of any palpable masses every 4 weeks beginning in drug week 26. A complete histopathological examination was performed on all animals found dead, killed moribund during the experiment or sacrificed at the end of the experiment.

IIIb. Sponsor's analysis

Survival data analysis: The survival data were analyzed using the extended Mantel-Haenszel test procedure (Tukey, J.W., Cimínera, J.L., Heyse, J.F. 1985). This approach compares the entire 'life-table' incidence patterns by summarizing the mortality data at, and cumulating over each week. Testing for trend proceeds sequentially starting with an evaluation through the highest dose of the test compound and stepping downward to the next highest dose each time a statistically significant ($P \leq .05$) trend is observed. Testing for trend stops at the highest dose of the test compound through which a statistically significant positive trend is not observed. Cumulative percent mortality or 'life-table' plots were also constructed using the methods described in the paper of Cutler and Adherer (1958).

² Continuity corrected normal test P-values

³ Dose was raised in week 6, because the previous dose did not appear to be close to the maximally tolerated dose.

The test did not show any statistically significant positive dose-response in the mortality in either sex.

Tumor data analysis: The tumor data were also analyzed using the extended Mantel-Haenszel test procedure (1985) using ordinal, arithmetic (real dose levels), and arithmetic-logarithmic score. Mortality adjustment was done using intervals 1-52, 53-65, 66-78, 79-91, 92-end of study, and terminal sacrifice. The smallest P-value found from the three scoring methods was used to test the trend. Data of tumor types with fewer than 10 tumor bearing animals were analyzed using the exact test procedure described in the paper of Ciminera (Ciminera, J.L., 1985). This method incorporates (i) time-to-tumor detection, (ii) time-to-death without tumor, and (iii) context of observation.

Adjustment for multiple testing was performed using the procedure described in the paper of Heyse and Rom (Heyse J.F., Rom, D. 1957).

The test did not show any statistically significant positive linear trend in the incidences of tumor types tested in either sex. The P-values for the trend test in pancreas acinus adenoma and lung adenoma in female rats was found to be .009 and .042, respectively. However, after the adjustment for multiple testing using the above stated procedures none of these was considered to be statistically significant.

IIIc. Reviewer's analysis

The reviewer independently performed analyses on the survival and the tumor data. For survival data analysis the methods described in the papers of Cox (1972) and of Gehan (1965) were used. The tumor data analyses were performed using the methods described in the paper of Peto et al. (1980) and the method of exact permutation trend test, developed by the Division of Biometrics. All data used in the reviewer's analysis were provided by the sponsor on a floppy diskette.

Survival analysis: The intercurrent mortality data of the rat study are given in table 4. The plots of Kaplan-Meier estimates of the survival distributions for male and female rats are given in Figures 2a and 2b, respectively. The homogeneity of survival distributions of four groups (Control, Low, Medium, and High) were tested separately for male and female rats using the Cox test and the Generalized Wilcoxon test. The test did not show any statistically significant (at .05 level) positive linear trend in the mortality among treatment groups in either sex. In male rats pairwise comparisons showed a statistically significant increased mortality in the medium dose group when compared with the control.

The p-values of the trend and the pairwise tests are given in Tables 5a and 5b.

Tumor data analysis: The reviewer performed the trend test on data of all tumor types and the pairwise comparisons of the treated groups with the control for some selected tumor types. Since the sponsor classified the tumor types as 'cause of death' or 'not a cause of death', following Peto et al. (1980), the reviewer applied the 'death rate method' and the 'prevalence method' for testing the positive linear trend in these two categories of tumor types, respectively. For tumor types occurring in both categories a combined test was performed. The exact permutation trend test was used to calculate the p-values of all trend tests, except when the tumors were found in the both categories, in those cases the continuity corrected normal test was used. The scores used were 0, 15, 45, and 270 for control, low, medium, and high dose groups, respectively. The time intervals used were 0-52, 53-78, 79-94, 95-104 weeks, and terminal sacrifice for both male and female rats.

The incidence rates of tumor type with p-value less than .05 are listed below.

<u>Female rats</u> <u>Organ/Tumor</u>	<u>Tumor rate</u>				<u>P-value</u>	
	<u>C</u>	<u>L</u>	<u>M</u>	<u>H</u>	<u>Trend</u>	<u>Pairwise</u>
Pancreas Acinus, Adenoma	130	75	75	75	.0084	.0434 (C,H)
	0	0	0	3		

On the basis of Haseman's rule the positive linear trend in Pancreas acinus adenoma in female rats is considered to be statistically significant. Again on the basis of Haseman's rule the P-value of the pairwise comparison of the high dose group with the control is considered to be statistically significant. None of the tested tumor types in male rats showed statistically significant positive linear trend.

The incidence rates and p-values of all tumor types tested for positive linear trend are given in Table 6.

V. Summary

Mouse study: The tests on mortality data did not show any statistically significant (at .05 level) positive linear trend or differences in mortality among treatment groups in male mice. Mortality data of female mice showed a statistically significant (at $\alpha=.01$) positive linear trend across the dose levels. Pairwise comparisons on the data showed a statistically significant (at $\alpha=.01$) increment in mortality in the high dose group when compared with the low and the medium dose group. The pairwise comparison of the high dose group with the control however, was not statistically significant.

The tests on tumor data showed a statistically significant positive linear trend in the incidences of lung adenocarcinoma in male mice. None of the tested tumor types in female mice showed a

statistically significant positive linear trend. The pairwise comparison of the incidences of lung adenocarcinoma in the high dose group in male mice with those in the control was not found to be statistically significant.

The rat study: The tests on the mortality data did not show any statistically significant (at .05 level) positive linear trend in mortality among treatment groups in either sex. Pairwise comparisons showed a statistically significant increase in mortality in the medium dose group when compared with the control.

The tests on the tumor data showed a statistically significant positive linear trend in pancreas acinus adenoma in female rats. For the same tumor type the P-value of the pairwise comparison of the high dose group with the control is also considered to be statistically significant. None of the tested tumor types in male rats showed a statistically significant positive linear trend.

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Table 1

Intercurrent mortality rates in the mouse study

Sex	Time(wks)	Control	Low	Medium	High
MALE					
	0 - 52	10/100 (10.00)	6/ 50 (12.00)	3/ 50 (6.00)	12/ 50 (24.00)
	53- 78	24/ 90 (34.00)	12/ 44 (36.00)	14/ 47 (34.00)	8/ 38 (40.00)
	79- 91	26/ 66 (60.00)	5/ 32 (46.00)	8/ 33 (50.00)	9/ 30 (58.00)
	TERM. SACR	40/100 (40.00)	27/ 50 (54.00)	25/ 50 (50.00)	21/ 50 (42.00)
FEMALE					
	0 - 52	7/100 (7.00)	1/ 50 (2.00)	2/ 50 (4.00)	10/ 50 (20.00)
	53- 78	31/ 93 (38.00)	7/ 49 (16.00)	10/ 48 (24.00)	13/ 40 (46.00)
	79- 91	17/ 62 (55.00)	7/ 42 (30.00)	9/ 38 (42.00)	10/ 27 (66.00)
	TERM. SACR	45/100 (45.00)	35/ 50 (70.00)	29/ 50 (58.00)	17/ 50 (34.00)

Note: Except the TERM. SACR. row, an entry of this table = number of animals dying or sacrificed in the time interval/number of animals entering the time interval. An entry in parenthesis = cumulative mortality rate; i.e. cumulative percent of animals dying up to the end of the time interval. An entry in the TERM. SACR. row = number of animals surviving to terminal sacrifice / initial number of animals. An entry in parenthesis in this row = percent of animals (of the initial number) surviving to terminal sacrifice.

Table 2a

P-values of tests for positive linear trend in mortality
in the mouse study.

<u>Test of homogeneity</u>		
<u>Sex</u>	<u>Test</u>	<u>P-value</u>
		(One tail Chi-Sqr.)
Male	Cox	.4495
	Wilcoxon	.4308
Female	Cox	.0003
	Wilcoxon	.0001

<u>Test of Positive linear trend</u>		
<u>Sex</u>	<u>Test</u>	<u>P-value</u>
		(One tail Normal)
Male	Cox	.2988
	Wilcoxon	.1947
Female	Cox	.0046
	Wilcoxon	.0021

Table 2b

P-values of pairwise tests for the differences in mortality between treatment groups in the mouse study

Male mouse

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR)

DSNAME: a11ta.mms

GROUP	EXACT ONE TAIL TEST	212 CHI- SQUARE USING N IN DEN	DIRECTION OF 212 CHI-SQ	COY'S TEST		GENERALIZED K/M ANALYSIS	
				EXACT	INVERSE CONSERVATIVE	EXACT	INVERSE CONSERVATIVE
0 VS. 1	CHISQ	2.1073	NEG	1.0333	1.0312	.4223	.4218
	PROB	.0734		.3094	.3099	.5158	.5161
0 VS. 2	CHISQ	.9808	NEG	.9884	.9874	1.1252	1.1245
	PROB	.1610		.3201	.3204	.2888	.2890
0 VS. 3	CHISQ	.0035	NEG	.0207	.0207	.5694	.5692
	PROB	.4751		.8856	.8856	.4753	.4755
1 VS. 2	CHISQ	.0401	POS	.0003	.0003	.1209	.1208
	PROB	.4207		.9868	.9865	.7261	.7282
1 VS. 3	CHISQ	1.0016	POS	1.0042	1.0030	1.3381	1.3368
	PROB	.1585		.2978	.2980	.2474	.2476
2 VS. 3	CHISQ	.3623	POS	1.0535	1.0521	2.2064	2.2029
	PROB	.2737		.3047	.3050	.1374	.1376

Female mouse2

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR)

DSNAME: a11ta.fms

GROUP	EXACT ONE TAIL TEST	212 CHI- SQUARE USING N IN DEN	DIRECTION OF 212 CHI-SQ	COY'S TEST		GENERALIZED K/M ANALYSIS	
				EXACT	INVERSE CONSERVATIVE	EXACT	INVERSE CONSERVATIVE
0 VS. 1	CHISQ	7.3562	NEG	8.3022	8.2692	9.8401	9.8021
	PROB	.003088		.004081	.004081	.001781	.001781
0 VS. 2	CHISQ	1.7636	NEG	2.2382	2.2354	2.9916	2.9879
	PROB	.0920		.1346	.1349	.0837	.0839
0 VS. 3	CHISQ	1.2406	POS	2.3344	2.3325	3.6002	3.5975
	PROB	.1325		.1263	.1267	.0578	.0579
1 VS. 2	CHISQ	1.0051	POS	1.2924	1.2909	1.8035	1.8017
	PROB	.1488		.2556	.2539	.1793	.1795
1 VS. 3	CHISQ	11.3785	POS	14.6266	14.4810	17.8225	16.8464
	PROB	.000318		.000188	.000188	.000081	.000081
2 VS. 3	CHISQ	4.6712	POS	6.8844	6.8563	8.8964	8.8664
	PROB	.01348		.008711	.008881	.002911	.002911

Table 3

Tumor rates and p-values of the tested tumor types for positive linear trend in mouse study

MALE MICE

<u>Organ Name/ Tumor Name</u>	<u>Exact P-Value</u>	<u>Asymptotic P-value</u>	<u>C</u>	<u>L</u>	<u>M</u>	<u>H</u>
ADRENAL CORTEX/ ADENOMA	0.9771	0.91465	3	1	0	0
EYE HARDERIAN GLAND/ ADENOMA	0.3759	0.37740	10	5	10	5
LIVER/ HEMANGIOSARCOMA	0.9209	0.86855	2	1	0	0
LIVER/ HEPATOCELLULAR ADENOMA	0.1217	0.11295	9	2	5	6
LIVER/ HEPATOCELLULAR CARCINOMA	0.2168	0.21375	9	8	4	7
LUNG/ ADENOCARCINOMA	0.0074	0.00400	5	3	3	8
LUNG/ ADENOMA	0.5568	0.56020	13	9	9	6
NERVE/ SCHWANNOMA	0.1858	0.02455	0	0	0	1
PANCREAS ISLET/ ADENOMA	1.0000	0.77285	1	0	0	0
PITUITARY/ ADENOMA	0.4071	0.43760	0	0	1	0
PRIMARY SITE UNDETERMINED/ HISTIOCYTIC SARCOMA	0.3713	0.34250	1	1	0	1
PRIMARY SITE UNDETERMINED/ LEUKEMIA	0.6017	0.70985	0	1	0	0
PRIMARY SITE UNDETERMINED/ LYMPHOMA	0.1139	0.10135	0	2	3	2
SEMINAL VESICLE/ ADENOMA	1.0000	0.77285	1	0	0	0
SKELETAL MUSCLE/ HEMANGIOSARCOMA	0.5822	0.70270	0	1	0	0
SKIN/ HEMANGIOSARCOMA	1.0000	0.76860	1	0	0	0
SKIN/ HIBERNOMA	0.4071	0.43760	0	0	1	0
SKIN/ LIPOMA	1.0000	0.77285	1	0	0	0
SKIN/ OSTEOGENIC SARCOMA	1.0000	0.76200	1	0	0	0
SMALL INTESTINE/ HEMANGIOMA	1.0000	0.77285	1	0	0	0
SMALL INTESTINE/ POLYP	0.6506	0.66275	1	0	1	0
SPLEEN/ HEMANGIOSARCOMA	0.6358	0.65330	1	0	1	0
TESTIS/ HEMANGIOMA	1.0000	0.74500	1	0	0	0
TESTIS/ INTERSTITIAL CELL TUMOR	0.4542	0.46375	2	1	2	1
TESTIS EPIDIDYMIS/ LEIOMYOSARCOMA	0.1379	0.01080	0	0	0	1
TESTIS RETE TESTIS/ ADENOMA	1.0000	0.77285	1	0	0	0
THYROID FOLLICULAR CELL/ ADENOMA	0.5616	0.51830	3	0	0	1

Table 3 continued to the next page

Table 3 continued from the previous page

FEMALE MICE

<u>Organ Name/Tumor Name</u>	Exact	Asymptotic	Incidence Rates			
	<u>P-Value</u>	<u>P-value</u>	<u>C</u>	<u>L</u>	<u>M</u>	<u>H</u>
ADRENAL/ PHEOCHROMOCYTOMA	1.0000	0.75740	1	0	0	0
ADRENAL/ SPINDLE CELL TUMOR	0.2367	0.18005	1	0	1	1
BONE/ OSTEOMA	1.0000	0.78430	1	0	0	0
BONE/ OSTEOSARCOMA	1.0000	0.75720	1	0	0	0
EYE HARDERIAN GLAND/ ADENOMA	0.2533	0.25845	2	3	1	2
HEART/ HEMANGIOMA	1.0000	0.75740	1	0	0	0
KIDNEY PELVIC EPITHELIUM/ TRANSITIONAL CELL CARCINOMA	0.3651	0.37720	0	0	1	0
LARGE INTESTINE ANUS/ SQUAMOUS CELL CARCINOMA	0.3651	0.37720	0	0	1	0
LIVER/ HEMANGIOMA	0.9844	0.90385	3	1	0	0
LIVER/ HEPATOCELLULAR ADENOMA	0.8743	0.80165	1	1	0	0
LIVER/ HEPATOCELLULAR CARCINOMA	1.0000	0.83915	2	0	0	0
LUNG/ ADENOCARCINOMA	0.6445	0.65395	7	1	0	2
LUNG/ ADENOMA	0.7757	0.77455	15	7	7	5
LUNG/ OSTEOMA	1.0000	0.87195	1	0	0	0
MAMMARY GLAND/ ADENOACANTHOMA	1.0000	0.88665	3	0	0	0
MAMMARY GLAND/ ADENOCARCINOMA	0.7481	0.74040	5	1	1	1
OVARY/ ADENOMA	0.6429	0.68995	0	1	0	0
OVARY/ GRANULOSA CELL TUMOR	0.6594	0.69590	1	1	1	0
PITUITARY/ ADENOMA	0.7760	0.76410	2	0	1	0
PRIMARY SITE UNDETERMINED/ HISTIOCYTIC SARCOMA	0.3387	0.30205	2	0	1	1
PRIMARY SITE UNDETERMINED/ LYMPHOMA	0.4644	0.48210	4	5	4	2
PRIMARY SITE UNDETERMINED/ PLASMA CELL MYELOMA	0.3651	0.37720	0	0	1	0
SKELETAL MUSCLE/ RHABDOMYOSARCOMA	0.5967	0.60875	1	0	1	0
SKIN/ HEMANGIOMA	1.0000	0.75720	1	0	0	0
SKIN/ RHABDOMYOSARCOMA	0.6762	0.76155	0	2	0	0
SMALL INTESTINE/ ADENOCARCINOMA	0.3850	0.40765	0	0	1	0
SMALL INTESTINE/ POLYP	1.0000	0.75740	1	0	0	0
STOMACH NONGLANDULAR MUCOSA/ PAPILLOMA	0.6047	0.73215	0	1	0	0
THYROID FOLLICULAR CELL/ ADENOMA	0.3651	0.37720	0	0	1	0
UTERUS/ HEMANGIOMA	0.1698	0.12010	0	1	0	1
UTERUS/ LEIOMYOMA	0.6743	0.75925	0	2	0	0
UTERUS/ POLYP	0.9144	0.89725	3	3	1	0
UTERUS/ ENDOMETRIAL STROMA/ SARCOMA	0.2759	0.14340	1	0	0	1
VAGINUS/ LEIOMYOSARCOMA	1.0000	0.75880	1	0	0	0

Table 4

Intercurrent mortality rates in the rat study

Sex	Time(wks)	Control	Low	Medium	High
MALE					
	0 - 52	19/130 (14.62)	3/ 75 (4.00)	7/ 75 (9.33)	9/ 75 (12.00)
	53- 78	28/111 (36.15)	13/ 72 (21.33)	12/ 68 (25.33)	17/ 66 (34.67)
	79- 94	45/ 83 (70.77)	29/ 59 (60.00)	16/ 56 (46.67)	15/ 49 (54.67)
	95-104	17/ 38 (83.85)	11/ 30 (74.67)	14/ 40 (65.33)	8/ 34 (65.33)
	TERM. SACR	21/130 (16.15)	19/ 75 (25.33)	26/ 75 (34.67)	26/ 75 (34.67)
FEMALE					
	0 - 52	3/130 (2.31)	2/ 75 (2.67)	3/ 75 (4.00)	9/ 75 (12.00)
	53- 78	28/127 (23.85)	17/ 73 (25.33)	15/ 72 (24.00)	11/ 66 (26.67)
	79- 94	39/ 99 (53.85)	28/ 56 (62.67)	21/ 57 (52.00)	26/ 55 (60.00)
	95-104	22/ 60 (70.77)	8/ 28 (73.33)	16/ 36 (73.33)	11/ 30 (74.67)
	TERM. SACR	38/130 (29.23)	20/ 75 (26.67)	20/ 75 (26.67)	19/ 75 (25.33)

Note: Except the TERM. SACR. row, an entry of this table = number of animals dying or sacrificed in the time interval/number of animals entering the time interval. An entry in parenthesis = cumulative mortality rate; i.e. cumulative percent of animals dying up to the end of the time interval. An entry in the TERM. SACR. row = number of animals surviving to terminal sacrifice / initial number of animals. An entry in parenthesis in this row = percent of animals (of the initial number) surviving to terminal sacrifice.

Table 5a

P-values of tests for positive linear trend in mortality
in the rat study

<u>Test of homogeneity</u>		
<u>Sex</u>	<u>Test</u>	<u>P-value</u>
		(One tail Chi-Sqr.)
Male	Cox	.0083
	Wilcoxon	.0270
Female	Cox	.8380
	Wilcoxon	.7503

<u>Test of Positive linear trend</u>		
<u>Sex</u>	<u>Test</u>	<u>P-value</u>
		(One tail Normal)
Male	Cox	.0566
	Wilcoxon	.2339
Female	Cox	.3026
	Wilcoxon	.2717

Table 5b

P-values of pairwise tests for the differences in mortality between treatment groups in the rat study

Male rat

GROUP	EXACT ONE TAIL TEST	2X2 CHI- SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST		GENERALIZED K/M ANALYSIS	
				EXACT	INVERSE CONSERVATIVE	EXACT	INVERSE CONSERVATIVE
0 VS. 1	CHISQ	2.0000	NEG	3.9400	3.9282	3.2060	3.1958
	PROB	.0797		.04728	.04751	.02251	.02261
0 VS. 2	CHISQ	0.2067	NEG	0.6699	0.5610	6.9359	6.8948
	PROB	.002388		.003281	.003481	.008418	.008681
0 VS. 3	CHISQ	0.2067	NEG	4.0019	4.0403	2.0974	2.0917
	PROB	.002388		.02718	.02781	.1476	.1481
1 VS. 2	CHISQ	1.1429	NEG	.0179	.0139	.3214	.3206
	PROB	.1425		.3658	.3670	.5708	.5713
1 VS. 3	CHISQ	1.1429	NEG	.0654	.0652	.2524	.2520
	PROB	.1425		.7981	.7984	.6154	.6157
2 VS. 3	CHISQ	.0000	POS	.1623	.1621	.7022	.7016
	PROB	.5681		.6870	.6872	.4020	.4022

Female rat

GROUP	EXACT ONE TAIL TEST	2X2 CHI- SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST		GENERALIZED K/M ANALYSIS	
				EXACT	INVERSE CONSERVATIVE	EXACT	INVERSE CONSERVATIVE
0 VS. 1	CHISQ	.0337	POS	.4434	.4426	.7413	.7405
	PROB	.4108		.9055	.9059	.3092	.3093
0 VS. 2	CHISQ	.0337	POS	.0155	.0155	.0134	.0134
	PROB	.4108		.9010	.9011	.9080	.9080
0 VS. 3	CHISQ	.1919	POS	.3008	.3005	.6602	.6598
	PROB	.3327		.5372	.5373	.4163	.4166
1 VS. 2	CHISQ	.0000	POS	.2017	.2011	.9605	.9594
	PROB	.9732		.6334	.6338	.4341	.4343
1 VS. 3	CHISQ	.0000	POS	.0064	.0064	.0051	.0050
	PROB	.9000		.9361	.9361	.9433	.9434
2 VS. 3	CHISQ	.0000	POS	.1094	.1093	.3643	.3641
	PROB	.9000		.7409	.7410	.9461	.9462

Table 6

Tumor rates and p-values of the tested tumor types for positive linear trend in rat study

MALE RATS

Organ Name/ Tumor Name	Exact Asymptotic		C	L	M	H
	P-Value	P-value				
ADRENAL/ PHEOCHROMOCYTOMA	0.9678	0.96090	18	7	10	4
ADRENAL CORTEX/ ADENOMA	0.2032	0.12610	1	1	0	2
ADRENAL CORTEX/ CARCINOMA	0.5716	0.73215	0	1	2	0
BONE/ OSTEOSARCOMA	0.8815	0.79675	1	1	0	0
BRAIN/ GLIOMA	1.0000	0.75035	1	0	0	0
BRAIN/ GRANULAR CELL TUMOR	0.3678	0.44330	1	1	4	1
BRAIN/ MENINGIOMA	0.4209	0.59225	0	0	1	0
EAR/ SCHWANNOMA	0.1429	0.00785	0	0	0	1
EAR ZYMBAL'S GLAND/ CARCINOMA	0.3096	0.27980	1	0	1	1
HEART ATRIUM/ MESOTHELIOMA	0.4400	0.55980	0	0	1	0
KIDNEY/ ADENOMA	0.0880	0.05515	0	0	1	2
KIDNEY/ HEMANGIOMA	0.1429	0.00785	0	0	0	1
KIDNEY/ MESENCHYMAL TUMOR	0.5797	0.70485	0	2	0	0
LARGE INTESTINE/ POLYP	0.4876	0.29450	1	0	0	1
LIVER/ HEPATOCELLULAR ADENOMA	0.2917	0.26420	4	2	2	4
LIVER/ HEPATOCELLULAR CARCINOMA	0.1157	0.10145	4	4	3	5
LIVER BILE DUCT/ CARCINOMA	0.4400	0.55980	0	0	1	0
LUNG/ ADENOCARCINOMA	0.2826	0.05750	0	0	0	1
LUNG/ ADENOMA	0.3735	0.61975	0	1	1	0
LYMPH/ NODEHEMANGIOMA	0.6779	0.63405	5	0	0	1
MAMMARY GLAND/ ADENOCARCINOMA	0.0547	0.05130	0	1	1	2
MAMMARY GLAND/ ADENOMA	0.7717	0.75280	0	1	0	0
MAMMARY GLAND/ FIBROADENOMA	0.4831	0.50710	3	7	6	4
PANCREAS ACINUS/ ADENOMA	0.0577	0.03770	4	2	0	5
PANCREAS ISLET/ ADENOMA	0.9912	0.98815	20	10	14	6
PANCREAS ISLET/ CARCINOMA	0.4622	0.43775	4	3		
PARATHYROID/ ADENOMA	0.4183	0.44150	2	0	1	
PERITONEUM/ OSTEOSARCOMA	1.0000	0.70650	1	0	0	0
PITUITARY/ ADENOMA	0.8319	0.83070	63	45	55	39
PRIMARY SITE UNDETERMINED/ ADENOCARCINOMA	1.0000	0.75460	1	0	0	0
PRIMARY SITE UNDETERMINED/ HISTIOCYTIC SARCOMA	0.7128	0.71830	4	3	3	2
PRIMARY SITE UNDETERMINED/ LEUKEMIA	0.1429	0.00785	0	0	0	1
PRIMARY SITE UNDETERMINED/ LYMPHOMA	0.9230	0.90295	4	8	1	1
PROSTATE/ CARCINOMA	0.4206	0.58995	0	0	1	0
SKIN/ FIBROMA	0.5247	0.52940	6	1	4	3
SKIN/ FIBROSARCOMA	0.6086	0.55295	1	2	0	1
SKIN/ KERATOACANTHOMA	0.6634	0.63210	4	2	1	2
SKIN/ LIPOMA	0.4622	0.48540	4	1	3	2
SKIN/ LIPOSARCOMA	0.7407	0.73285	0	1	0	0
SKIN/ NEUROFIBROMA	0.4400	0.55980	0	0	1	0
SKIN/ PAPILLOMA	0.2682	0.25340	3	2	2	3
SKIN/ RHABDOMYOSARCOMA	1.0000	0.73580	1	0	0	0
SKIN/ SARCOMA	0.1600	0.01225	0	0	0	1
SKIN/ SCHWANNOMA	1.0000	0.74800	1	0	0	0
SKIN/ SEBACEOUS ADENOMA	0.4765	0.66175	0	0	2	0
SKIN/ TRICHOEPITHELIOMA	0.9275	0.82745	2	1	0	0
SMALL INTESTINE/ ADENOCARCINOMA	0.7717	0.75280	0	1	0	0
SMALL INTESTINE/ LEIOMYOMA	0.2826	0.05750	0	0	0	1
SPLEEN/ HEMANGIOMA	0.7717	0.75280	0	1	0	0
SPLEEN/ HEMANGIOSARCOMA	1.0000	0.79285	1	0	0	0
STOMACH/ LEIOMYOSARCOMA	1.0000	0.73580	1	0	0	0
STOMACH NONGLANDULAR MUCOSA/ PAPILLOMA	1.0000	0.73580	1	0	0	0
STOMACH NONGLANDULAR MUCOSA/ SQUAMOUS CELL CARCINOMA	0.3953	0.52000	0	0	1	0
TESTIS/ MESOTHELIOMA	0.5797	0.70485	0	2	0	0
TESTIS/ LEYDIG CELL ADENOMA	0.9035	0.89680	11	4	3	3
THYROID/ FOLLICULAR CELLADENO CARCINOMA	0.4534	0.54305	2	0	3	1
THYROID/ FOLLICULAR CELLADENOMA	0.3208	0.35215	4	1	4	3
THYROID PARAFOLLICULAR CELL/ ADENOMA	0.8165	0.81695	15	11	3	7
THYROID PARAFOLLICULAR CELL/ CARCINOMA	0.2391	0.20500	0	0	1	1
URINARY BLADDER/ TRANSITIONAL CELL CARCINOMA	0.4172	0.59040	0	0	1	0

Table 6 continued to the next page

FEMALE RATS

Organ Name/ Tumor Name	Exact Asymptotic INCIDENCE RATES		C	L	M	H
	P-Value	P-value				
ADRENAL/ PHEOCHROMOCYTOMA	0.8390	0.81455	4	4	1	1
ADRENAL CORTEX/ ADENOMA	0.5016	0.50630	4	2	2	2
ADRENAL CORTEX/ CARCINOMA	0.4231	0.46945	1	2	1	1
BONE/ OSTEOSARCOMA	1.0000	0.86995	0	0	0	0
BRAIN/ GLIOMA	0.7319	0.69610	1	1	1	1
BRAIN/ GRANULAR CELL TUMOR	1.0000	0.87010	3	0	0	0
EAR/ SCHWANNOMA	0.6141	0.69615	0	1	0	0
EAR ZYMBAL'S GLAND/ CARCINOMA	0.4203	0.33355	1	1	0	1
KIDNEY/ ADENOMA	1.0000	0.74935	1	0	0	0
KIDNEY/ MESENCHYMAL TUMOR	0.4021	0.57840	0	0	1	0
LARGE INTESTINE/ FIBROMA	1.0000	0.74595	1	0	0	0
LIVER/ HEPATOCELLULAR ADENOMA	0.2485	0.25730	4	1	3	3
LIVER/ HEPATOCELLULAR CARCINOMA	0.1183	0.10015	0	0	1	1
LUNG/ ADENOMA	0.0378	0.00230	0	0	0	2
LYMPH NODE/ HEMANGIOMA	0.1825	0.11740	0	1	0	1
MAMMARY GLAND/ ADENOCARCINOMA	0.9966	0.99435	27	15	18	5
MAMMARY GLAND/ ADENOLIPOMA	1.0000	0.73805	1	0	0	0
MAMMARY GLAND/ ADENOMA	0.7862	0.77790	9	5	3	3
MAMMARY GLAND/ FIBROADENOMA	0.0791	0.07690	78	37	37	45
OVARY/ SERTOLI CELL TUMOR	1.0000	0.73805	1	0	0	0
PANCREAS ACINUS/ ADENOMA	0.0084	0.00035	0	0	0	3
PANCREAS ISLET/ ADENOMA	0.9306	0.92420	10	10	9	3
PANCREAS ISLET/ CARCINOMA	0.5705	0.53575	1	3	0	1
PARATHYROID/ ADENOMA	1.0000	0.74595	1	0	0	0
PERITONEUM/ LEIOMYOSARCOMA	1.0000	0.73805	1	0	0	0
PERITONEUM/ MESOTHELIOMA	0.6210	0.70610	1	0	1	0
PITUITARY/ ADENOMA	0.7416	0.74235	107	63	66	57
PITUITARY/ CARCINOMA	1.0000	0.73805	1	0	0	0
PLEURA/ HIBERNOMA	0.6549	0.70265	0	1	0	0
PRIMARY SITE UNDETERMINED/ HISTIOCYTIC SARCOMA	0.8477	0.78970	1	1	0	0
PRIMARY SITE UNDETERMINED/ LYMPHOMA	0.2951	0.34510	2	1	4	2
SKELETAL MUSCLE/ FIBROSARCOMA	0.6405	0.70125	0	1	0	0
SKIN/ FIBROMA	0.5688	0.54595	5	2	1	2
SKIN/ FIBROSARCOMA	0.1203	0.03705	1	0	0	2
SKIN/ HEMANGIOMA	0.6549	0.70265	0	1	0	0
SKIN/ HISTIOCYTOMA	0.4070	0.59915	0	0	1	0
SKIN/ KERATOACANTHOMA	0.6083	0.68820	0	1	0	0
SKIN/ LEIOMYOMA	1.0000	0.73805	1	0	0	0
SKIN/ LIPOMA	0.9857	0.95575	5	3	1	0
SKIN/ PAPILOMA	0.3958	0.61075	0	0	2	0
SMALL INTESTINE/ LEIOMYOMA	1.0000	0.73805	1	0	0	0
SMALL INTESTINE/ POLYP	1.0000	0.73805	1	0	0	0
SPLEEN/ LEIOMYOMA	0.6141	0.69615	0	1	0	0
STOMACH/ LEIOMYOMA	0.1930	0.02215	0	0	0	1
STOMACH NONGLANDULAR MUCOSA/ PAPILOMA	0.1939	0.02280	0	0	0	1
THYMUS/ THYMOMA	0.6202	0.37675	1	0	0	1
THYROID/ GANGLIONEUROMA	1.0000	0.74935	1	0	0	0
THYROID FOLLICULAR CELL/ ADENOCARCINOMA	0.7186	0.83555	0	1	1	0
THYROID FOLLICULAR CELL/ ADENOMA	1.0000	0.90300	4	0	0	0
THYROID PARAFOLLICULAR CELL/ ADENOMA	0.9685	0.96010	16	7	7	3
THYROID PARAFOLLICULAR CELL/ CARCINOMA	0.6879	0.73800	1	0	1	0
UTERUS/ FIBROMA	0.5069	0.69865	0	1	1	0
UTERUS/ LEIOMYOSARCOMA	0.5085	0.69850	0	1	1	0
UTERUS/ POLYP	0.8021	0.77905	2	6	0	1
UTERUS ENDOMETRIAL STROMA/ SARCOMA	0.4021	0.57840	0	0	1	0
VAGINA/ LEIOMYOSARCOMA	0.4100	0.57965	0	0	1	0

Figure 1a

Kaplan-Meier Estimates of the survival distributions
(Male mice)

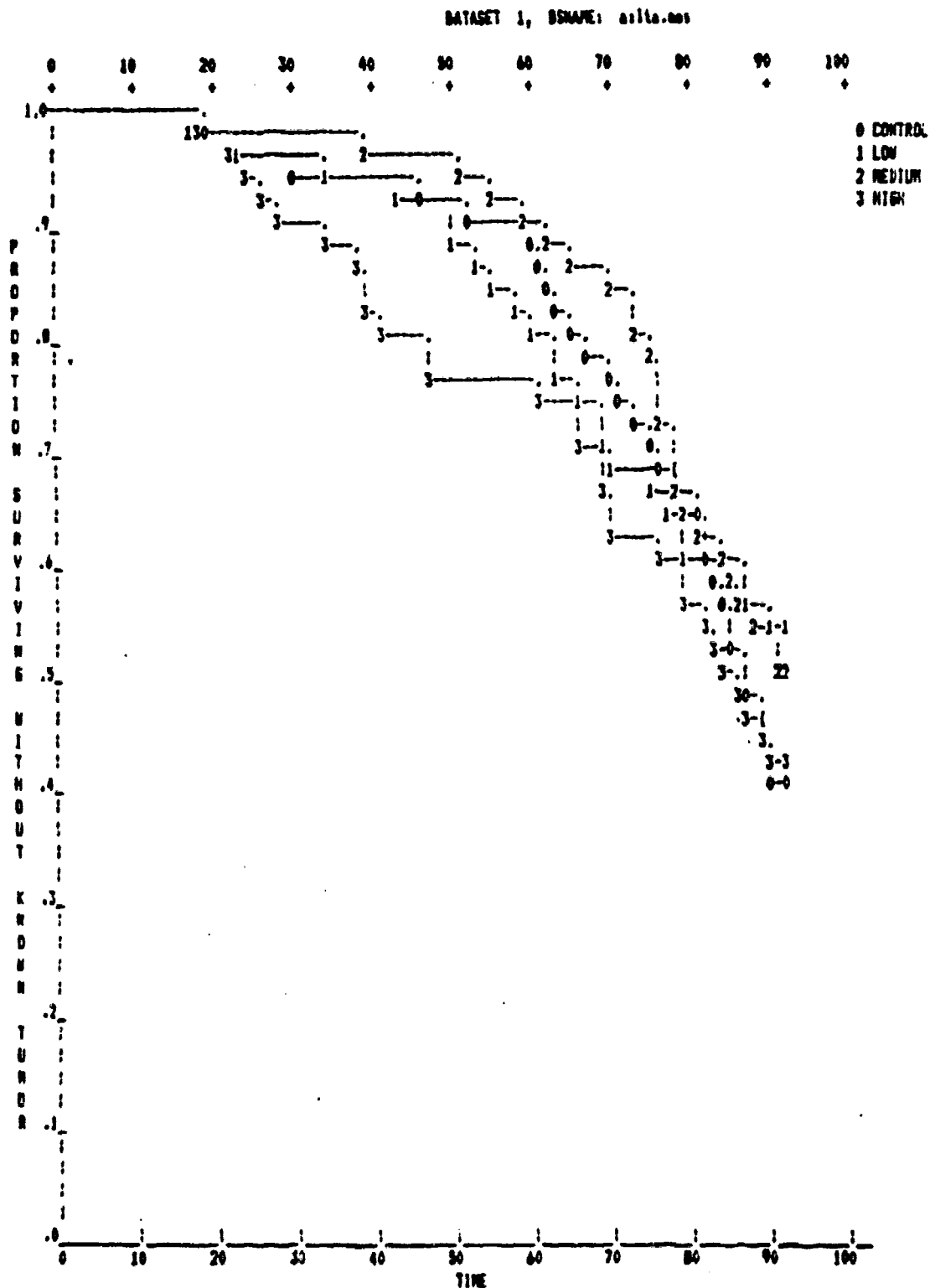


Figure 1b

Kaplan-Meier Estimates of the survival distributions
(Female mice)

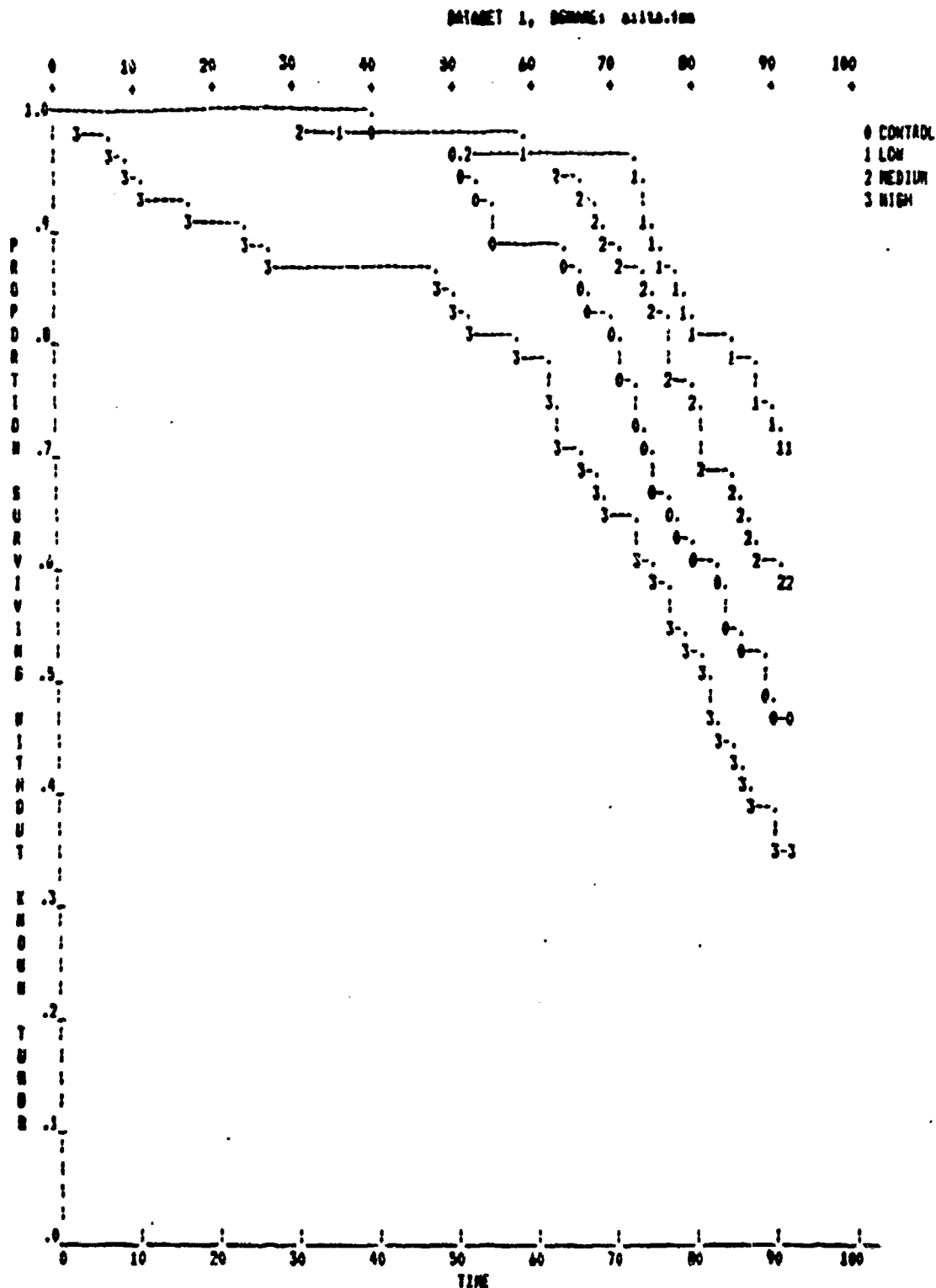


Figure 2a

Kaplan-Meier Estimates of the survival distributions
(Male rats)

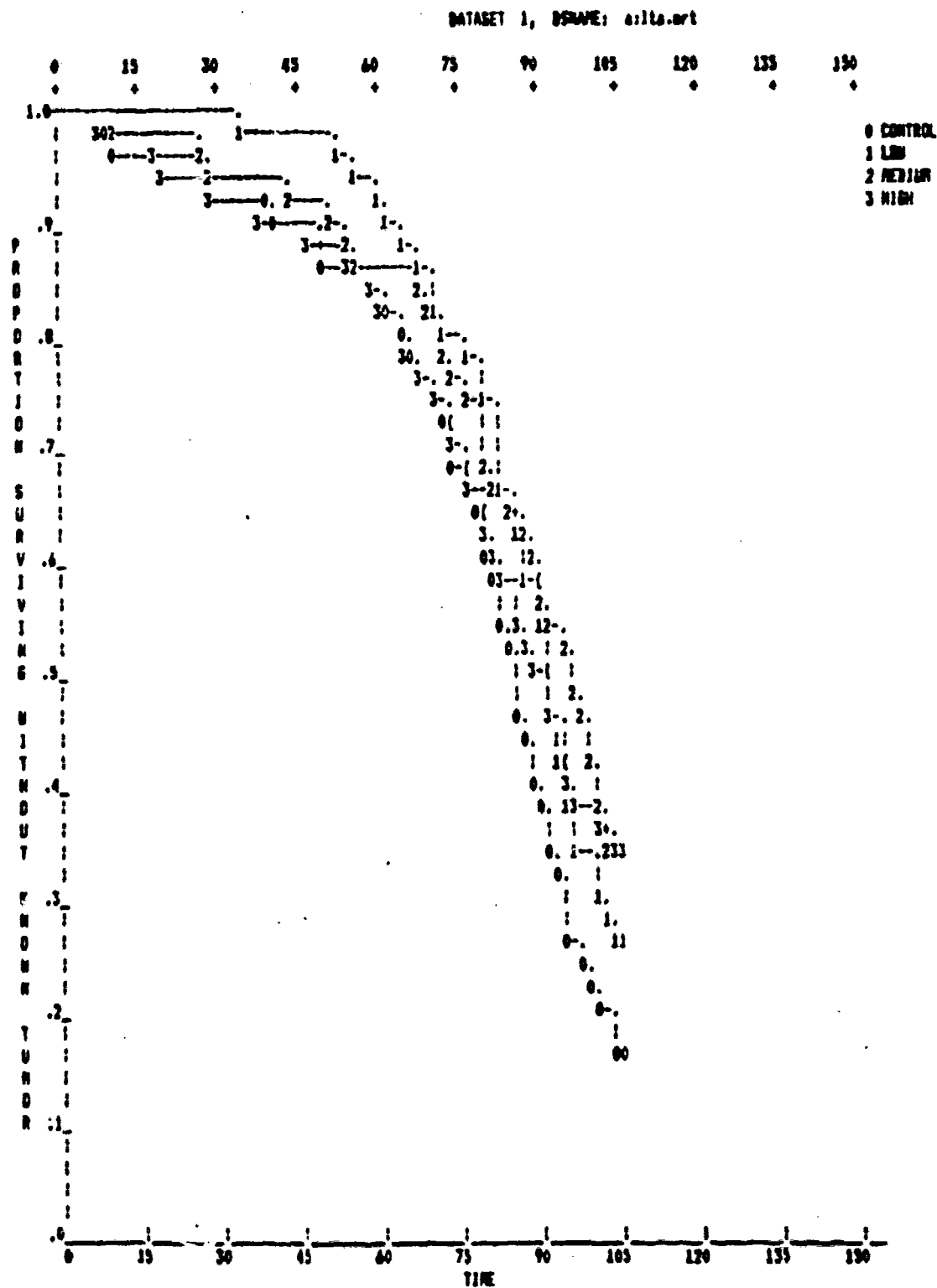
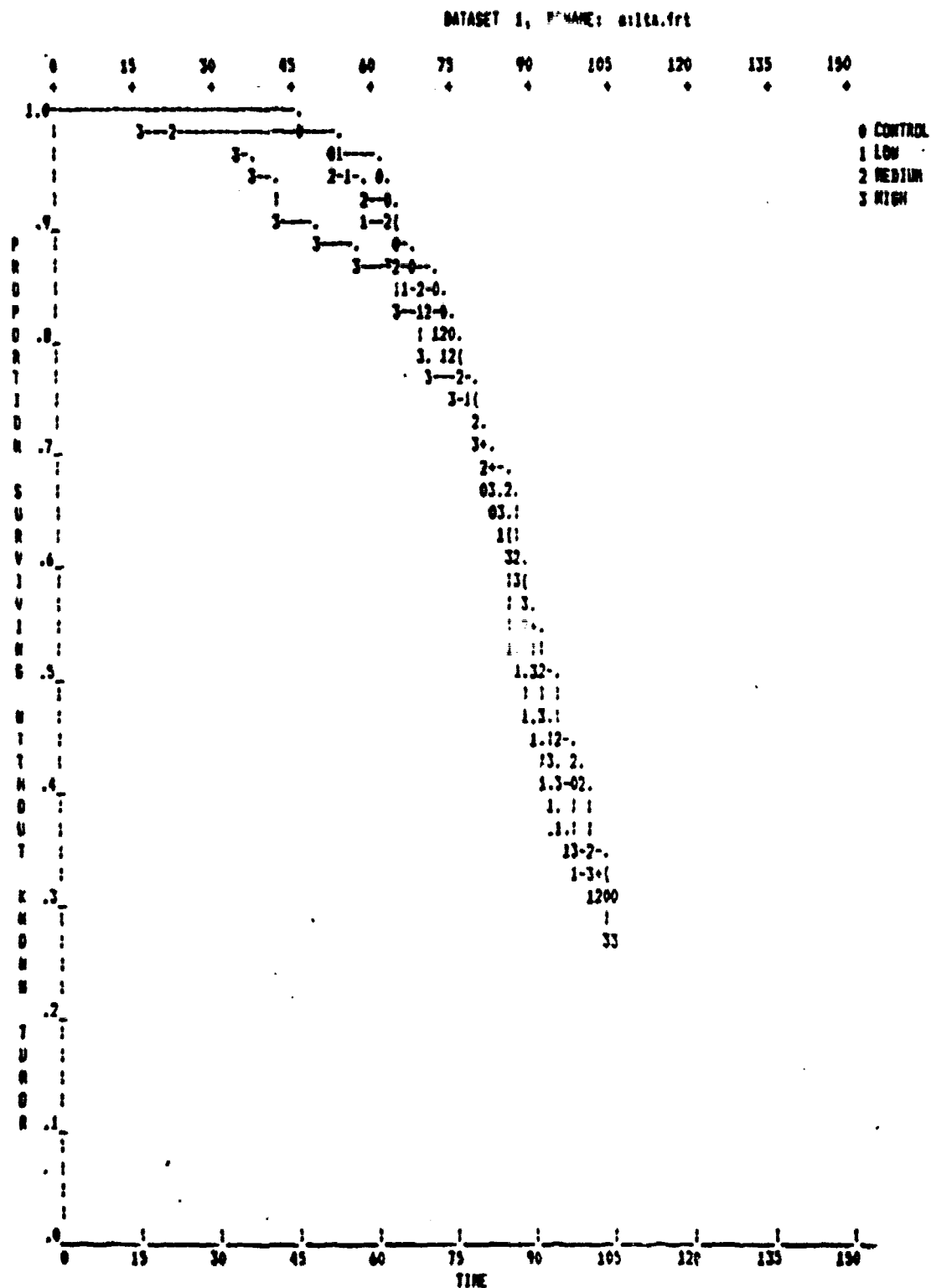


Figure 2b

Kaplan-Meier Estimates of the survival distributions
(Female rats)



ENVIRONMENTAL ASSESSMENT

ENVIRONMENTAL ASSESSMENT
AND
FINDING OF NO SIGNIFICANT IMPACT
FOR

COZAAR Tablets
(Losartan Potassium)
25, 50 and 100 mg

NDA 20-386

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIO-RENAL DRUG PRODUCTS
(HFD-110)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-386

COZAAR Tablets

(Losartan Potassium)

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decisionmaker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for **COZAAR Tablets**, **Merck Research Laboratories** has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Losartan potassium is a synthetic drug which is administered as an oral tablet in the treatment of hypertension. A proprietary drug substance intermediate will be manufactured by Merck & Co., Inc., Albany, GA. The drug substance will be manufactured at Merck Sharp & Dohme, Ballydine Plant, county Tipperary, Ireland. The drug product will be manufactured and packaged at DuPont Merck Pharmaceutical Co., Garden City, NY or Merck & Co., Inc., Wilson, NC. Packaging operations may occur at alternate packaging facilities identified in the environmental assessment. The finished drug product will be used in hospitals, clinics and by patients in their homes.

Chemical and physical test results and information indicate that losartan potassium will most likely be restricted to the aquatic environment. The compound degrades rapidly ($t_{1/2} < 18$ hours) upon exposure to light. As the compound or photodegradants are expected to persist in the aquatic environment for some time, toxicity studies were conducted. Acute toxicity studies using water fleas (*Daphnia magna*), fathead minnows (*Pimephales promelas*) and rainbow trout (*Oncorhynchus mykiss*) and chronic toxicity studies using green alga (*Selenastrum capricornutum*) and blue-green alga (*Microcystis aeruginosa*) indicate that the drug substance is not toxic to aquatic organisms at concentrations of at least 3 orders of magnitude greater than the maximum expected environmental concentration (MEEC) of losartan potassium.

Microbial inhibition studies indicate that respiration in activated sludge is not inhibited at concentrations of at least 4 orders of magnitude greater than the maximum expected environmental concentration (MEEC).

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, pharmaceutical processing waste, and user disposal of empty or partly used product and packaging. Waste drug product and pharmaceutical processing waste will be disposed of predominantly at licensed incineration facilities although small quantities may be emitted in effluent waste streams. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system while some unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

3/27/95
DATE

Nancy B. Sager

Prepared By
Nancy B. Sager
Review Chemist
Center for Drug Evaluation and Research

3/31/95
DATE

Phillip G. Vincent

Approved
Phillip G. Vincent, Ph.D.
Environmental Assessment Officer
Center for Drug Evaluation and Research

3/31/95
DATE

Robert A. Jerussi

Concurred
Robert A. Jerussi, Ph.D.
Associate Director for Chemistry
Center for Drug Evaluation and Research

Attachments:

- I: Environmental Assessment
- II: Environmental Assessment Addendum
- II: Material Safety Data Sheet

ATTACHMENT I

Tablets Losartan Potassium
Chemical and Pharmaceutical Manufacturing and
Control Documentation

F-1

I. Summary

F. Environmental Assessment

F. Environmental Assessment

1. Date

February 1, 1995

2. Name of Applicant

Merck Research Laboratories
Merck & Co., Inc.

3. Address

West Point, PA 19486-0004

4. Description of the Proposed Action

a. Requested Action

Merck Research Laboratories, Division of Merck & Co., Inc. has filed a New Drug Application for Tablets Losartan Potassium 25 mg, 50 mg, and 100 mg. Losartan potassium, the first in a new class of antihypertensives is an angiotensin II receptor (type AT₁) antagonist. Tablets Losartan Potassium may be used alone or in combination with other antihypertensive agents.

Tablets Losartan Potassium will be packaged as follows:

High Density Polyethylene (HDPE) Bottles

The bottles are white, opaque, 75 mL and 7 oz., high density polyethylene (HDPE). White polypropylene child-resistant caps with pulp and polyethylene liner and tamper evident PS-22 inner

I. Summary

F. Environmental Assessment

a. Requested Action (Cont.)

seal will be used for the 75 mL HDPE bottles and metal screw caps with white faced pulpboard coated with wax and a tamper evident PS-22 inner seal will be used for the 7 oz. bottles. Physician's samples will be packaged in 30 mL HDPE bottles with white polypropylene non child-resistant caps lined with white faced pulpboard and tamper evident PS-22 inner seal.

Opaque PVC/PE/PVDC Coated Blister Packages - Peelable

The unit dose package is an opaque, white 200 micron polyvinyl chloride/25 micron polyethylene/90 g/m² polyvinylidene chloride blister with lidding material of vinyl heat seal coating/25 micron soft temper foil/30 lb. paper.

b. Need for Action

Tablets COZAAR offer patients effective therapy for hypertension. In light of the therapeutic benefits associated with its use and that the quantities to be marketed in the United States in the fifth year are expected to be less than Kg/yr, approval is justified and preferable to non-approval.

I. Summary

F. Environmental Assessment

c. Locations Where the Product will be Produced and the Types of Environments Adjacent to those Locations

The bulk drug substance (Losartan potassium) will be manufactured at Merck's facilities in Albany, Georgia and Ballydine, Kilsheelan, Ireland. The Albany facility will initiate the production process and produce the Trityl-losartan (CAS #133909-99-6) intermediate. The Trityl-losartan intermediate will then be shipped to Merck's Ballydine facility in Ireland to continue the manufacturing process where the drug substance, losartan potassium (CAS #124750-99-8), will be produced.

For the U.S. market, the drug product (COZAAR) will be formulated and packaged at the DuPont Merck Pharmaceutical Company Garden City, New York facility or the Merck facility in Wilson, North Carolina. Alternatively, pharmaceutical packaging is planned

. Returned and outdated materials will be disposed of at the Merck West Point, PA facility.

The types of environments present at the locations mentioned above, specific to the vicinity of product manufacture, formulation, and packaging are described in the following sections. Environments specific to the vicinity of alternate packaging facilities are described in Appendix III.

I. Summary

F. Environmental Assessment

1) Albany, Georgia

Merck & Co., Inc.
Flint River Plant
3517 Radium Springs Road
Albany, Georgia 31708
U.S.A.

a) Geographic Conditions

The Albany, Georgia plant occupies approximately 780 acres in Dougherty County, Georgia on the west side of Georgia Route 3, approximately 0.5 miles east of the Flint River. It is situated approximately five miles south of the city of Albany, Georgia. The coordinates of the plant's location are latitude 31° 29'N and longitude 84° 7' W. Annual rainfall in the area is approximately 49 inches (124.5 cm). The mean summer temperature is 92°F (33°C). Dougherty County, which includes the city of Albany, contains an approximate population of 125,000.

b) Air Resources

The entire state of Georgia is in attainment with the National Ambient Air Quality Standards (NAAQS) for particulates, sulfur oxides, and nitrogen oxides. The plant is located in the southwest Georgia Intrastate Air Quality Control region which is in attainment with the secondary standards for carbon monoxide and ozone. The state of Georgia has been delegated authority to enforce new and existing air pollution regulations including the New Source Performance Standards (NSPS), National Emission

I. Summary

F. Environmental Assessment

b) Air Resources (Cont.)

Standards for Hazardous Air Pollutants (NESHAPS), and Prevention of Significant Deterioration (PSD). There are no Class I visibility areas within 50 km of the plant.

c) Water Resources

The plant obtains its potable water from two on-site wells. All process and non-contact cooling water is obtained from six other on-site wells. The plant has been issued two permits from the Georgia Department of National Resources for the above referenced well water. Withdrawal of groundwater from these wells is authorized by Permit Number 0470003. The treatment and distribution of drinking water is authorized by Permit Number PG0950023.

The only surface water body within 1000 ft. of the plant property boundary is the Flint River which is approximately 0.2 miles west of the plant area.

d) Land Resources

The land use of the area surrounding the plant site is primarily undeveloped and agricultural with low density residential housing to the north and east. The closest major population center is the city of Albany approximately five miles to the north.

d) Land Resources (Cont.)

The 100-year flood-plain elevation at the site is approximately 179 feet above mean sea level. All existing buildings and improvements are located above this elevation.

2) Ballydine, Ireland

Merck Sharp & Dohme
Ballydine Plant
Ballydine, Kilsheelan
Clonmel, County Tipperary, Ireland

a) Geographic Conditions

The Merck Sharp & Dohme (Ireland) Ltd. manufacturing facility is located in Ballydine, Kilsheelan, County Tipperary. The facility occupies a 180 acre site situated on the north side of the River Suir, midway between Clonmel and Carrick-on-Suir. The coordinates of the location are latitude 52°N and longitude 7°W. The area around the plant is predominantly agricultural with dairy farming and tillage being the main activities. The Ballydine area has a population of approximately 100. The village of Kilsheelan, which is approximately 3 miles west of the plant, has a population of approximately 1000.

b) Air Resources

While the plant is surrounded by sparsely populated farm-land, there are four sources of industrial air pollution within a radius of

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b) Air Resources (Cont.)

ten (10) miles of the plant. They are as follows: a creamery, a crystal glass manufacturing plant, a fiber board processing plant and a soft drink and cider processing facility.

c) Water Resources

All water used on the site is pumped from the adjacent River Suir (dry weather flow is approximately 180 million gallons per day). All river water is treated to potable grade. The treatment process consists of flocculation, pH adjustment, sand filtration and chlorination. Approximately 158 million gallons of potable water are processed annually. This water is used for fire, cooling and drinking water.

Approximately 27 million gallons of potable water are demineralized annually to serve as process and boiler feed water.

There are no wells in the vicinity of the plant and the neighborhood drinking water supply is provided by the local authority. Livestock drink from the river and tributaries as well as troughs fed from the public supply.

d) Land Resources

The site is located approximately 29 meters above sea level. Terrain in the area consists of gently rolling hills. Soil in the area can

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d) Land Resources (Cont.)

generally be described as an acid brown earth of glacial till origin of mixed old red sandstone and carboniferous limestone. The soil has a sandy loam texture and is free draining with good structure.

3) Garden City, NY

DuPont Merck Pharmaceutical Co.
1000 Stewart Ave.
Garden City, New York
U.S.A.

a) Geographic Conditions

The DuPont Merck Garden City site is located 20 miles east of New York City on a 7.2 acre plot, at the intersection of Meadowbrook Parkway and Stewart Avenue. This location is at latitude 40° 44' 18" N and longitude 73° 35' 13" W. Land use surrounding the plant is commercial and residential. The site is located 92 feet above mean sea level.

b) Air Resources

The annual average temperature near the plant is 50°F(26°C) with an annual average rainfall of 39 inches (99 cm). Prevailing winds are from the west-northwest at an average windspeed of 9.4 miles (15.7 km) per hour. The New York region ambient air quality does

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b) Air Resources

not meet all of EPA's National Ambient Air Quality Standards (NAAQS), but is addressed as part of New York State's State Implementation Plan (SIP) under the Clean Air Act. The Garden City facility meets all local requirements.

c) Water resources

Potable water is obtained from the local public water supply for the Town of Hempstead. The primary source for the municipal water supply is groundwater. Wastewater from the facility is routed to the Town of Hempstead's wastewater collection system which is treated at the Nassau County Wastewater Treatment Plant. In the developed area of the property, there are no natural drainage tributaries entering or exiting the plant property. Stormwater releases from the plant site are not monitored.

d) Land resources

The plant site is fairly flat with limited contours. It is underlain by terminal moraine soils with sand and clay layers completing the geologic profile.

4) West Point, Pennsylvania

Merck & Co., Inc.
Sumneytown Pike
West Point, PA 19486
U.S.A.

a) Geographic Conditions

The West Point plant is located on a site (~450 acres) in Upper Gwynedd Township, Montgomery County, which is approximately 30 miles northwest of Philadelphia. The center of the West Point plant is located near latitude 40° 12' 54" N and longitude 75° 17' 59" W. Land use surrounding the plant is primarily residential and agricultural with other industrial sites approximately one-half mile away.

b) Air Resources

Air quality in this area is in compliance with the Environmental Protection Agency's (EPA) National Ambient Air Quality Standards (NAAQS) of the Clean Air Act for total suspended particulates, sulfur oxides, and nitrogen oxides. This compliance is based on monitoring and reporting by the Pennsylvania Department of Environmental Resources (PA DER) under the requirements of the State Implementation Plan. At this time, Montgomery County does not meet the ozone standard set forth by the NAAQS. The West Point plant lies within the outer zone of the Southeast Pennsylvania air basin. Pennsylvania is part of the EPA Region III and PA DER is responsible for implementing the State Implementation Plan which includes new stationary source permits for manufacturing. Meteorological data for the region is collected at the Philadelphia International Airport. Annual rainfall is approximately 42 inches (107 cm) and the mean ambient monthly temperature varies between 33 and 77°F (0.5-25°C). Pre-dominant winds are from west to southeast.

c) Water Resources

Potable water is supplied to the plant operations via an on-site storage tank which is supplied by on-site wells and a public water supplier, North Wales Water Authority. The North Wales Water Authority operates as many as three public wells within a half-mile of the plant property. The plant potable water quality meets all requirements of the Federal Safe Drinking Water Act and the Pennsylvania Safe Drinking Water Act. Compliance with these standards are also required in Applicable Good Manufacturing Practices.

Stormwater drainage is controlled using detention basins which maintain site runoff at levels estimated for undeveloped property and to minimize erosion. This runoff is discharged into an unnamed tributary of the Towamencin Creek.

All wastewater from the plant manufacturing operations is collected, pretreated and discharged to a publicly owned treatment works, the Upper Gwynedd Township Authority Wastewater Treatment Plant (UGTA), which discharges treated effluent to the Wissahickon Creek. The location of the discharge from the UGTA is downstream from the West Point site. The Wissahickon Creek is a tributary of the Schuylkill River. The Schuylkill River is a drinking water source for the Philadelphia area. Pennsylvania DFR limits the wasteload allocation and water pollutant limits (established by the Pennsylvania Water Toxic Management) from the UGTA into the Wissahickon Creek by means of the National

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c) Water Resources (Cont.)

Pollutant Discharge Elimination System discharge permit number PA0023256. The wasteload allocation and water pollutant limits are used to determine the allowable contribution limits from the West Point plant to UGTA.

d) Land Resources

The plant is underlain by Triassic age sedimentary rocks, mapped as the Brunswick and Locketong formations. These formations occur as layered beds of red and very dark gray shale with occasional layers of sandstone. Although these rocks generally have low primary porosities, permeability is maintained and improved by the presence of fractures and joint sets.

5) Wilson, North Carolina

Merck & Co., Inc.
I-95 and Highway 264
Wilson, North Carolina
U.S.A.

a) Geographic Conditions

Wilson is located 45 miles east of Raleigh, North Carolina. The plant is located 4.5 miles west of Wilson on a 235 acre plot, near the intersection of Interstate Highway 95 and US Highway 264, at latitude 35° 45' N and longitude 78° 00' W. Land use surrounding the plant is primarily residential and agricultural.

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b) Air Resources

Air quality in the region meets the National Ambient Air Quality Standards (NAAQS) for sulfur oxides, nitrogen oxides, total suspended particulates and ozone. The annual rainfall is approximately 42 inches (107 cm), and the average annual temperature is 59°F (15°C). Prevailing winds are from the southwest at an average annual speed of 7.7 mph.

c) Water resources

Potable water is obtained from the local public water supply for the City of Wilson. The plant potable water quality meets or exceeds all requirements of the Federal Safe Drinking Water Act. Compliance with these standards is also required in applicable Good Manufacturing Practices. Wastewater from the facility is routed to the city of Wilson treatment facility. In the developed area of the property, there are six natural drainage tributaries exiting the plant property and one entering the property. There is an established stormwater monitoring point for monitoring all stormwater releases from the plant site.

d) Land Resources

The plant site consists mainly of gently sloping terrain with forest and open farmland underlain by the Coastal Plain Providence to the east and the geologic Piedmont Geologic Providence to the west. The coastal plain soils are marine deposits and the piedmont soils

d) Land Resources (Cont.)

are residual, formed from the chemical decomposition of the underlying bedrock. Both soils are interbedded sands, silts, and clays with an average depth to bedrock of 20-40 feet. The plant site elevation is about 160 feet above mean sea level.

- 6) Appendix III provides descriptions of the packaging locations identified in section 4.c. above.

d. Locations where the Product will be Used and the Types of Environments Present at and Adjacent to those Locations

The product is a film-coated tablet intended for use throughout the United States for management of hypertension. Consumption will be on an in-patient and out-patient basis. The maximum expected environmental concentration (MEEC) of losartan potassium as a result of patient use (both monotherapy and in combination with other therapeutic agents) is anticipated to be extremely low (mcg/L(ppb)).

e. Locations where the Product will be Disposed of and the Types of Environments Present at and Adjacent to those Locations

Merck & Company, Inc. has a domestic return goods practice which involves the return of any unused market packages to the West Point, Pennsylvania location or an approved contract facility for evaluation and inventory. This results in a designated location for the control of product disposal. The incineration of the waste

I. Summary

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e. Locations where the Product will be Disposed of and the Types of Environments Present at and Adjacent to those Locations (Cont.)

will be conducted at the West Point facility. Any ash generated at West Point is landfilled at an approved off-site facility. In the event that the West Point facility is unable to accept these wastes, the wastes will be disposed of at an alternate, off-site facility approved by federal, state and/or local environmental agencies. All permitted off-site facilities for returned goods undergo rigorous environmental review prior to approval. The types of environment present at the disposal plant site are those described in 4.c.4 for the West Point plant site.

Drug substance intermediates are consumed in the reaction steps leading to the final drug substance with the exception of very small amounts which may be discharged with the liquid emissions or become solid waste. Disposal of liquid and solid waste generated in the production of the drug substance is discussed in Section 6.b. under the liquid emissions and solid waste sections.

The residual losartan potassium waste associated with the drug product formulation and rejected product will be disposed of by off-site incineration at a facility approved by federal, state or local environmental agencies.

5. Identification of Chemical Substances that are the Subject of the Proposed Action

Chemical Abstracts Name

1H-Imidazole-5-methanol,2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, monopotassium salt

CAS Registry No. 124750-99-8

Information regarding the chemical structure, empirical formula, molecular weight, chemical and other names and physical properties can be found in Appendix I. Appendix I also contains confidential information regarding drug substance impurities and impurity specifications.

Appendix II includes information regarding additives.

6. Introduction of Substances into the Environment

a. Substances expected to be emitted and estimated releases

1) Bulk Drug Synthesis

Part 2 of Appendix II summarizes the chemical substances which may reasonably be expected to enter various environmental compartments (atmospheric, aquatic and terrestrial) as a result of bulk drug substance production. Part 5 of Appendix II outlines the permit name, number, expiration dates and issuing agencies for permits applicable to bulk drug substance production.

1) Bulk Drug Synthesis (Cont.)

Production of losartan potassium will take place at the Merck facilities in Albany, GA and Ballydine, Kilsheelan, Ireland. Estimated maximum concentrations of drug substance in the Ballydine facility on-site wastewater treatment plant will be approximately mg/L. As a result of the on-site wastewater treatment and subsequent dilution, maximum receiving water concentrations of drug substance will be approximately mcg/L (ppb). (Based on the fifth year total production volume of losartan potassium [kg].)

2) Dosage Form Production

Appendix II (Part 3) summarizes the substances which may reasonably be expected to enter various compartments as a result of drug product manufacture, filling and packaging. Drug product manufacturing and packaging will take place at the DuPont Merck Garden City, New York facility and the Merck facility in Wilson, North Carolina for the U. S. market.

Pharmaceutical packaging is also planned

Appendix II (Part 5) summarizes the permit information for the dosage form production. Packaging activities will not result in significant emissions to either air, aquatic or terrestrial environments. The generation of solid wastes that contain small amounts of the drug product will be collected and disposed of under the local manufacturing controls.

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F. Environmental Assessment

3) Use Sites

Administered dosage form will normally enter the environment in highly diluted aqueous domestic sewage which will be subject to further local treatment. The maximum expected emitted concentration (MEEC) resulting from the use of losartan potassium alone (monotherapy) and in combination with other therapeutic agents is estimated to be approximately mcg/L (ppb) based on projected fifth year production levels for the U. S. market. This assumes that 74% of the total drug volume administered will be discharged in sewage (reflects the fraction of the U.S. population which discharge sanitary waste to Publicly Owned Treatment Works), a uniform distribution throughout the U. S. population, a per capita water usage of 150 gallons per day, and excretion of 100% of drug activity. Lifetime exposure to this concentration would result in ingestion of approximately mcg of a .100 mg. daily dose. Use of the drug is not expected to result in emissions to the atmospheric or terrestrial compartments.

4) Disposal Site

Merck & Company, Inc. has a domestic return goods practice which involves the return of any unused market packages to the West Point, Pennsylvania location or an approved contract facility for evaluation and inventory. This results in a designated location for the control of product disposal. The incineration of the waste will be conducted at the West Point facility. Any ash generated at West Point is landfilled at an approved off-site facility. In the event that the West Point facility is unable to accept these wastes, the

4) Disposal Site (Cont)

wastes will be disposed of at an alternate, off-site facility approved by federal, state and/or local environmental agencies. All permitted off-site facilities for returned goods undergo rigorous environmental review prior to approval. The types of environment present at the disposal plant site are those described in 4.c.4 for the West Point plant site.

The incineration operation at West Point, Pennsylvania is considered to be a high temperature incineration. It has a minimum primary combustion chamber exit gas temperature of 1400°F and a minimum secondary combustion chamber exit gas temperature of 1600°F with a residence time of 1 second in the secondary chamber for gases. The feed rate to the incinerator is limited to 2000 pounds/hour. The incinerator is required to meet < 0.08 gr/dscf for particulates and < 23.6 lb/hour of acid gas (including hydrochloric acid and sulfur dioxide).

Polyvinyl chloride (PVC) generates hydrochloric acid when burned and therefore the limit set by PADER for acid gas is appropriate to control emissions from burning PVC. Emissions are controlled to meet PADER requirements by regulating the feed rate and composition of the waste into the incinerator.

4) Disposal Site (Con't)

Merck and DuPont-Merck (DMPC) manufacturing facilities use various off-site waste disposal contractors and waste transporters. In the event that off-site incineration facilities are used, such services are contracted for on a competitive bid selection basis and will change. A major factor in the selection process is the contract facility's compliance with all federal, state and local environmental regulations.

Drug substance intermediates are consumed in the reaction steps leading to the final drug substance with the exception of very small amounts which may be discharged with the liquid emissions or become solid waste. Disposal of liquid and solid waste generated in the production of the drug substance is discussed in Section 6.b. under the liquid emissions and solid waste sections.

The residual losartan potassium waste associated with the drug product formulation and rejected product will be disposed of by off-site incineration at a facility approved by federal, state or local environmental agencies.

b. Control Procedures for Expected Emissions

1) Albany, GA

a) Air Emission Controls

Air emissions from bulk manufacture of losartan potassium drug substance include organic and inorganic compounds as listed in Part 2 of Appendix II. The emissions will be controlled by surface

I. Summary

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a) Air Emission Controls (Cont.)

condensers, a fume incinerator and wet caustic scrubbers, where necessary, so that the facility complies with applicable air emission permits.

Dust collectors will be used to control the atmospheric release of total suspended particulate matter in the drying process for the drug substance with a control efficiency of > 99%, however, trace quantities of product dust may be emitted. Particulate emission rates will be less than the allowable emission rate based on the process charge rates for new and existing equipment specified in the Georgia Rules for Air Quality Control Chapter 391-3-1-.02(2)(e) Table Ia and Ib. For example, a typical process charge rate of less than or equal to 100 lb/hr has an associated emission rate of 0.55 lb/hr.

b) Liquid Emission Controls

The plant has separate sanitary, process and stormwater sewer systems. All process and sanitary wastewater from laboratory, production and administration areas are sent to the on-site wastewater treatment plant. The treatment plant consists of the following processes: equalization, neutralization, primary clarification, activated sludge, secondary settling, thickening, sludge dewatering and off-site sludge disposal. The residence time for the on-site treatment plant is approximately 35 to 47 hours.

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b) Liquid Emission Controls (Cont.)

The stormwater collection system is equipped with a deluge containment to collect any spills and allow subsequent rerouting to the wastewater treatment plant. Uncontaminated stormwater may be discharged directly to the Flint River.

Organic liquid waste streams generated from the manufacture of drug substance will be subject to on-site recovery of the organic solvents. Organic solvent streams are recovered by either pot still or fractionation techniques. Depending on the waste stream, recovery efficiencies can be in the range of 65% to almost 100% of the primary organic compound for subsequent reuse. Residues from the solvent recovery operations are sent to the plant's wastewater treatment plant or, if necessary, shipped off-site to a permitted hazardous waste management facility.

Aqueous waste streams generated from the manufacture of drug substance will be sent to the on-site wastewater treatment facility as described above prior to discharge to the Flint River. Chemical substances that may be discharged to wastewater treatment are listed in Part 2 of Appendix II.

c) Solid Emission Controls

Waste water treatment plant sludge is containerized and shipped off-site to a permitted hazardous waste management facility. RCRA non-hazardous waste including paper trash, solid residues

c) Solid Emission Controls (Cont.)

from dust collectors and filters and non-hazardous filter media generated from the production of drug substance will be shipped off-site to a permitted local landfill.

Empty containers are re-sold or sent to a drum reconditioning facility to the maximum extent practical.

d) Employee Protection

Material Safety Data Sheets (MSDS) are available on-site for all chemicals required by the Occupational Safety Act of 1971 and the Hazards Communication Act of 1985. Employees associated with the manufacture of losartan potassium have the appropriate MSDSs available for their review. The MSDS for losartan potassium is contained in Appendix IV. Employee protective clothing, such as gloves, uniforms, and safety shoes, and protective equipment, such as safety glasses, are used during the manufacturing process to assure compliance with the Occupational Safety Act (OSHA) of 1971 and the Hazards Communication Act of 1985.

2) Ballydine, Ireland

a) Air Emission Controls

Air emissions from bulk manufacture of losartan potassium may include substances identified in Part 2 of Appendix II generated from process and drying operations. Emissions to the atmosphere

NDA 020386

FIRM:

MERCK

9 OF 10

TRADE NAME:

COZAAR (LOSARTAN POTASSIUM) 25/50 MG TAB

GENERIC NAME:

LOSARTAN POTASSIUM

I. Summary

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a) Air Emission Controls (Cont.)

from bulk drug manufacturing are controlled by equipment such as surface condensers, fume oxidizers and wet scrubbers so that the facility complies with applicable emissions requirements.

Particulate materials are handled in areas equipped to protect the employee and contain product/raw material loss. Containment facilities provided to prevent emission of particulate matter from processing activities may include: enclosed charge stations, bag filters, rotoclones, and HEPA filters. Where appropriate, a plant wide Preventative Maintenance (PM) program identifies critical equipment and specifies the frequency and extent of PM required. Control equipment and operating parameters are referenced as necessary on written operational procedures.

A program of industrial hygiene monitoring is in place to evaluate loss points and exposure risks. Written safety captions, material safety data sheets, operator training programs and safety audits ensure the safe handling and control of airborne particulates.

b) Liquid Emission Controls

Solvent-containing waste streams are generated from production operations and equipment clean-outs. Solvent-containing waste streams may consist of chemicals listed in Part 2 of Appendix II.

Used solvents,

will be recovered to the extent practical. Organic solvents are recovered by either pot still or fractionation techniques in the

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b) Liquid Emission Controls (Cont.)

Solvent Recovery Plant. Recovery efficiencies can be in the range of 95 to 99% of the primary organic component for subsequent reuse. Aqueous and organic purges, containing the balance of materials, may be treated in-house by discharge to the wastewater treatment plant or by incineration off-site.

Organic materials not recovered will be disposed of in an on-site solvent incinerator permitted under the Air Pollution Act of 1987 (Permit #ENV/A.P/2/91) and the BEC Toxic and Dangerous Waste Regulations, 1982 (Permit #ENV/D/3) or shipped to a permitted hazardous waste treatment facility.

On-site incineration of waste solvent is completed on a batch basis consistent with license ENV/A.P./2/91. The waste solvent is sampled prior to each burn and tested against license conditions. Approval to burn is obtained from the licensing authority prior to each burn. The incinerator consists of a dual natural gas/waste solvent burner, furnace and vertical stack operated typically between 900 to 1000°C. There is no emission control equipment installed on the incinerator. Off-gas emissions are monitored consistent with license requirements.

Aqueous waste streams are discharged to the chemical sewer and treated in an on-site biological wastewater treatment plant. The treatment plant consists of the following processes: equalization,

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b) Liquid Emission Controls (Cont.)

flow control, neutralization, primary clarification, extended aeration, secondary clarification and tertiary lagoon treatment. The residence time in the on-site wastewater treatment plant at normal hydraulic flows is ca. 8 days.

Waste sludge is dewatered using a belt press or vacuum filter and disposed of in an approved solid waste management facility. The waste treatment plant operation is permitted by the county council of Tipperary County, Ireland.

c) Solids Emission Controls

Waste sludge, general trash and paper at the site will be disposed of off-site in an approved solid waste management facility (a local authority operated landfill). Other solid waste contaminated with pharmaceutical residues or determined to be hazardous are disposed via off-site incineration which fully conforms to local regulatory policy. In the event that off-site incineration facilities are used, such services are contracted for on a competitive bid selection process and will change. A major factor in the selection process is the contract facility's compliance with all applicable environmental regulations.

3) Garden City, NY

a) Air Emission Controls

The manufacturing process does not utilize solvents that would result in solvent or volatile organic chemical (VOC) emissions.

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a) Air Emission Controls (Cont.)

The manufacturing process is designed to control particulate emissions that can become entrained in the exhaust air from the manufacturing process. This is accomplished by means of baghouse dust collectors and specific ventilation exhausts with separate dry filters with an overall removal efficiency of >99% for particulates. Also, the film-coating of the compressed tablets is designed to capture 99% of the excess overspray solids exhausted in the aqueous film-coating solution.

b) Liquid Emission Controls

Liquid emissions controls reflect good housekeeping practices that minimize the discharge of manufacturing residues to the site wastewater collection system. The plant wastewater is collected and routed to the Nassau County New York wastewater treatment plant. There is no pretreatment at this site. Quarterly monitoring of the discharge is conducted. Discharge from the DuPont Merck facility is only a minor input to the publicly owned treatment works (POTW). Source collection of chemicals (such as QC laboratory solvents) that can have an adverse impact on the POTW is provided as part of the site's operating procedures.

c) Solid Emissions Controls

All product discards, including unused market packages, will be sent to an approved incineration facility, permitted for disposal of pharmaceutical products. This will be accomplished through site

I. Summary

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c) Solid Emissions Controls (Cont.)

operating procedures. The expected destruction efficiency of the drug substance, that is present in the product waste as a small portion of the total weight, is expected to exceed 99%.

4) West Point, Pennsylvania

a) Air Emissions Controls

The on-site incineration facility employs necessary operating conditions to ensure compliance with permitted emission levels. As a contingency, off-site incineration will be conducted at a permitted facility (equipped with the necessary and required emission controls).

b) Liquid Emissions Controls

The liquid from the incineration operation will be discharged into the site wastewater collection system and will undergo pretreatment along with other sanitary waste. This wastewater is discharged for further treatment to the UGTA under the limits conditions of the UGTA contract limits.

c) Solid Waste Controls

Controls for the disposal of unused market packages are part of the site solid waste management program. The waste is incinerated at permitted disposal facilities. Ash generated from the on-site incineration process is disposed of at a permitted facility and is monitored to confirm its acceptability with solid waste regulations.

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d) Employee Protection

Material Safety Data Sheets are available on-site for all chemicals required by the Occupational Safety Act of 1971, the Hazards Communication Act of 1985 and Title 29 Code of Federal Regulations Part 1910.1200. Employees associated with the manufacture of drug substance have appropriate MSDSs available for their review. Employee protective clothing, such as gloves, uniforms, and safety glasses are used during the manufacturing process to assure compliance with the Occupational Safety Act of 1971 and the Hazard Communication Act of 1985 and Title 29 Code of Federal Regulations, Subpart I. Refer to Appendix IV for a copy of the MSDS for the drug product.

5) Wilson, North Carolina

a) Air Emissions Controls

The Wilson facility employs specific ventilation systems for manufacturing and packaging. The vented air passes through a cyclone followed by a baghouse filter with a control efficiency greater than 99% before discharge to the atmosphere. The Wilson, NC facility is in an Attainment Area and is not considered a major source of air pollution. The manufacturing process does not utilize solvents that would result in solvent or volatile organic chemicals (VOC) emissions. Particulates released from manufacturing and packaging operations are minimized and controlled by the use of dust collectors. Air emissions from drug product manufacturing and packaging may include trace particulates as described in Appendix II.

b) Liquid Emissions Controls

The plant wastewater is collected and routed directly to the City of Wilson Treatment Facility as regulated by the site's Sewer Discharge Permit Number 8406. No pretreatment takes place at the site. A flow meter and wastewater sampler monitor discharge quantity and quality, and the data is submitted biannually to the City of Wilson.

Liquid emissions as a result of drug product packaging are detailed in Appendix II. Liquid waste from packaging will result from equipment washouts. Equipment is cleaned with water and detergent after a batch campaign. Prior to washing out the equipment, it is customary to remove any loose product residues. This practice minimizes liquid emissions of chemical substances.

c) Solid Emissions Controls

All unused market packages will be sent to West Point, PA for incineration at permitted disposal facilities. Any solid residuals resulting from packaging will be disposed of by off-site incineration at a permitted facility.

Non-hazardous wastes resulting from manufacturing and packaging may consist of paper, aluminum, plastic, drums, and Tyvek® suits and product filter solids. Product filter solids and chemical contaminated wastes are sent to a permitted incineration facility able to accept such waste streams. Other non-hazardous wastes

c) Solid Emissions Controls (Cont.)

which cannot be recycled are disposed of at a state licensed land-fill. In order to minimize the amount of material for disposal, excess raw materials may be returned to the customer or supplier for further use.

d) Employee Protection

Material Safety Data Sheets are available on-site for all chemicals as required by the Occupational Safety Act of 1971, the Hazards Communication act of 1985 and Title 29 Code of Federal Regulations (CFR) Part 1910. Employees associated with the manufacture of drug product have appropriate MSDSs available for their review. Employee protective clothing, such as gloves, uniforms and safety glasses are used during the packaging process to assure compliance with the Occupational Safety Act of 1971 and the Hazard Communication Act of 1985 and Title 29 CFC Subpart I.

c. Applicable Emission Citations and Statements of Compliance Requirements

1) Albany, Georgia

a) Air Citations

Air emissions are subject to and in compliance with the rules of the Georgia Department of Natural Resources, Environmental Protection Division, Chapter 391-3-1, Air Quality Control. Air emissions are discharged subject to the Air Quality Permit Number 2833-047-10356 and 2833-047-11517, as amended.

a) Air Citations (Con't)

Particulate emissions from the manufacture of drug substance are subject to and in compliance with the emission rates set forth by regulation under Table Ia and Ib, Chapter 391-3-1-.02(2)(e), for new and existing equipment. Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements. No new regulated parameters are anticipated as a result of the proposed action.

b) Liquid Citations

Effluent from the on-site wastewater treatment plant is discharged to the Flint River and is subject to and in compliance with the National Pollutant Discharge Elimination System (NPDES) Permit Number GA0001619. The NPDES permit is administered by the Georgia Department of Natural Resources. The existing NPDES permit limits plant effluent to a BOD₅ daily maximum of 2,100 lb/d (June-Oct.), 4375 lb/d (Nov.- May); TSS daily maximum of 4,200 lb/d and pH between 6.0 and 9.0. Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements and no new permit limits are anticipated as a result of the proposed action.

c) Solid Citations

Hazardous solid waste is subject to and conforms with the Georgia Hazardous Waste Management Rules, Chapter 391-3-11, Standards Applicable to Generators of Hazardous Waste. The USEPA

c) Solid Citations (Cont.)

hazardous waste permit identification number for the plant is GA0003324985. The plant has a RCRA permit for the storage of hazardous waste in tanks and containers (permit no. HW008(S)). There are no numerical permit limits associated with the manufacture of losartan potassium at the Albany facility although efforts will be made to minimize the amount of solid waste generated. No new permit conditions are anticipated as a result of the proposed action.

2) Ballydine, Ireland

a) Air Citations

Air emissions are subject to, and in compliance with the Regulations of the Ireland Department of the Environment under the Air Pollution Act, 1987. Permit number ENV/A.P/2/91, issued by the Tipperary County Council, governs the sources of atmospheric emissions from processing activities, waste solvent incinerator, steam boilers and dust emissions from the dry processing equipment.

b) Liquid Citations

Aqueous waste streams are subject to and in compliance with Ireland's Department of the Environment, Local Government (Water Pollution) Regulations of 1977. The wastewater treatment plant operation is permitted by the county council of Tipperary County, Ireland (Permit # ENV/W/36/80, which also governs the effluent discharge to the River Suir).

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c) Solid Citations

Hazardous wastes are disposed of in a manner which fully conforms to local regulatory policy. Hazardous solid wastes are subject to, and in compliance with the Department of the Environment Waste Regulation (1979 and 1984) and the Transfrontier Shipment of Hazardous Waste Regulations, 1985.

3) Garden City, New York

a) Air Citations

Air emissions from site operations are subject to limits established under permits granted by the Nassau County Health Department, which has authorization delegated by the US EPA Clean Air Act.

These permits include:

C-282011-0886-00001 W-CA&CB for the Dust Collection Equipment

C-282011-0886-00007 W-CA, CB & CC for the Main Building.

C-282011-0886-00008 W-CA & CB, for the R&D Building

C-282011-0886-0021 W through C-282011-0886-00023

These permits are subject to Nassau County Health Department inspection on an annual basis, require annual reporting and must be

a) Air Citations (Cont.)

renewed every two years. The current copies of these permits are maintained by plant engineering personnel. Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements.

b) Liquid Citations

The discharge of plant wastewater to the Town of Hempstead wastewater collection system is approved under Sewer Discharge Permit Number 33. The Cedar Creek Water Pollution Control Plant operated by Nassau County is approved under NPDES permit NY0026859. The county discharge permit requires pH of the site discharge to be maintained between 5.5 and 9.5 at all times. No new permit limits are anticipated as a result of the proposed action.

c) Solid Citations

The collection of waste solvents and related hazardous chemicals not directly involved with the proposed action is approved under a hazardous waste permit, authorized by the US Resource Recovery and Conservation Act. The USEPA hazardous waste identification number for the plant is NYD001315209. Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements.

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4) West Point, Pennsylvania

a) Air Citations

The air emission controls for the disposal of this product meet the requirements of the Pennsylvania Air Pollution Control Regulations under Title 25 of the Pennsylvania Code, Part 1 - Department of Environmental Resources (PA DER), Chapters 121-141. Emissions of volatile organic compounds (VOC) from this site are currently regulated under PA DER No. 46-313-117. VOC emission limit for the site are 50 tons/year, 1000 lbs/day, and 100 lbs/hr. Particulate emissions are limited to 0.04 grains/dscf by regulation

Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements. No new permit limits are anticipated as a result of the proposed action.

b) Liquid Citations

The effluent from the West Point site is treated by the UGTA, and this effluent is discharged from the UGTA under NPDES Permit Number PA 0023256. This permit is administered by PA DER. The wastewater from the treatment works is subject to and in compliance with the pretreatment standards for existing sources of the Pharmaceutical Manufacturing Category under Title 40 of the Code of Federal Regulations Part 439 (Subcategory A for fermentation products). The wastewater is also regulated by the UGTA and is in compliance with the existing contract and the "Rules and Regulations Governing the Discharge of Sanitary and Industrial Wastewaters into the Public Sewers of the Upper Gynedd

b) Liquid Citations (Cont.)

Township Authority." These regulations are based on the requirements of the Federal Clean Water Act and the Pennsylvania Clean Streams Law. The existing contract with UGTA limits plant effluent flow (calculated from a monthly average) to approximately 1,225,000 gallons/d; BOD = 250 mg/L (daily maximum); TSS = 300 mg/L; and pH between 5.5-9.0. In any event, the facility will be in compliance with their wastewater discharge limits. Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements and no new permit limits are anticipated as a result of the proposed action.

c) Solid Citations

Solid waste management at the West Point plant requires conformance with conditions set forth in Permits 300437, 400459, and 300501 issued by PA DER and Permit PAD002387926 issued by both EPA and PA DER. These requirements assure comprehensive control for management of waste throughout the plant including returned market packages. The requirements of the Pennsylvania Code, Title 25, Part 1 - Department of Environmental Resources, Chapter 75, are the primary regulations and are subject to the requirements of the Federal Resource Conservation and Recovery Act, the Federal Hazardous and Solid Waste Amendments, and the Pennsylvania Solid Waste Management Act. Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements.

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F. Environmental Assessment

5) Wilson, North Carolina

a) Air Citations

The operation of the Wilson manufacturing packaging and power generating facilities is in compliance with Air Permit Number 4884 R9 issued by the North Carolina Department of Natural Resources and Community Development in accordance with Article 21B, Chapter 143, General Statutes of North Carolina and "Other Laws, Rules and Regulations". Approval of the proposed action will not impact the facility's ability to comply with the permit.

b) Liquid Citations

The discharge of wastewater to the City of Wilson Wastewater Collection System is allowed under the site Sewer Connection and Discharge Permit Number 8406. The site discharge is limited to daily maximum discharges of BOD=582 lbs/d, COD=932 lbs/d, TSS=349 lbs/d, and pH 5-9. These permits are established under the city's "Rules and Regulations for the Discharge of Wastewaters into the Wastewater Treatment System of the City of Wilson, North Carolina". The City of Wilson Department of Public Works Wastewater Treatment Plant operates under National Pollutant Discharge Elimination System (NPDES) Permit Number NC 0023906. No new permit limits are anticipated as a result of the proposed action. Manufacturing and packaging at Wilson will not impact the facility's compliance with the site's sewer Discharge Permit Number 8406.

I. Summary

F. Environmental Assessment

c) Solid Citations

The Wilson plant is in compliance with the North Carolina Hazardous Waste Management Rules and manages all hazardous waste in compliance with North Carolina Hazardous Waste Management Permit NCD 980798839. No new permit limits are anticipated as a result of the proposed action. Approval of the proposed action will not impact the facility's ability to comply with the permit.

d. Effect of Application Approval on Compliance with Current Emissions Requirements

Merck & Co., Inc. states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders as well as emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the production of losartan potassium at its facilities in Albany, Georgia, Ballydine, Kilsheelan, Ireland and at its tablet manufacturing and packaging facility in Wilson, NC and for the incineration of unused and returned goods at West Point, PA.

Dupont Merck Pharmaceutical Co., Inc. states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of drug product as well as emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the production of Tablets COZAAR at its facilities in Garden City, New York.

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e. Expected Maximum Annual Production

It is expected that the total 5th year production volume will be on the order of _____ kilograms per year and includes losartan potassium used alone (monotherapy) or in combination with other therapeutic agents. Pollution prevention, solvent recovery and recycle will be implemented to the extent practical to minimize the release of chemicals into the environment. In addition, control equipment as indicated in section 6(b) & 6(c) are employed to further reduce chemical emissions. The anticipated production activities represents _____ of total capacity at the Albany facility and _____ of total capacity at the Ballydine facility. Facilities used for manufacture of losartan potassium drug product are subject to, and in compliance with, applicable regulations. Environmental effects as a result of manufacturing, product use and disposal are minimal.

7. Fate of Emitted Substances to the Environment

Environmentally relevant chemical/physical and ecotoxicological properties of losartan potassium have been evaluated by standard and widely accepted laboratory procedures. Except where noted, all studies were conducted by the Merck Research Laboratories, Rahway, New Jersey and West Point, Pennsylvania and the DuPont Merck Pharmaceutical Company, Wilmington, Delaware. Results and studies presented in the technical sections of the NDA document or appendices are only summarized here. Copies of the environmental fate and effect study reports are provided in Appendix V.

a. Physico-Chemical Properties

1) Aqueous Solubility

Losartan potassium is freely soluble in water (>500 g/L) at ambient temperature (~25°C). The resulting pH is 9.7.

2) Partition Coefficient

The distribution coefficient for losartan between octanol and aqueous phosphate buffer (pH 7; approximately 0.1M PO₄) was determined by the following experimental procedure. A measured volume of an aqueous phosphate buffer solution of losartan (about 0.01M in losartan) was stirred for one hour at room temperature with an equal volume of n-octanol. After the equilibration period, the mixture was centrifuged and the octanol and aqueous phases separated, diluted where necessary and analyzed by HPLC. This was done in triplicate. A more dilute aqueous phosphate buffer solution of losartan (about 0.001M in losartan) was prepared and again a measured volume of the solution was stirred for one hour at room temperature with an equal volume of n-octanol. After the equilibration period, the mixture was centrifuged and the octanol and aqueous phases separated, diluted where necessary and analyzed by HPLC. This was also done in triplicate. The average distribution coefficient, expressed as log P, was found to be 1.19±0.03. The average losartan recovery from the experiments starting with 0.01M losartan aqueous solution was 95% based on the HPLC concentrations and 93% for the 0.001M losartan solutions.

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3) Solution pH

The pH of a solution of losartan potassium (1% w/w) in water is about 8.2.

4) Disassociation Constant (pKa)

The pKa value for the tetrazole hydrogen of losartan potassium is 4.9, determined by the potentiometric titration of losartan potassium in 1:1 methanol:water under acidic conditions. The pKa in aqueous solution containing 1% methanol is 4.1, as determined by ultraviolet spectroscopy using buffers from 1 to 13. The difference in measured pKa values is due to the different levels of methanol present in the solution.

The pKa of losartan was determined by acid titration as follows: The titration was performed with a Metrohm 670 Titroprocessor using a combination glass electrode. The electrode was standardized at pH values of 4.0, 7.0 and 10.0. The hydrochloric acid titrant was standardized against tris (hydroxymethyl) amino methane and was about 0.1M HCl. The sample (about 13 mg) was dissolved in 25 ml of methanol and 25 ml of water was added. The solution was titrated with acid past the equivalent (end) point and pKa calculated as the pH at 1/2 the equivalence point (4.9).

The pKa was also estimated by the change in the UV spectra as a function of pH. The UV spectra for losartan was determined in 1 to 2M HCl and buffers ranging in pH from 1 to 13 containing 1

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4) Dissociation Constant (pKa) (Cont.)

volume % methanol using a Perkin-Elmer Lambda 5 spectrophotometer. Losartan (10 mg) was dissolved in 10 ml of methanol (spectrophotometry grade). Aliquots (0.1 ml) of the solution were diluted with the appropriate buffer to a final volume of 10 ml. The UV absorbances of the acid and base forms of losartan were determined at appropriate wavelengths. The UV absorbances at the same wavelengths for losartan at intermediate pH values were determined and the pKa calculated from the following equation:

$$pKa = pH - \log(A - Aa) / (Ab - A)$$

where Aa = UV absorbance of the acid form of losartan,
Ab = UV absorbance of the base form of losartan,
A = UV absorbance of losartan at an intermediate pH.

The absorbances (Aa, Ab and A) are all measured at the same wavelength. An average value for the pKa of 4.1 ± 0.1 was determined from a combination of intermediate pH values and wavelengths.

5) Chirality and Specific Rotation

Losartan potassium is achiral and, thus, is not optically active.

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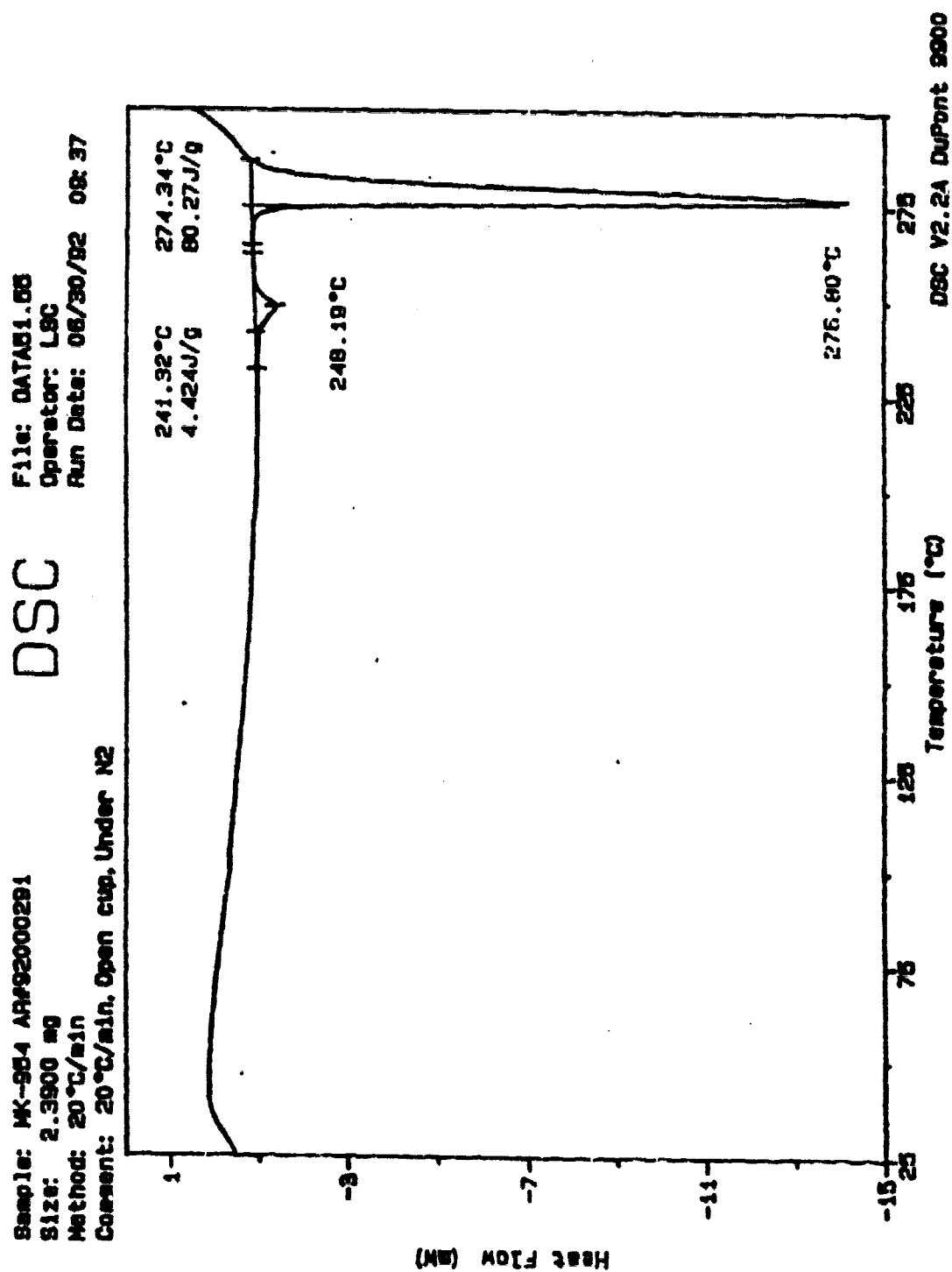
6) Thermal Behavior

The thermal behavior of losartan potassium has been investigated (MRL, West Point, PA) with a combination of differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD) techniques in an inert and oxidizing atmosphere.

Losartan potassium has been found to exist in two polymorphic forms. The differential scanning calorimetry (DSC) curve for losartan potassium (refer to Figure F1), obtained at 20° C/min in an open cup under nitrogen flow, is characterized by two endotherms. The minor endotherm with an extrapolated onset temperature of ~241° C and a heat of ~4 joule/g corresponds to the enantiotropic polymorphic transition between the two polymorphs. The major endotherm corresponds to the melting of the higher temperature polymorph and occurs at an extrapolated onset temperature of ~274° C (peak temperature ~277° C) with a heat of 80 joule/g. Visual inspection of the sample after the minor endotherm showed no evidence of melting. Inspection by X-ray powder diffraction (XRPD) of a sample heated to above the minor endotherm indicated a change in the crystal structure, and, no chemical change in the heated sample was seen by NMR spectroscopy or HPLC.

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Figure F1 Differential Scanning Calorimetry Curve For Losartan Potassium



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6) Thermal Behavior (Cont.)

These results confirm the existence of two polymorphic forms of losartan potassium, which have been designated Form I for the low temperature stable form (up to the transition temperature of about 240°C) and Form II for the polymorph stable above the transition temperature.

An additional study was conducted by MRL, Rahway, NJ in both an inert and oxidizing atmosphere over the entire temperature range at 10°C/min heating rate. Under nitrogen, the low intensity endotherm is observed to occur at ~240°C, followed by a more intense endotherm initiating at 270°C. The absence of a characteristic weight change at 240°C implies a purely physical solid state transition rather than a chemical transformation; thus, confirming the results of the initial study. Furthermore, following termination at 280°C, an exothermic signal occurs, and, at this point, the initiation of a weight loss is observed. This behavior is interpreted as fusion followed by melt decomposition. In an oxidizing atmosphere, the onset of fusion is ~260°C. Exothermic oxidation appears to start at melt termination (endotherm signal peak).

In the inert environment, the melt undergoes a two-stage pyrolysis.

The first stage, probably due to tar formation, is mildly exothermic. The loss of volatiles during tar to char conversion is not accompanied by well defined thermal activity, although there are indications of endothermicity.

6) Thermal Behavior (Cont.)

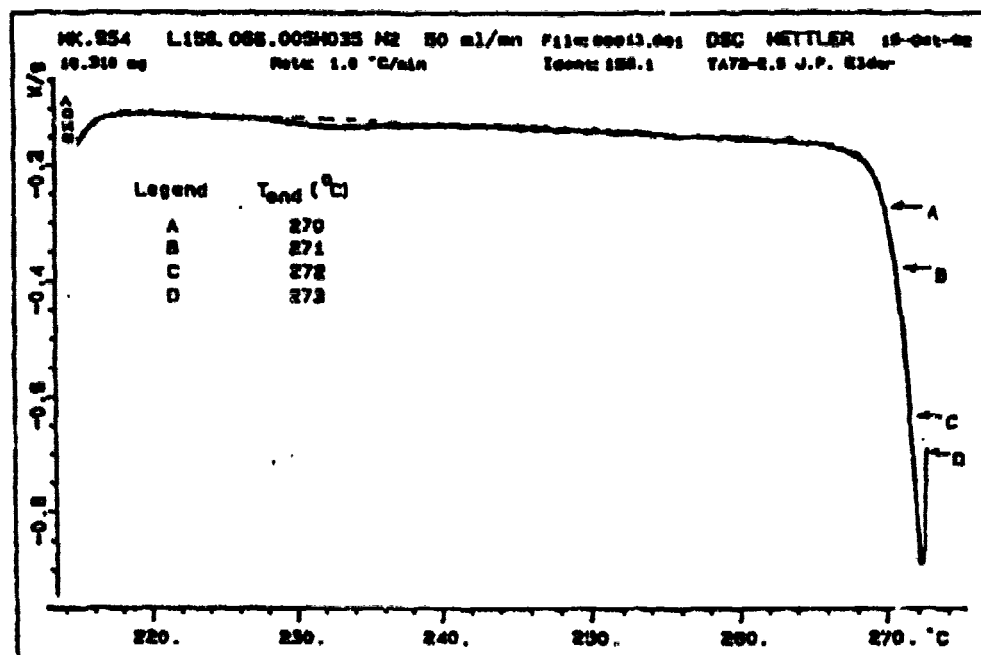
In the oxidizing atmosphere, the exothermic oxidation of the two-step release of gaseous pyrolysis products is more clearly defined in both the heat flow and weight loss profiles in the 300-310°C and 450-515°C regions. Furthermore, at ~550°C, exothermic combustion of char proceeds, leaving ~20% mineral ash residue.

There is apparently no weight change until the onset of the melt decomposition in the 260-270°C region, where a small linear loss is observed to occur. In the nitrogen atmosphere at 10°C/min, between 25-270°C, a 1.12% weight loss was obtained. At 1°C/min, between 25-262°C the loss is 1.07%. These losses can be attributed to sublimation and the start of thermal degradation. In the oxygen atmosphere, the monitored weight losses are much less; thus, at 1°C/min between 25-260°C, the loss is 0.51%, while at 1°C/min between 25-240°C, a 0.64% loss was measured. It is conjectured that oxygen chemisorption offsets the purely thermally induced weight losses.

A series of experiments were conducted in which samples of losartan potassium were heated at 10°C/min from 200°C, through the solid state transition region (230-240°C) and beyond the onset of fusion at 269.8°C. The partially melted samples were rapidly cooled to room temperature, examined and weighed. Several heat flow profiles were developed for end-point temperatures at 270, 271, 272, 273 and 274°C. The heat flow profiles are shown superimposed in Figure F2a. The true melting point was deter-

Figure F2a

Thermal Gravimetric Analysis of Losartan Potassium - Heat Flow Profiles



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6) Thermal Behavior (Cont.)

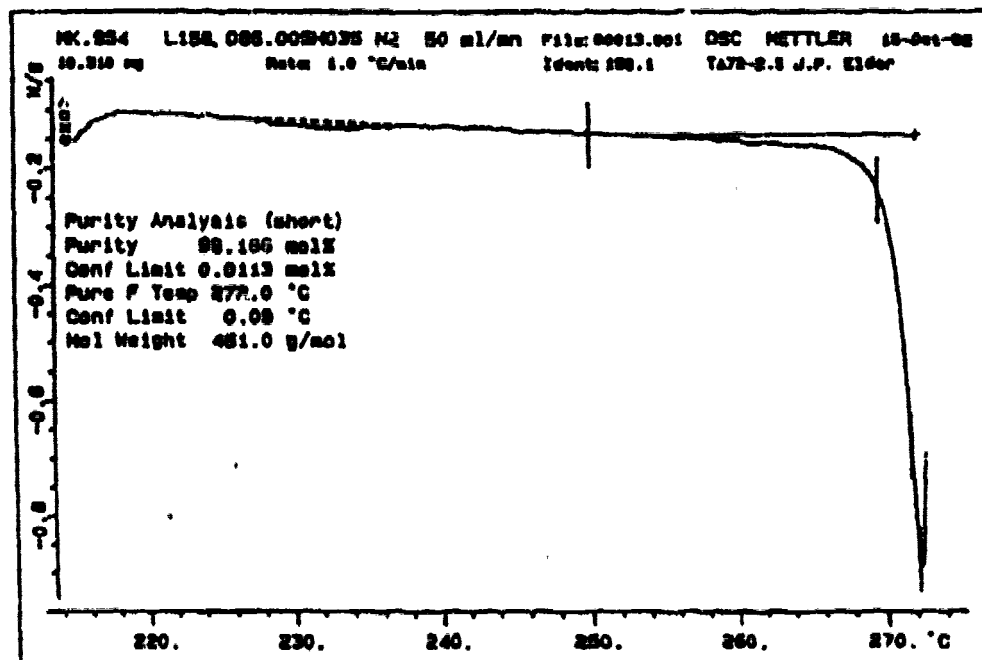
mined to be $T_f = 272^\circ\text{C}$. The melting point was determined by analyzing the leading edge of the fusion endotherm using the "short" van't Hoff purity analysis program as shown in Figure F2b. The calculated heat of fusion was 85.8 J/g.

In order to determine if thermal stressing can effect the 244°C polymorphic transition, two losartan potassium samples were subjected to 5-hour stresses in an inert atmosphere at two temperatures. Stressing at 220°C does not cause the change. Stressing at 235°C , just below the onset of the Form I to II transition, does effect the change. These measurements define the upper temperature limit for extended period isothermal TG measurements of possible sublimative loss.

A weight loss-time profile was determined for losartan potassium over a 15-hour period under nitrogen at three temperatures, 200, 225 and 245°C . The data indicates that the Form II polymorph readily decomposes in the solid state. After an induction period of ~1.5 hours, degradation proceeds. The total loss is 13% and the degradative residue is a dark-brown tarry material. At 225°C , there was a 0.8% loss during the 15 hours, and the powdered residue was yellow in color. At 200°C , the weight loss appears linear with time, indicative of sublimation, but the residue appeared very pale yellow. Refer to Figure F3a. At or below 180°C , weight losses were very low during periods of isothermal stress. This is shown in Figure F3b. A best fit of the data was determined and the vapor

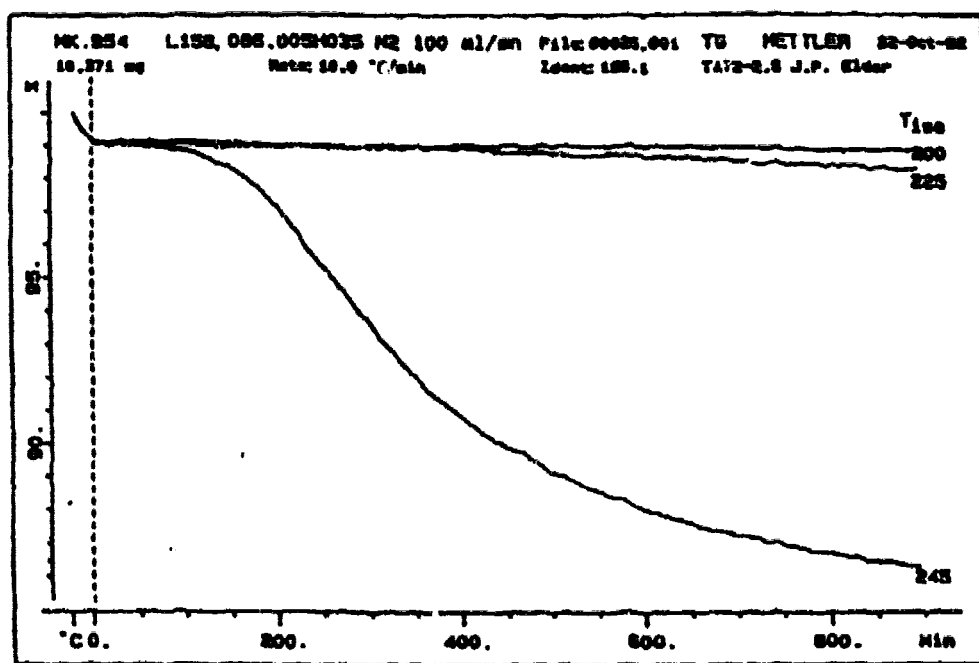
Figure F2b

Determination of the Melting Point of Losartan Potassium



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Figure F3a Thermal Gravimetric Analysis of Losartan Potassium

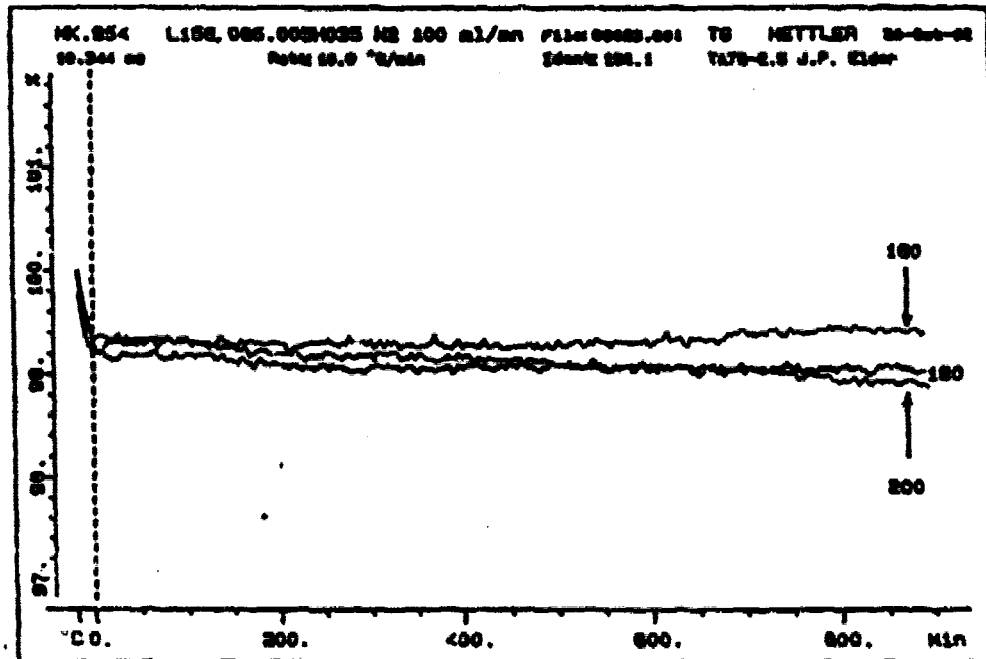


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Figure F3b

Thermal Gravimetric Analysis of Losartan Potassium



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6) Thermal Behavior (Cont.)

pressure and heat of sublimation were estimated. The heat of sublimation is estimated at $H = 58$ kJ/mol. The vapor pressure, at or below 59°C , is $<10^{-7}$ torr.

To monitor the combustive behavior of losartan potassium, samples were heated in a TG furnace at $50^{\circ}\text{C}/\text{min}$ from room temperature to two chosen upper limits, 550 and 600°C , and then heated at these limits for 30 minutes. The results indicate that a less than two-minute burn in oxygen at 550°C is sufficient to destroy losartan potassium completely to the ash stage.

7) UV-Visible Light Spectrum

The ultraviolet absorbance spectrum of losartan potassium in methanol (Figure F4) was obtained using a Aviv Associates Model 118DS ultraviolet-visible spectrophotometer. The spectrum is characterized by absorbance shoulders at ~ 250 and ~ 228 nm (A 1% 1 cm values of ~ 320 and ~ 574 , dry basis).

b. Stability

The stability characteristics of losartan potassium drug substance have been extensively evaluated, both for solid state material and in solution.

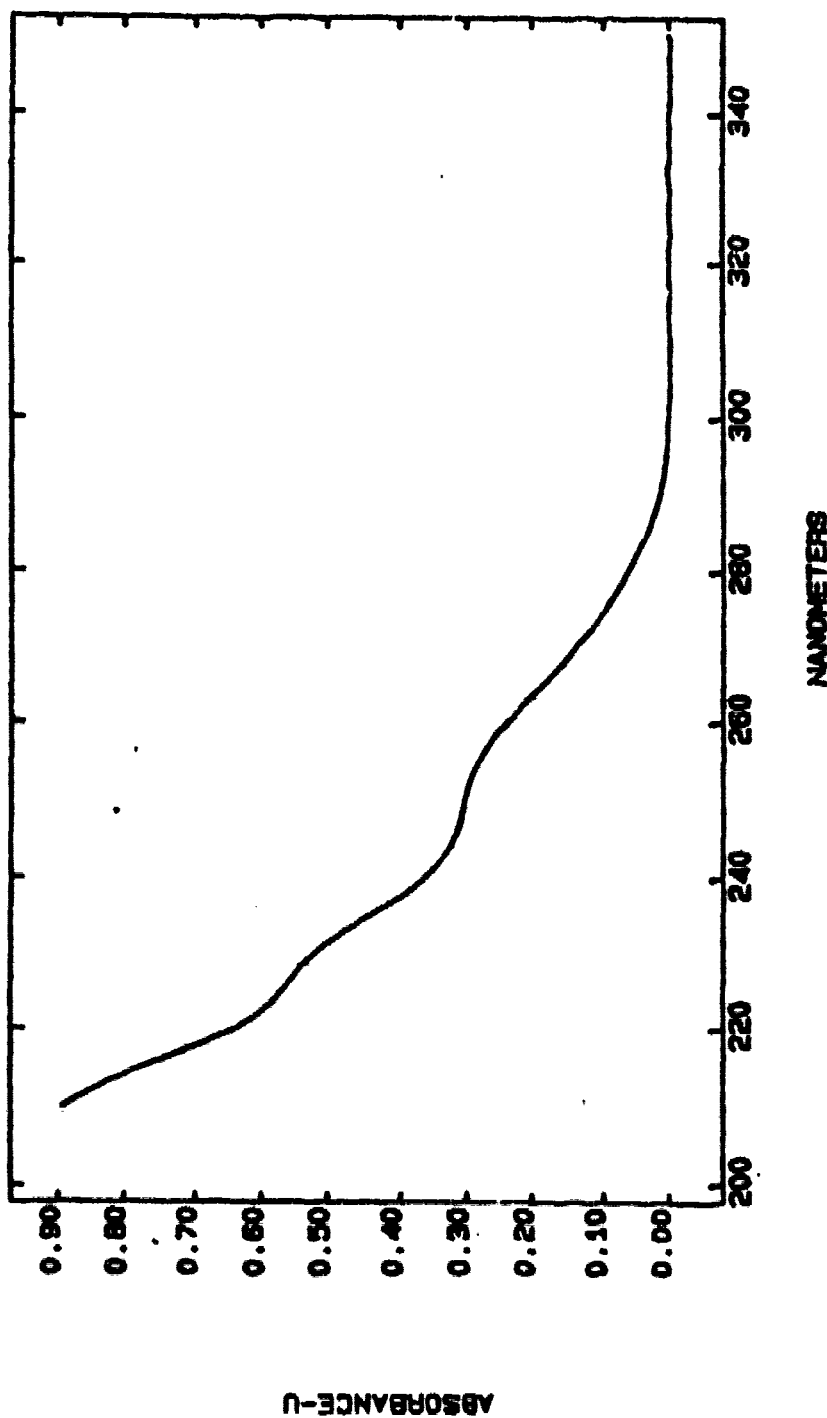
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Figure F4

Ultraviolet Absorbance Spectrum of Losartan Potassium

AVIV PLOT V3.3m cr T. 100.0C. date. 8-11-92 time. 12:48:59 c
taken 09-11-92 at 12:48:00, ref 7.050. AVT 0.2 sec
scan from 350.00 nm to 210.00 nm every 0.20 nm w/ 0.20 nm bw 92000291.smd
y lower lim -0.0048. y upper lim 0.8928 Absorbance-U



I. Summary

F. Environmental Assessment

1) Solid State Stability

a) Ambient Temperature and Relative Humidity Conditions

Solid losartan potassium drug substance has been stored in double polyethylene bags inside cardboard shipping containers under conditions of ambient temperature and relative humidity for up to three years. HPLC was used to monitor the stability of losartan potassium drug substance during the evaluation. No evidence of decomposition was observed during this period.

Additional ambient stability data have been generated by DuPont Merck. These data confirm that losartan potassium stored in double polyethylene bags within a fiber drum is stable for at least two years under ambient conditions.

b) Under Elevated Temperature and Relative Humidity Conditions

Solid losartan potassium has been stored in screw-capped amber glass bottles at 40°C for up to 6 months and at 60°C for up to 12 weeks. The results of these stability studies, conducted by DuPont Merck, showed no changes in physical appearance of the drug substance for the duration of the evaluation and no changes in the HPLC impurity profile or weight percent assay. Losartan potassium is stable for at least 6 months at 40°C and for at least 12 weeks at 60°C.

Three lots of solid losartan potassium were stored at 40°C and 75% relative humidity in double polyethylene bags inside fiber drums. In less than one month the material was no longer free flowing,

b) Under Elevated Temperature and Relative Humidity Conditions (Cont.)

though no degradates were detected by HPLC impurity profile or weight percent analysis. After six months at 40°C/75% RH, the material was still a non-flowing white mass. No changes in HPLC area percent or weight percent were detected and the water content had not increased significantly.

Solid losartan potassium has been stored at 80°C in capped amber glass bottles for four weeks. Analysis of this material by the HPLC assay and impurity analysis showed no change after 4 weeks.

c) Photochemical

Solid losartan potassium was stored in an open dish at 25°C in the presence of light (600 foot candles) for up to 12 weeks. The formation of two degradation products (retention times of ~18 and ~23 minutes) at levels of up to 0.8% total (HPLC) was observed. This study was conducted by DuPont Merck. Losartan potassium solid appears to be slightly photosensitive. Drug substance lots produced later in development, exhibited less photosensitivity than earlier lots as exhibited when solid losartan potassium was stored in transparent glass tubes at ambient temperature and exposed to cool fluorescent light for a total of 1.8 million lux hours (over ~25 days). No photodegradation was observed over the duration of the study. The results were obtained using the HPLC assay and impurity analysis methods.

I. Summary

F. Environmental Assessment

c. Stability in Aqueous Solution

1) Hydrolysis

In a study conducted by Toxikon Environmental Sciences (Jupiter, FL), the stability of losartan potassium in aqueous solution was evaluated at 50°C and pH 5 (0.01 M sodium acetate buffer), pH 7 (0.067M phosphate buffer) and pH 9 (0.025 M sodium tetraborate buffer) for a test period of five days. Using the criteria ($\geq 10\%$ hydrolysis in five days at 50°C) provided in the US FDA Technical Assistance Document, Section 3.09 (1987), the results from the pH 5, 7 and 9 hydrolysis testing indicate that losartan potassium in water was not susceptible to hydrolysis.

The 5 day study was conducted at a concentration of 100 mg/L in pH 5, 7 and 9 aqueous buffers. The samples were placed on a rotatory shaker located in an incubator maintained at $50 \pm 1^\circ\text{C}$. At day 5, the samples were removed and analyzed by HPLC. The concentration of losartan potassium after five days was compared to the initial concentration. The mean percent initial concentration for the pH 5, 7 and 9 samples was $98.3\% \pm 0.07$, $98.9\% \pm 2.6$ and $97.7\% \pm 0.28$, respectively. The pH of the samples were measured on day 0 and 5 and did not change significantly in any of the test samples.

a) Photochemical

In a study conducted by Toxikon Environmental Sciences (Jupiter, FL), photodegradation of losartan potassium in an aqueous solution exposed to sunlight was studied at three different pHs .

I. Summary

F. Environmental Assessment

a) Photochemical (Cont.)

Losartan potassium was found to be susceptible to photolysis. The parent compound degrades rapidly under clear sky conditions. Two photodegradates are formed during photolysis; one less polar than the parent compound (formed primarily in neutral and alkaline conditions); one more polar than the parent compound (formed primarily in slightly acidic conditions). The maximum half-life for losartan potassium is less than 18 hours (at pH 9) in direct sunlight.

Losartan potassium solutions were prepared in each of the three buffer solutions, viz, pH 5 (0.01M sodium acetate buffer), pH 7 (0.067M phosphate buffer) and pH 9 (0.025 M sodium borate buffer).

The concentrations of losartan potassium were less than one-half of the water solubility of the test article. Buffer solutions were sterile and saturated with air before use. Controls (dark controls) consisted of losartan potassium solutions of the same concentration and pH as the test solutions. During the test, light was excluded from these solutions. The analysis for losartan potassium was performed by HPLC.

To estimate the photolysis rate of losartan potassium, a 14-hour preliminary study was conducted at a nominal concentration of 100 mg/L (2×10^{-4} M) in pH 5, 7 and 9 aqueous buffers. A chem-

I. Summary

F. Environmental Assessment

a) Photochemical (Cont.)

ical actinometer, PNAP/PYR (2×10^{-5} M / 1.0 M) was exposed for 6.0 hours to estimate the reaction quantum yield, ΦF_E^* . At each sampling point, the test and actinometer solutions were removed from the photolysis chamber and analyzed by HPLC to determine the percent parent compound concentration. Based on these analyses, the half-life of losartan potassium was <10 hours, and the half-life of the actinometer was <3 hours.

The definitive study was conducted at a nominal losartan potassium concentration of 100 mg/L (2×10^{-4} M) in the same aqueous buffers used in the preliminary study. In an attempt to decrease the rate of photolysis, the concentration of pyridine in the PNAP / PYR actinometer was reduced from 1.0 M to 0.55 M. The concentration of PNAP was maintained at 2×10^{-5} M. Test and actinometer solutions were removed from the photolysis chamber at seven regular time intervals for up to 36 hours. The degradation of the test substance was monitored by HPLC.

The photolysis rate constant (k_p^c) and half-life ($t_{1/2}$) for the pH 5 test samples were determined to be 0.0637 hr^{-1} and 10.9 hours, respectively, for the exposed samples and indeterminate (infinite half-life) for the dark controls. The k_p^c and $t_{1/2}$ for the pH 7 test samples were determined to be 0.0587 hr^{-1} and 11.8 hours, respectively, for the exposed samples and 0.0004 hr^{-1} and 1733 hours for the dark control samples. The k_p^c and $t_{1/2}$ for the pH 9 test samples were determined to be 0.0394 hr^{-1} and 17.6 hours,

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a) Photochemical (Cont.)

respectively, for the exposed samples and indeterminate (infinite half-life) for the dark samples. The correlation coefficient for the rate of disappearance of the test substance and exposure time (hours) was determined to be 0.9776 for the pH 5 samples, 0.9830 for the pH 7 samples, and 0.9771 for the pH 9 samples. The correlation coefficient for the rate of disappearance of the test substance versus cumulative UV radiation was determined to be 0.9770 for the pH 5 samples, 0.9785 for the pH 7 samples, and 0.9840 for the pH 9 samples.

The photolysis rate constant and half-life for the actinometer were determined to be 0.2290 hr^{-1} and 3.03 hours, respectively. The correlation coefficient for the rate of disappearance of the actinometer versus exposure time was determined to be 0.9905. The correlation coefficient for the rate of disappearance of the actinometer versus cumulative UV radiation was determined to be 0.9971.

The HPLC chromatograms of exposed samples revealed two primary photodegradation products. A degradate appeared at a retention time of 13-14 minutes in all pH 5, 7 and 9 exposed samples. As the parent test substance concentration declined over time; the concentration of this degradate increased. In addition to this degradate, another more polar photoproduct formed with increasing exposure time in the pH 9 samples.

I. Summary

F. Environmental Assessment

a) Photochemical (Cont.)

Losartan potassium was susceptible to photodegradation in all of the study treatments, based on the criteria set forth in the US FDA Technical Assistance Document, Section 3.10 (1987). The measured concentrations of the dark controls approximated that of each respective sample; no other dark control analysis was deemed necessary. Additionally, the pH did not change significantly in any of the test samples.

d. Biodegradability

Losartan potassium does not appear to be readily biodegradable when exposed to an unacclimated mixed microbial population (activated sludge). Presence of an easily metabolizable cosubstrate such as glucose failed to induce transformation or degradation of losartan potassium. The average recovery of the drug substance at the completion of the 28-day study was 92.1%. Virtually no hydrolysis of losartan potassium was observed during the 28-day test which was performed using phosphate buffer. An average of 98.1% of the drug substance was recovered from the abiotic controls.

A biodegradation study was conducted at Toxikon Environmental Sciences, Jupiter, FL. The study employed losartan potassium in aqueous media with four different bacterial and 1 algal (periphyton) inoculum. Each inoculum was acclimated to the test substance for a maximum of 60 days prior to the initiation of the study.

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d. Biodegradability (Cont.)

After the acclimation period, an aliquot of the inoculum solution was transferred to a biodegradation reaction flask containing mineral salts media and losartan potassium (10 mg carbon/liter) and aerobically incubated for 28 days. After 14 and 28 days, subsamples of each test solution were taken and the concentration of losartan potassium was determined by HPLC. After 28 days, the losartan potassium concentration in each of the 4 bacterial inocula test solutions was greater than 90% of the initial concentration. The losartan potassium concentration in the periphyton inoculum test solution after 28 days was 71% of the initial concentration. The HPLC chromatograms of the periphyton sample showed the presence of two additional peaks, indicating biotransformation of losartan potassium.

e. Aquatic Toxicity

1) Toxicity to *Daphnia magna*

The static acute toxicity of losartan potassium to *Daphnia magna* was evaluated under a standard laboratory operating procedure (SOP) based on US-EPA test protocol (1). Results obtained from a 48-hour *Daphnia magna* static acute aquatic toxicity study with losartan potassium yielded an LC₅₀ of 331 mg/L with a 95% confidence interval of 270 to 404 mg/L. Measured concentrations were 96.4 - 99.6% of the nominal concentrations at the start and 92.6 - 99.6% at the conclusion of the test. The *Daphnia magna* used in the study were obtained from stock cultures maintained by

I. Summary

F. Environmental Assessment

1) Toxicity to *Daphnia magna* (Cont.)

the Environmental Engineering Laboratory, MRL, Rahway, NJ. *Daphnia magna* stock cultures are kept at 20°C in aerated containers using spring water (hardness ~256 mg/L as CaCO₃). The cultures are maintained on a 12-hourlight/dark cycle and are fed five times a week with a suspension of trout chow, yeast, and alfalfa, 1.5 mg/L, and *Selenastrum capricornutum* (7 to 10-day-old algal culture), 20 mg/L. Neonates less than 24 hours old were used for the test. All statistical analyses were performed using the Moving Average Angle Method. Water quality parameters (pH, dissolved oxygen, hardness, alkalinity, conductivity) and HPLC analyses of losartan potassium were determined at test initiation and termination.

Sodium lauryl sulfate was used as a reference toxicant to determine the sensitivity of the organisms used in the toxicity test. Acceptable test organisms are those which exhibit a 48-hour LC₅₀ within ± two standard deviations of the average value as determined by the cumulative summation control chart for the reference toxicant. The LC₅₀ obtained was 14.5 mg/L which fell within the acceptable range of 11.3 to 26.6 mg/L.

2) Toxicity to *Pimephales promelas* (Fathead Minnows)

The static acute toxicity of losartan potassium to *Pimephales promelas* was evaluated under a standard laboratory operating procedure (SOP) based on a US-EPA test protocol (1). Results obtained from a 48-hour *Pimephales promelas* static acute aquatic

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2) Toxicity to *Pimephales promelas* (Fathead Minnows) (Cont.)

toxicity study with losartan potassium, based on nominal concentrations, yielded an LC_{50} of >1000 mg/L. The measured concentration of the compound was 94.3% of the nominal at the start and 92.4% at the conclusion of the test.

The *Pimephales promelas* (Fathead minnows) used in the study were obtained from Aquatic Research Organisms (ARO), Hampton, New Hampshire. The cultures were acclimated in spring water (hardness ~256 mg/L as $CaCO_3$) at 21°C, 12 hour light-dark cycle and fed dry flake food daily for a period of five days. Seventeen-day-old fish were used in the reference toxicant and losartan potassium static acute studies. Water quality parameters (pH, alkalinity, hardness, conductivity, dissolved oxygen) and HPLC analyses of the drug substance were performed at test initiation and termination. All statistical analyses were performed using the Moving Average Angle Method.

Sodium lauryl sulfate was used as the reference toxicant to determine the sensitivity of the Fathead minnows used in the toxicity test. Acceptable test organisms are those which exhibit a 48-hour LC_{50} which is within $\pm$ two standard deviations of the average value as determined by the cumulative summation control chart for the reference toxicant. The LC_{50} obtained was 15.0 mg/L which fell within the acceptable range (9.8 - 23.4 mg/L).

3) Toxicity to *Oncorhynchus mykiss* (Rainbow Trout)

The static acute toxicity of losartan potassium to rainbow trout, *Oncorhynchus mykiss*, was determined in laboratory toxicity tests conducted by Toxikon Environmental Sciences (Jupiter, FL). The 96-hour median lethal and no-observed-effect concentration (LC₅₀ and NOEC) based on mean measured concentrations of losartan potassium were >929 mg/L. Confidence limits to these estimates could not be calculated due to lack of treatments with intermediate levels of mortalities and effects, respectively. Average measured concentrations of losartan potassium ranged from 92-93% of the nominal concentrations.

Rainbow trout, *Oncorhynchus mykiss*, used in tests with losartan potassium were obtained as juveniles from a commercial hatchery (Stoney Creek Trout Farm, Grant, MI). The fish were maintained in the laboratory on treated Jupiter, Florida, town water prior to test initiation. The freshwater possessed a hardness of approximately 100 to 104 mg/L as calcium carbonate (CaCO₃). Holding water temperature ranged from 10.6 to 15.4°C during the 14 days immediately prior to test initiation. Fish used in tests with losartan potassium were approximately seven weeks old at the time of testing. There were no signs of disease among test fish at any time prior to the initiation of tests with losartan potassium. Consequently, these fish were not subjected to any therapeutic treatments.

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3) Toxicity to *Oncorhynchus mykiss* (Rainbow Trout) (Cont.)

The juveniles were offered a commercially manufactured pelleted food (#2 Salmon Starter, Zeigler Bros., Inc., Gardners, PA) and live brine shrimp (Aquarium Products, Glen Burnie, MD) nauplii daily. Food was not offered to prospective test fish for 48 hours prior to the initiation of either the screening or definitive test. Mortalities within fish stocks from which fish were taken for use in testing losartan potassium were <<1% immediately prior to the initiation of testing.

Screening and definitive tests with rainbow trout were conducted in static, 23.6 liter glass tanks, containing 12 liters of test solution. Water pH and dissolved oxygen were measured daily in each test vessel during both the screening and definitive tests. Water temperature was measured daily in the dilution water control. Alkalinity, hardness and conductivity were determined for solutions in each test vessel at the end of a test i.e. - when either 100% mortality was observed or at the end of the study. Samples for analysis by HPLC were collected from each replicate immediately prior to the addition of test fish to each exposure vessel and in each vessel either when 100% mortality was observed or at the end of the study. All samples were collected from midway in the water column with a glass pipette. The LC_{50} was estimated by a computer program (Wheat, 1989) using the following statistical methods: moving average angle, probit, logit and non-linear interpolation. The method selected for reporting the test results

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3) Toxicity to *Oncorhynchus mykiss* (Rainbow Trout) (Cont.)

was determined by the characteristics of the data, i.e., the presence or absence of 0 and 100% mortality and the number of concentrations in which mortalities between 0 and 100% occurred.

Mortality of rainbow trout, *Oncorhynchus mykiss*, exposed for 96 hours to losartan potassium was zero percent at all test concentrations tested, except 555 mg/L. The mortality at 555 mg/L losartan potassium occurred in only one replicate. Because the mortality for this concentration occurred in only one replicate and because 100 percent survival was observed at the higher concentration of test substance, another factor, other than the toxicity of the test compound, was likely the cause of the fish mortality in this replicate during the study. There was 5 percent mortality in the dilution water control.

4) *Photobacterium phosphoreum* (Microtox)

An EC_{50} of >1000 mg/L was obtained for losartan potassium using the standardized Microtox indicator organism (*Photobacterium phosphoreum*).

A Microtox 500 System was used for the determination of a dose-response curve from which the effective concentration (EC_{50}) of losartan potassium was obtained. The EC_{50} is the concentration at which the luminescence (light output) is 50% of the original luminescence, i.e., when the bacteria are not exposed to a toxicant. The indicator organism used is a bioluminescent marine bacteria

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4) Photobacterium phosphoreum (Microtox) (Cont.)

(*Photobacterium phosphoreum*) which has been grown, harvested, and then lyophilized (freeze dried under vacuum). The lyophilized bacteria were rehydrated with reconstitution solution and used in the assay as reagent.

The procedure employed a non-toxic control and four serial dilutions of losartan potassium. The mean response of the duplicate reagent blanks was used to normalize the duplicate responses of the four test concentrations. This normalization corrects for the deviation in response from normal drifts of light output with time. The dose-response measured was the decrease in light production (luminescence) of the bacteria caused by increasing toxicity. The EC_{50} is obtained at 30 minutes and 15°C.

Phenol was analyzed as a reference toxicant to evaluate bacterial sensitivity (luminescence). The EC_{50} determined at 30 minutes and 15°C was 19.4 mg/L. This response fell within the acceptable range of 15.7-24.1 mg/L obtained from the cumulative summation control chart for phenol.

5) Chronic Toxicity to Green Alga, *Selenastrum capricornutum*

The chronic toxicity of losartan potassium to the green alga, *Selenastrum capricornutum* was determined in a 10-day laboratory toxicity test conducted by Toxikon Environmental Sciences (Jupiter, FL). The criterion for effect was reduction in cell growth.

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5) Chronic Toxicity to Green Alga, *Selenastrum capricornutum* (Cont.)

The no-observed-effect concentration (NOEC) and minimum inhibitory concentration were calculated for the mean of the maximum standing crop and μ_{max} (maximum specific growth rate).

Maximum standing crop occurred by day 8. The NOEC and MIC values based on maximum standing crop were 143 and 245 mg/L. The largest specific growth rate occurred between days 0 and 2. The NOEC and MIC values based on μ_{max} were 245 and 381 mg/L. Mean measured concentrations of losartan potassium ranged from 106 to 124 percent of the nominal. The definitive exposure was conducted under static conditions in a temperature controlled room set at $24 \pm 2^\circ\text{C}$. All losartan potassium stock solutions were prepared using freshwater algal media as the diluent. Four 50 mL aliquots of each test solution were transferred to sterile 250 mL glass Erlenmeyer flasks. Dilution water controls were maintained concurrently with the six test solutions. All flasks were closed with gas exchange caps.

Each test solution was inoculated with approximately 3000 cells/ml *Selenastrum capricornutum*. The test chambers were impartially positioned in a temperature controlled chamber under continuous fluorescent lighting. Light intensity ranged between 4025 to 5100 lux. Test chambers were impartially re-positioned daily to eliminate spatial effects, and continuously agitated on an orbital shaker at approximately 100 rpm.

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5) Chronic Toxicity to Green Alga, *Selenastrum capricornutum* (Cont.)

Algal growth was measured by direct cell counts using a hemacytometer counting chamber with a compound microscope every 48 hours. Temperature was measured in one uninoculated flask of test medium daily during the test. The temperature range of the control chamber was monitored continuously during the test with a minimum/maximum thermometer and the diurnal temperature range recorded daily. Light intensity was measured daily at the level of each test solution, except on day 9. The pH was measured at test initiation and termination in all test treatments and control flasks. Concentrations of losartan potassium were measured by HPLC. Samples were collected at test initiation and termination from all composite solutions of the test treatments and the control.

Based on the results of the test, the no-observed-effect concentration (NOEC) and minimum inhibitory concentration (MIC) were calculated by analysis of variance (ANOVA) with statistical differences between mean cell density by Dunnett's procedure. All statistical differences were determined at a probability level of 0.05.

6) Chronic Toxicity to Bluegreen Alga, *Microcystis aeruginosa*

The chronic toxicity of losartan potassium to the blue green alga, *Microcystis aeruginosa* was determined in a 10-day laboratory toxicity test conducted by Toxikon Environmental Sciences (Jupiter, FL). The criterion for effect was reduction in cell growth.

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6) Chronic Toxicity to Bluegreen Alga. *Microcystis aeruginosa* (Cont.)

The no-observed-effect concentration (NOEC) and minimum inhibitory concentration (MIC) were calculated for the mean of the maximum standing crop and the μ_{max} (maximum specific growth rate).

Observations of cell morphology found no changes in losartan potassium-exposed cells as compared to cells in the controls. After 10 days of exposure, reduction in cell growth ranged from 9 percent at 566 mg/L to 26 percent at 949 mg/L. Maximum standing crop occurred by day 8. The NOEC and MIC values based on maximum standing crop were 556 and 949 mg/L, respectively. The maximum specific growth rate (μ_{max}) occurred between days 0 and 2. The NOEC and MIC values based on μ_{max} could not be determined (<75.9 mg/L, the lowest concentration tested). The discrepancy between NOEC and MIC values based on cell numbers and growth rates appears to be related to a slight lag in growth for all losartan potassium treatments during the first two days. Although control growth was very rapid during the first two days, it slowed and increased gradually between days 2 through 8.

During the same period, growth rates for losartan potassium treatments which lagged the control initially, increased to rates exceeding the control during days 2 through 8. Based on the growth rates during days 2 through 8, the NOEC and MIC value was ≥ 949 mg/L.

6) Chronic Toxicity to Bluegreen Alga, *Microcystis aeruginosa* (Cont.)

The definitive exposure was conducted under static conditions in a temperature controlled room at $24 \pm 2^\circ\text{C}$. All losartan potassium stock solutions were prepared using freshwater algal media as the diluent. Three 50 mL aliquots of each test solution were transferred to sterile 250 mL glass Erlenmeyer flasks. Dilution water controls were maintained concurrently with the six test solutions. All flasks were closed with gas exchange caps.

Each test solution was inoculated with approximately 50,000 cells/ml *Microcystis aeruginosa*. The test chambers were impartially positioned in a temperature controlled chamber under continuous fluorescent lighting. Light intensity ranged between 2142 to 2842 lux. Test chambers were impartially re-positioned daily to eliminate spatial effects, and continuously agitated on an orbital shaker at approximately 100 rpm.

Algal growth was measured by direct cell counts using a hemacytometer counting chamber with a compound microscope every 48 hours. Temperature was measured in one uninoculated flask of test medium daily during the test. The temperature range of the control chamber was monitored continuously during the test with a minimum/maximum thermometer and the diurnal temperature range recorded daily. Light intensity was measured at test initiation, day 7 and at test termination. The pH was measured at test initiation and termination in all test treatments and control flasks. Concentrations of losartan potassium were measured by

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F. Environmental Assessment

6) Chronic Toxicity to Bluegreen Alga, *Microcystis aeruginosa* (Cont.)

HPLC. Samples were collected at test initiation and termination from all composite solutions of the test treatments and the control. Based on the results of the test, the no-observed-effect concentration (NOEC) and minimum inhibitory concentration (MIC) were calculated by analysis of variance (ANOVA) with statistical differences between mean cell density by Dunnett's procedure. All statistical differences were determined at a probability level of 0.05.

f. Microbial Inhibition

A range-finding or screening test was conducted at Toxikon Environmental Sciences, Jupiter, FL, to define the concentration range within which losartan potassium produces complete inhibition on seven different microorganisms. The criterion for the effect was complete inhibition of growth.

Microbial growth inhibition of losartan potassium in agar plates was conducted with seven pure culture microorganisms, viz, *Scenedesmus quadricauda*, *Aspergillus niger*, *Azotobacter paspali*, *Anabaena flos-aquae*, *Fusarium acuminatum*, *Paramecium caudatum* and *Pseudomonas putida*. [Note: Microbial growth inhibition using *Anabaena flos-aquae* was conducted in Bristol's solution]. All seven organisms tested were able to grow on media containing 1

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f. Microbial Inhibition (Cont.)

g/L losartan potassium. Since the drug substance did not inhibit the growth of these organisms, the endpoint (Minimum Inhibitory Concentration - MIC) is greater than the highest concentration tested (1 g/L losartan potassium).

In a study conducted by MRL, Rahway, NJ, the maximum concentration of losartan potassium which is non-inhibitory to an activated sludge culture was determined. The maximum non-inhibitory effect concentration (MNIEC) procedure is based on the "Activated Sludge, Respiration Inhibition Test", which is described in OECD Guidelines for Testing of Chemicals, 1984, Method 209. The purpose of this test is to provide a rapid screening method whereby substances which may adversely affect aerobic microbial treatment plants can be identified and maximum non-inhibitory effect concentration of the test substance determined. This method assesses the effect of different concentrations of the test substance on heterogeneous microorganisms by measuring the respiration (i.e. oxygen uptake) under defined conditions. The MNIEC value is the maximum concentration of the test substance which does not inhibit oxygen uptake by the activated sludge culture. Inhibition is indicated by a decrease in the respiration rate of the microbes present in a test solution as compared to that exhibited in the controls.

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f. Microbial Inhibition (Cont.)

The MNIEC value of losartan potassium was determined by plotting the log of the concentration versus the R value. The R value corresponds to the dissolved oxygen uptake rate (DUR) of losartan potassium solution in relation to the DUR of the blank, monitored for a 20 minute period. Using this procedure, nominal concentrations up to 1000 mg/L of losartan potassium did not exert an inhibitory effect.

8. Environmental Effects of Released Substances

a. Bulk Chemical Production

1) Losartan potassium

Environmental concentrations of losartan potassium are estimated to be well below levels of environmental significance. Estimated concentrations of drug substance in the Ballydine facility's on-site wastewater treatment plant will be less than mg/L. As a result of on-site treatment and subsequent dilution, receiving water concentrations of drug substance will be below mcg/L (ppb). (Based on the fifth year total production volume of losartan potassium [kg].)

Aquatic concentrations of losartan potassium will be far below the levels which would cause environmental effects. The low environmental (aquatic) concentrations coupled with the low toxic effects at these concentrations and rapid photodegradation as well as potential biotransformation by periphyton in fresh water bodies indicate that the drug substance will have little impact on the aquatic environment.

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1) Losartan potassium (Cont.)

Losartan potassium is non-toxic to aquatic organisms at the expected environmental concentrations. It is neither toxic nor inhibitory to biological oxidation of other more easily metabolized carbon sources such as glucose and ethanol by an activated sludge system; although, losartan potassium itself is not readily biodegradable by an unacclimated activated sludge culture.

Losartan potassium is very stable in aqueous solution. However, it is biotransformed by periphyton, an algae rich microbial population, commonly found in fresh water bodies. Also, the drug degrades quite rapidly when exposed to natural sunlight. Losartan potassium is practically nontoxic to aquatic indicator organisms (fish, daphnia) and does not inhibit the activity of a marine bacteria and unacclimated mixed microbial population (activated sludge) at the expected environmental concentrations. Losartan potassium does not inhibit the growth of a number of representative microorganisms up to 1 g/L. Losartan potassium is slightly inhibitory to the green alga, *Selenastrum capricornutum* and *Microcystis aeruginosa*. However, there are no observable effects at the expected environmental concentrations. Little or no introduction of losartan potassium to the terrestrial environment will occur. Thermal studies indicate losartan potassium does not volatilize at ambient temperatures and, thus, transport of the drug substance to the air compartment is not deemed to be significant.

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a) Chemical Operations

Chemical manufacturing operations will be conducted in the United States and Ireland. The environmental impact of the emitted substances from the production of bulk drug and dosage form have been assessed through material balance considerations, physico-chemical and biological characterization of the emitted waste streams. Parameters considered include pH, oxygen demanding materials, nitrogenous materials, organic carbon, solids concentration, hydraulic and organic waste loading, extent of biodegradation, inhibitory effects on the mixed microbial population of the activated sludge system and aquatic toxicity.

Characterization of the waste streams indicate them to be non-inhibitory and readily biodegradable by an unacclimated mixed microbial population of activated sludge origin. Also, the untreated raw wastewater has been found to be only slightly toxic to aquatic indicator organisms, *Daphnia magna* and *Photobacterium phosphoreum*. A data summary is provided in Appendix II - Part 4.

It should be noted that, in the drug substance production process, the trityl intermediate is converted to the free acid, losartan, by removal of the triphenyl-methyl group in a homogeneous aqueous-organic system under acidic conditions. A similar transformation is likely to occur in the environment, albeit very much more slowly. Thus, the ultimate environmental fate of the trityl intermediate is likely to parallel that of losartan itself.

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a) Chemical Operations (Cont.)

In addition it should be noted that, with the exception of normal processing losses, all of the trityl intermediate produced at the Albany, GA facility is consumed in the manufacture of losartan potassium at the Ballydine, Ireland facility. The intermediate is shipped in sealed plastic bags within fiber drums which are themselves labeled and properly secured. Strict material accountability is maintained throughout and thus little opportunity exists for entry of the trityl intermediate into the environment.

Entry of the trityl intermediate into the environment in amounts likely to have an adverse effect is improbable. Thus, it is unusual to have detailed fate and effects information available. However, in this instance importation of trityl losartan into Ireland required notification under European Directive 67/548/EEC, as amended in 1984 (Sixth Amendment). Under the provisions of the Sixth Amendment, ecotoxicological characterization was carried out by an outside testing laboratory (Huntingdon Research Centre Ltd., Cambridgeshire, England). A summary of the testing results is provided in Appendix I - Part 2.

These studies indicate the trityl intermediate, although not readily biodegradable, is not inhibitory to activated sewage sludge microbial populations. In addition, saturated solutions containing ca. 0.07 mg/L (i.e. the highest test concentration that could be prepared due to the compound's low solubility in water and auxiliary solvents) were not toxic to Rainbow trout (NOEC $\geq$ 0.073

a) Chemical Operations (Cont.)

mg/L) or *Daphnia magna* (NOEC $\geq$ 0.069 mg/L) and did not inhibit the growth of the green alga, *Scenedesmus subspicatus* (NOEC $\geq$ 0.069 mg/L).

The LD₅₀ of trityl-losartan, administered orally, in mouse and rat is > 5000 mg/kg and >2000 mg/kg, respectively. There were no mortalities and no treatment related clinical observations noted during a 28-day study on male and female Sprague-Dawley rats. Trityl-losartan was administered orally every day for 28-days at dose rates of 15, 150, 1000 mg/kg/day. Based on this study, 1000 mg/kg/day represents a no observed effect level (NOEL) in the rat.

The material is a granular, free-flowing solid with a melting point range of 158-159°C, a relative density of 1.21, a vapor pressure of 1.1×10^{-5} Pa (25°C) and a water solubility < 0.23 mg/L (20°C). It exhibits a relatively high octanol-water partition coefficient; log P_{ow} > 3.9. The compound is not considered to be flammable or explosive and does not possess autoflammable or oxidizing properties.

Based on its physical-chemical properties (i.e. low aqueous solubility and relatively high octanol-water partitioning), the compound is likely to be preferentially sorbed to the activated sludge biomass and removed from the aqueous compartment. As noted previously, the UV-VIS absorbance spectrum of the trityl intermediate is similar to that of losartan potassium and, like

I. Summary

F. Environmental Assessment

a) Chemical Operations (Cont.)

losartan potassium, the trityl intermediate may be susceptible to photolysis and degrade rapidly under clear sky conditions. Like losartan itself, the trityl intermediate may also undergo biotransformation by algae rich microbial populations commonly found in fresh water bodies.

b) Tablets Losartan Potassium

Losartan potassium will enter the environment primarily by urinary excretion which becomes highly diluted during normal wastewater processing and treatment. When administered orally, about 4% is excreted as losartan and 6% is excreted as the active carboxylic acid metabolite. Following an oral dose of ¹⁴C labelled losartan potassium in man, about 35% of the radioactivity is recovered in urine and 58% in feces demonstrating that losartan potassium is extensively metabolized.

Maximum environmental concentrations in the United States resulting from losartan potassium use are estimated to be mcg/L (ppb). These are based on projected 5th year production estimates and do not include any metabolic or environmental depletion (e.g. photodegradation, microbial transformation). Lifetime exposure to these concentrations (2 L/day, for 365 days/year over a 70 year lifetime) would result in ingestion of approximately of a 100 mg daily dose.

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c) Losartan Potassium Toxicology

(1) Acute Toxicity

Significant lethality was observed in mice and rats after oral administration of 1000 mg/kg (3000 mg/m³) and 2000 mg/kg (11,800 mg/m³).

(2) Chronic Toxicity

The toxic potential of losartan potassium was evaluated in a series of repeated dose oral toxicity studies of up to three months in monkeys and up to one year in rats and dogs. There were no findings that would preclude administration at the therapeutic dosage level.

(3) Carcinogenicity

Losartan potassium was not carcinogenic when administered at maximum tolerated dosage levels to rats and mice for 105 and 92 weeks, respectively. These maximum tolerated dosage levels provided respective margins of systemic exposure for losartan and its pharmacologically active metabolite over that achieved in humans treated with 50 mg of losartan of approximately 270- and 150-fold in rats and 45- and 27-fold in mice .

(4) Mutagenicity

Losartan potassium was negative in the microbial mutagenesis and V-79 mammalian cell mutagenesis assays. In addition, there was no evidence of direct genotoxicity in the *in vivo* alkaline elution and *in vitro* chromosomal aberration assays at concentrations that

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(4) Mutagenicity (Cont.)

were approximately 1700 times greater than the maximum plasma level achieved in man at the recommended therapeutic dosage level. Similarly, there was no induction of chromosomal aberrations in bone marrow cells of male or female mice after the administration of toxic oral doses of up to 1500 mg/kg (4500 mg/m²) (750 times the maximum recommended daily human dose based on a patient weight of 50 kg). In addition the active metabolite showed no evidence of genotoxicity in the microbial mutagenesis, *in vitro* alkaline elution, and *in vitro* chromosomal aberration assays.

(5) Reproduction

Fertility and reproductive performance were not affected in studies with male and female rats given oral doses of losartan potassium up to approximately 150 and 300 mg/kg/day respectively. These dosages provide respective margins of systemic exposure for losartan and its pharmacologically active metabolite of approximately 150/125-fold in male rats and 300/170-fold in female rats over that achieved in man at the maximum recommended daily dose.

(6) Development

Losartan potassium has been shown to produce adverse effects in rat fetuses and neonates. The effects include decreased body weight, mortality and/or renal toxicity. Pharmacokinetic evaluation of fetal plasma samples showed significant levels of losartan and

(6) Development (Cont.)

its active metabolite on Gestation Day 20 compared to negligible value on Gestation Day 15. In addition, significant levels of losartan and its active metabolite were shown to be present in rat milk. Based on these findings, the fetal and neonatal effects of losartan in rats are attributed to drug exposure in late gestation and during lactation.

d) Pharmacokinetics

(1) Absorption

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan potassium tablets is approximately 33 %. Mean peak concentrations of losartan and the active metabolite are reached in 1 hour and in 3-4 hours, respectively. There was no clinically significant effect on the plasma concentration profile of losartan when the drug was administered with a standardized meal.

Distribution

Both losartan and the active metabolite are $\geq 99\%$ bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 liters. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

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(2) Distribution (Cont.)

About 14% of intravenously or orally-administered losartan is converted to the active metabolite. Following oral and intravenous administration of ¹⁴C-labeled losartan potassium, circulating radioactivity is primarily attributed to losartan and the active metabolite. Minimal conversion of losartan to the active metabolite was seen in about one percent of the individuals studied.

In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N-2 tetrazole glucuronide.

(4) Elimination

Plasma clearance of losartan and the active metabolite is about 600 mL/min and 50 ml/min, respectively. Renal clearance of losartan and the active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with losartan doses up to 200 mg.

Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal

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(4) Elimination (Cont.)

half-life of about 2 hours and 6-9 hours, respectively. During once a day dosing, neither losartan nor the active metabolite accumulates significantly in plasma.

Both urinary and biliary excretion routes are important for the elimination of losartan and its metabolites. Following an oral dose of ¹⁴C-labeled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the feces. Following an intravenous dose of ¹⁴C-labeled losartan in man, about 43% of radioactivity is recovered in urine and 50% in the feces.

(5) Characteristics in Patients

The plasma concentrations of losartan and the active metabolite observed in elderly male hypertensives are not significantly different from those observed in young male volunteers.

Following oral administration in patients with stable alcoholic cirrhosis of the liver, plasma concentrations of losartan and the active metabolite were, respectively, 5-fold and 1.7-fold than those seen in young male volunteers.

Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 ml/min. Compared to patients with normal renal function, the AUC for losartan is about 2-fold greater in hemodialysis patients. Neither renal impairment nor

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F. Environmental Assessment

(5) Characteristics in Patients

hemodialysis affects plasma concentrations of the active metabolite. Neither losartan nor the active metabolite can be removed by hemodialysis.

9. Use of Resources and Energy

The raw materials utilized to manufacture the drug substance and dosage form are common chemicals all of which are in ample commercial supply. Energy commitment for dosage form production in the United States is nominal and not excessive. Only very small increases in the utilization of energy is anticipated since production occurs at existing facilities. No effects upon endangered or threatened species and upon property listed in or eligible for listing in the National Register of Historic Places are anticipated.

10. Mitigation Measures

No potential adverse environmental impacts are foreseen from the production and use of drug substance and product. The manufacture, distribution and use of the product takes place under highly regulated and controlled conditions which act to further mitigate against negative environmental consequences.

A variety of pollution prevention initiatives were evaluated during development of the current process and, where appropriate, incorporated into the process. Two competing chemical pathways to the drug substance were considered. The more attractive

10. Mitigation Measures (Cont.)

environmental profile of the current process was a major reason this pathway was selected. Additionally, the cumulative effect of many small process improvements resulted in substantial yield improvement which implies less raw material usage per unit of product and less waste generated.

Specifically, the current process avoids the use of tributyl-tin chloride, an environmentally toxic compound used in the original process. The current process also uses less solvent and the solvents used are generally more environmentally benign (more biodegradable and less toxic). Methylene chloride was used in an earlier process. The current process avoids the use of methylene chloride, a priority pollutant, or other suspect carcinogens. The original process used larger quantities of solvents and included a greater number of SARA 313 solvents compared to the current process. Overall, 50% less aqueous waste is generated and these are biodegradable and of low aquatic toxicity.

In addition, a number of process changes were introduced during the course of the laboratory and pilot plant development; many of which further improved the environmental profile of the current process. Particularly noteworthy in this regard are the use of a sequestrant and mixed solvent system. Use of a sequesterant to remove a transition metal catalyst eliminated a recrystallization step and resulted in reduced solvent usage and a 5% overall waste reduction. In another step, a mixed solvent system is used to carry

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10. Mitigation Measures (Cont.)

out the desired reaction rather than sequential use of the two pure solvents. This facilitates cost effective recovery and reuse of the mixed solvent. Increased productivity in the crystallization procedure resulted in 30% less solvent usage. Productivity improvements in the final synthesis step also resulted in substantially reduced solvent usage. The overall process yield improvement achieved by the accumulation of multiple enhancements to the process was 25%. This provided the added benefit of reducing the amount of waste generated by the process.

11. Alternatives to the Proposed Action

The use of COZAAR will directly benefit patients by providing patients safe and effective therapy necessary for the management of hypertension.

Approval of COZAAR is justified from an environmental perspective and is preferable to non-approval.

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Date

Michael J. Angelo

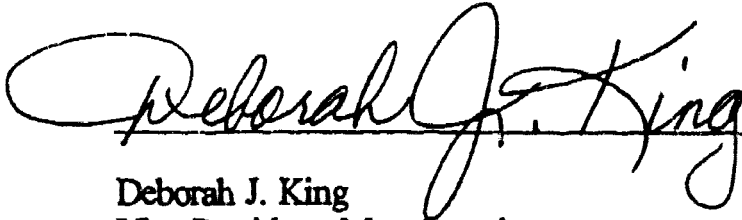
Michael J. Angelo, Ph.D.
Vice President
Safety & the Environment
Merck & Co., Inc.

2/3/95
Date

Tablets Losartan Potassium
Chemical and Pharmaceutical Manufacturing and
Control Documentation
I. Summary
F. Environmental Assessment

F-93

The undersigned certifies that the information presented is true, accurate, and complete to the best of my knowledge and that of the DuPont Merck Pharmaceutical Company.



Deborah J. King
Vice President, Manufacturing
The DuPont Merck Pharmaceutical Company

2/3/95
Date

Tablets Losartan Potassium
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14. References

1. Methods for Measuring the Acute Toxicity of Effluents to Freshwater and Marine Organisms, EPA/600/4-85/013, 1985.

ATTACHMENT II

REGULATORY AFFAIRS

MAR 09 1995

LARRY P. BELL, M.D

NDA 20-386

COZAAR Tablets

Non-Confidential Addendum to February 1, 1995

Environmental Assessment for COZAAR

Item a. Contract Packaging Sites

Alternate Packaging Facilities

1. PACO Pharmaceutical Services, Inc., Lakewood, New Jersey

Packaging of the drug product will occur at the PACO facility located at 1200 PACO Way, Lakewood, NJ-08701. The type of environment present at this location specific to the drug product packaging operation is described in the following sections. The Lakewood site environment is described in the following section.

a. Geographic Condition

The PACO plant is located on approximately 11 acres of land in the Township of Lakewood, Ocean County, New Jersey. The plant is near latitude 40°3'32"N; longitude 74°11'7"W; about 60 miles south of Newark, NJ.

The site consists of one building covering approximately 150,000 sq. ft. and employing an average workforce of about 800-900 people. Lakewood has a population of approximately 11,000. The surrounding neighborhood includes light industry, wooded area and residential homes.

b. Air Resources

Air quality in this area is in compliance with the National Air Quality Standards (NAAQS) of the Clean Air Act for total particulates, sulfur oxides and nitrogen oxides. The entire state of New Jersey is in non-attainment with the NAAQS for ozone. New

b. Air Resources (Cont.)

Jersey is part of the EPA Region II and NJDEPE is responsible for implementing the state implementation plan. The mean summer temperature is 70°F (21°C) and the mean winter temperature is 37°F (28°C). Annual rainfall is about 42 inches (107 cm).

c. Water Resources

All potable water used at the PACO plant is supplied by the "Englishtown Raritan Aquifer" and the town of Lakewood public water supply. It is estimated that the daily average use is 19,178 gallons with an annual consumption of approximately 7 million gallons. Process waters are directly discharged into the Ocean County Sewage Treatment Plant in compliance with the Ocean County Utility Authority and local ordinances. Storm water from the roof drains and parking are run off to Cedar Creek which eventually flows to the Metedeconk River. The plant is located in a 100 year flood zone.

d. Land Resources

The 11 acre site is level terrain covered by one building, driveways, walkways, parking and landscaped areas. It is surrounded by light industry, woods and residential communities. Prior to 1979, the land was a pinewood forest. The mean elevation above sea level is 120 feet. The soil is sandy loam and sandy gravel. The water table is between 14 to 18 ft.

e. Identification of Chemical Substances that are subject to proposed action

Information concerning the chemical name, empirical formula, molecular weight, chemical structure, laboratory codes, generic name, trade name, and CAS (Chemical Abstract Substance Registry) number can be found in Appendix I.

f. Introduction of Substance into the Environment

1) Substances Expected to be Emitted

a) Bulk Drug Synthesis

No bulk synthesis of losartan potassium will occur at the PACO, Lakewood, NJ facility.

b) Dosage Form Production

No dosage form production will occur at the PACO, Lakewood, NJ facility.

2) Control Procedures for Expected Emissions

a) Air Emission Controls

Air emissions from drug product packaging operations may include trace levels of particulates as described in Appendix II for emitted substances from dosage form production. In general, particulate emissions generated from packaging of film-coated tablets is extremely low.

As there is a virtual absence of particulates generated during packaging, specific air emissions controls are preventative or precautionary by design. Local exhaust ventilation is provided in the tablet packaging area to provide protection from incidental occupational exposure (e.g. as might result from a broken tablet).

2) Control Procedures for Expected Emissions(Cont.)

a) Air Emission Controls (Cont.)

Dry vacuuming conducted as part of the equipment clean-up during changeover of the packaging line will capture loose or broken tablets. With the exception of an alcohol solution used to sanitize the equipment, no organic solvents are used in the packaging operation. Air emissions resulting from this practice are expected to be negligible.

b) Liquid Emission Controls

Wastewater releases will be generated only during clean-up and changeover of the packaging equipment. Dry vacuum clean-up of the filling equipment during product changeover is supplemented with a water rinse. The film-coated tablet itself provides a measure of containment because of the film-coat and the reduced friability imparted to the tablet. Liquid emission controls are preventative in nature with little wastewater generation expected.

c) Solid Waste Controls

Non-hazardous wastes resulting from packaging may consist of paper, aluminum, plastic, drums and Tyvek® suits and product filter solids. Product filter solids and chemical contaminated wastes are sent to an off-site permitted incineration facility. Other non-hazardous wastes which cannot be recycled are disposed of at a state licensed landfill. In order to minimize the amount of material for disposal, excess raw materials may be returned to the customer for reuse.

d) Employee Protection

Material Safety Data Sheets are available on-site for all chemicals as required by the Occupational Safety Act of 1971, the Hazards Communication act of 1985 and Title 29 Code of Federal Regulations (CFR) Part 1910. Employees associated with the manufacture of drug product have appropriate MSDSs available for their review. Employee protective clothing, such as gloves, uniforms and safety glasses are used during the packaging process to assure compliance with the Occupational Safety Act of 1971 and the Hazard Communication Act of 1985 and Title 29 CFR, Subpart I.

3) Applicable Emission Citations and Statements of Compliance

a) Lakewood, New Jersey

(1) Air Citations and Statements of Compliance

Air emissions and controls in place for the manufacture of drug product meet the requirements of the New Jersey Administrative Code, Title 7, Chapter 27 governing air pollution control. In all instances where particulate emissions are expected, the plant will be in compliance with the associated regulatory limits. No permits are required and no new permits are expected as a result of the proposed action. No incineration takes place at the PACO Lakewood, NJ facility.

(2) Liquid Citations and Statements of Compliance

Discharge of process wastewater to the Ocean County Utilities Authority is subject to, and in compliance with, the local authorities rules and regulations.

(2) Liquid Citations and Statements of Compliance (Cont.)

Wastewater discharges from packaging will consist of aqueous equipment washouts as discussed above, which will be further combined with sanitary wastes for the site. Currently no wastewater permit is required for this building, and none will be necessary as a result of packaging of the drug product at PACO.

(3) Solid Citations and Statements of Compliance

Solid waste management at the Lakewood, NJ site requires overall conformance with the requirements of New Jersey Administrative Code, Title 7, Department of Environmental Protection and Energy, Chapter 26 and all other applicable rules and regulations governing solid and hazardous waste management. The facility waste generator number is NJ009722257. The Lakewood site is in compliance with these rules and the proposed action will not impact the facility's ability to comply with such requirements. The site is not governed by any solid or hazardous waste permits and no permits are expected to be required as a result of packaging Tablets Losartan Potassium.

4) Effect of Application Approval on Compliance with Current Emission Requirements

PACO Pharmaceutical Services, Inc. of Lakewood, NJ states that it will be in compliance with all emission requirements set forth in permits, consent decrees and administrative orders applicable to the packaging of Tablets Losartan Potassium at its facility in Lakewood, NJ as well as emission regulations applicable to the packaging of Tablets Losartan Potassium at its facility in Lakewood, NJ.

2. Packaging Coordinators, Inc., Philadelphia, PA

The future packaging of the drug product will occur at the PCI facility located at K Street and Erie Avenue, Philadelphia, PA 19124. The type of environment present at this location specific to the drug product packaging operation is described in the following section.

a. Geographic Condition

The PCI plant is located on approximately 3 acres of land in the City of Philadelphia, Pennsylvania. The plant is near latitude 40° N; longitude 75° W. The site consists of a five story building covering approximately 164,000 square feet with the packaging area occupying four floors. All rooms are self-contained and completely enclosed. The facility employs approximately 450 people. Philadelphia has a population of approximately 1,680,000. The surrounding neighborhood includes retail business, light industry and residential homes.

b. Air Resources

Air quality in the area is in compliance with the National Ambient Air Quality Standards (NAAQS) of the Clean Air Act for suspended particulates, sulfur oxides and nitrogen oxides. This compliance is based on monitoring and reporting by the Pennsylvania Department of Environmental Resources (PADER) under the requirements of the state implementation plan, as required by the Clean Air Act. The area is in non-attainment with the NAAQS for ozone. Pennsylvania is part of the EPA Region III and PADER is responsible for implementing the State Implementation Plan which may require new stationary source permits for manufacturing. Meteorological data for the region is

b. Air Resources (Cont.)

collected at the Philadelphia International Airport located 20 miles from the PCI facility. Annual rainfall is approximately 42 inches (107 cm) and the mean ambient temperature varies between 33 and 77°F (0.5 - 25°C). Predominant winds are from west to southeast.

c. Water Resources

All potable water used at the PCI plant is supplied by the Philadelphia Water Authority. It is estimated that the daily average use is 2068 gallons with an annual consumption of approximately 517,000 gallons. Process waters are directly discharged into the Philadelphia Municipal Sewerage Treatment Plant in compliance with the sewage authority limits.

d. Land Resources

The 3 acre site is level terrain covered by 1 building, 5 stories high. It is surrounded by light industry, commercial establishments and residential communities. The facility, built in 1930, has no green areas. The mean elevation above sea level is 121 ft.

e. Identification of Chemical Substances that are Subject to Proposed Action

Information concerning the chemical name, empirical formula, molecular weight, chemical structure, laboratory codes, generic name, trade name, and CAS Registry number are in Appendix I.

f. Introduction of Substance into the Environment

1) Substances Expected to be Emitted

a) Bulk Drug Synthesis

No bulk drug synthesis of losartan potassium will occur at the PCI, Philadelphia facility.

b) Dosage Form Production

No dosage form production will occur at the PCI, Philadelphia facility.

2) Control Procedures for Expected Emissions

a) Air Emission Controls

Air emissions from drug product packaging operations may include trace levels of particulates as described in Appendix II for emitted substances from dosage form production. In general, particulate emissions generated during packaging of film-coated tablets are extremely low.

As there is a virtual absence of particulates generated during packaging, specific air emissions controls are preventative or precautionary by design. Product retention filters are employed on the equipment handling substances for packaging. These filters provide for an average of 72% arrestance for particulates. Local exhaust ventilation is provided in the tablet packaging area to provide protection from incidental occupational exposure (e.g. as might result from a broken tablet). Dry vacuuming conducted as part of the equipment clean-up during changeover of the packaging line will capture loose or broken tablets. With the exception of an alcohol solution used to sanitize the equipment, no organic solvents are used in the packaging operation. Air emissions resulting from this practice are expected to be negligible.

b) Liquid Emission Controls

Waste water releases will be generated only during clean-up and changeover of the packaging equipment. Dry vacuum clean-up of the filling equipment during product changeover is supplemented with a water rinse. The film-coated tablet itself provides a measure of containment because of the film-coat and the reduced friability imparted to the tablet. Liquid emission controls are preventative in nature with little wastewater generation expected.

c) Solid Waste Controls

Non-hazardous wastes resulting from packaging may consist of paper, aluminum, plastic, drums and Tyvek® suits and product filter solids. Product filter solids and chemical contaminated wastes are sent to a permitted incineration facility. Other non-hazardous waste which cannot be recycled are disposed of at a state licensed landfill. In order to minimize the amount of material for disposal, excess raw materials may be returned to the customer for further use.

d) Employee Protection

Material Safety Data Sheets are available on-site for all chemicals as required by the Occupational Safety Act of 1971, the Hazards Communication Act of 1985 and Title 29 Code of Federal Regulations (CFR) Part 1910. Employees associated with the manufacture of drug product have appropriate MSDSs available for their review. Employee protective coating, such as gloves, uniforms and safety glasses are used during the packaging process to assure compliance with the Occupational Safety Act of 1971 and the Hazard Communication Act of 1985 and Title 29 CFR, Subpart I.

3) Applicable Emission Citations and Statements of Compliance

a) Philadelphia, PA

(1) Air Citations and Statements of Compliance

The site is not governed by any air permits and no permits are expected to be required as a result of packaging losartan potassium at this location.

No on-site incineration takes place at the PCI Philadelphia, PA facility.

(2) Liquid Citations and Statements of Compliance

Discharge of process wastewater to the Philadelphia Water Treatment Authority is subject to, and in compliance with, the local authorities rules and regulations.

Wastewater discharges from packaging will consist of aqueous equipment washouts as discussed above, which will be further combined with sanitary wastes for the site. Compliance with these regulatory limits will not be impacted by the proposed action.

(3) Solid Citations and Statements of Compliance

Solid waste management at the Philadelphia, PA site requires overall conformance with the requirements of all applicable rules and regulations governing solid and hazardous waste management. The Philadelphia site is in compliance with these rules and proposed action will not impact the facility's ability to comply with such requirements. The site is not governed by any solid or hazardous waste permits and no permits are expected to be required as a result of packaging Tablets Losartan Potassium at this location.

4) Effects of Application Approval on Compliance with Current Emission

Requirements

PCI of Philadelphia, Inc. states that it is in compliance with all emissions requirements set forth in permits, consent decrees and administrative orders applicable to the packaging of Tablets Losartan Potassium at its facility in Philadelphia, PA as well as emission regulations applicable to the packaging of Tablets Losartan Potassium at its facility-in Philadelphia, PA.

Item b. Drug Substance Information

A. Drug Substance Information Summary

1. Nomenclature

International Non-Proprietary Name:

Losartan potassium

U. S. Adopted Name:

Losartan potassium

Chemical Name:

1H-Imidazole-5-methanol,2-butyl-4-chloro-1-
[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-
yl]methyl]-,monopotassium salt

2-n-Butyl-4-chloro-1-(2'-tetrazol-5-yl)-1,1'-
biphenyl-4-yl-methyl)-1H-imidazole-5-
methanol,potassium salt

Laboratory Codes:

L-158,086-005H

MK0954

DUP-753

Other Names:

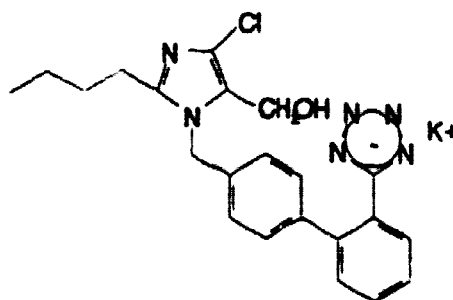
COZAAR

Chemical Abstracts Service (CAS) Registry No.:

124750-99-8

2. Description

Structural Formula



Molecular Formula



Molecular Weight

461.0

3. Environmental Fate

a. Solubility, aqueous

> 500 mg/mL at ambient (~25°C)

b. Dissociation Constant

pKa = 4.1 (1% methanol)

c. n-Octanol - Water Partitioning

log P = 1.19 @ pH 7.0

d. Thermal Behavior

$$T_r = 272^\circ\text{C}$$

$$H_r = 85.8 \text{ J/g}$$

In an oxidizing environment, exothermic pyrolysis occurs between 300 - 515°C. Above 550°C, combustion of char proceeds, leaving ~20% ash.

Vapor pressure

$$< 10^{-7} \text{ torr @ } 59^\circ\text{C}$$

e. UV - Vis Spectrum

Absorbance shoulders observed:

$$\sim 250 \text{ nm (A1\% 1cm } \sim 320)$$

$$\sim 228 \text{ nm (A1\% 1cm } \sim 574)$$

f. Biodegradation

Losartan potassium is not readily biodegradable when exposed to an unacclimated mixed microbial population (activated sludge). Exposure to a well-acclimated periphyton (algal) culture resulted in ~ 29% loss of parent compound in 28 days.

g. Hydrolysis

Losartan potassium is not susceptible to hydrolysis in aqueous solution.

@50°C

pH 5	(acetate buffer)	<10% (5 days)
pH 7	(phosphate buffer)	<10% (5 days)
pH 9	(borate buffer)	<10% (5 days)

h. Photolysis

Losartan potassium is susceptible to photolysis and degrades rapidly under clear sky conditions.

		t ^{1/2}
pH 5	(acetate buffer)	10.9 hr.
pH 7	(phosphate buffer)	11.8 hr.
pH 9	(borate buffer)	17.6 hr.

4. Environmental Effects

a. Aquatic Toxicity

- 1) *Daphnia magna* (water flea)
48-hour LC₅₀ = 331 mg/L
NOEC = 80 mg/L
- 2) *Pimephales promelas* (Fathead Minnow)
48-hour LC₅₀ > 1000 mg/L
NOEC = 100 mg/L
- 3) *Oncorhynchus mykiss* (Rainbow trout)
96-hour LC₅₀ > 929 mg/L
NOEC > 929 mg/L

b. Microbial Inhibition

<i>Azotobacter paspali</i>	MIC > 1000 mg/L
<i>Scenedesmus quadricauda</i>	MIC > 1000 mg/L
<i>Fusarium acuminatum</i>	MIC > 1000 mg/L
<i>Aspergillus niger</i>	MIC > 1000 mg/L
<i>Pseudomonas putida</i>	MIC > 1000 mg/L
<i>Anabaena flos-aquae</i>	MIC > 1000 mg/L
<i>Paramecium caudatum</i>	MIC > 1000 mg/L

b. Microbial Inhibition (Cont.)*Photobacterium phosphoreum* (Microtox™)EC₅₀ (30 min, 15°C) ≥ 1000 mg/Lc. Maximum Non-Inhibitory Effect Concentration (Activated Sludge)

≥ 1000 mg/L

d. Algal Toxicity (10 day)

Algae	End Point	NOEC MIC	
		(mg/L)	(mg/L)
<i>S. capricornutum</i>	cell growth	143	245
(green algae)	growth rate	245	245
<i>M. aeruginosa</i>	cell growth	556	949
(blue-green algae)	growth rate	≥ 949	≥ 949

Item c. Site Permit Information

Site Permit Information

Permit Name	Permit Number	Expiration Date	Issuing Agency
Ballydine, Ireland *			
Air Permit - Solvent Incinerator	#ENV/A.P/2/91 #ENV/D/3	None	Tipperary County Council
Wastewater Treatment Plant Operation	#ENV/W/36/80	None	Tipperary County Council
Albany, Georgia			
Air Quality Permit	#2833-047-10356	NA	Georgia Department of Natural Resources, Environmental Protection Division (EPD)
Air Quality Permit	#2833-047-11517	NA	Georgia Department of Natural Resources, EPD
NPDES Permit Wastewater	GA0001619	September, 1999	Georgia Department of Natural Resources, EPD
Hazardous Waste Permit	HW0008(S)	December 29, 1999	Georgia Department of Natural Resources, EPD
Ground Water Permit	047-0003	March, 2005	Georgia Department of Natural Resources, EPD
Drinking Water	PG0950023	March, 2004	Georgia Department of Natural Resources, EPD
Garden City, NY			
Air - Dust Collection Equipment	C-282011-0886-00001 W-CA & CB	October, 1995	Nassau County Health Department
Air - Main Building	C-282011-0886-00007 W-CA, CB & CC	October, 1995	Nassau County Health Department
Air - R&D Building	C-282011-0886-00008 W-CA, CB	October, 1995	Nassau County Health Department
Air	C-282011-0886-00021 W through C-282011-0886-00023 W	October, 1995	Nassau County Health Department
Wastewater - Sewer Discharge Permit	#33	June 14, 1996	Cedar Creek Water Pollution Control Plant, Nassau County

* The Ballydine, Ireland facility applied for an Integrated Pollution Control License from the Irish EPA in August 1994. Once this license is granted, the license numbers listed above will be superseded.

Site Permit Information (Continued)

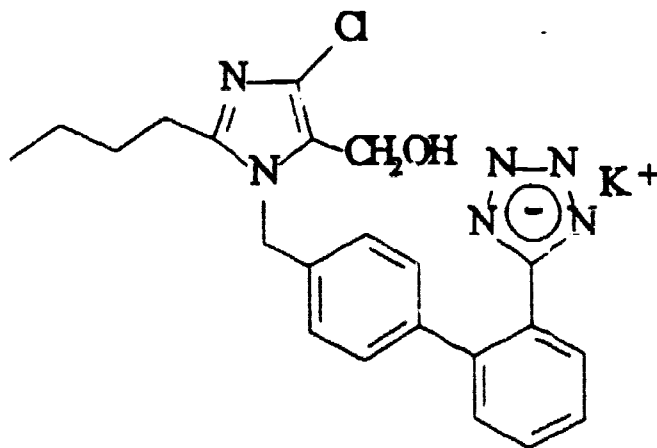
Permit Name	Permit Number	Expiration Date	Issuing Agency
West Point, PA - Permits Applicable to the Incineration of Returned Goods			
Air - Operating Permit for Rotary Kiln Incinerator with a tray scrubber and the Waste Heat Incinerator	#46-301-191B	August 8, 1998	Pennsylvania Department of Environmental Resources
Solid Waste - Waste Heat Incinerator Permit	PA No. 400459	None	Pennsylvania Department of Environmental Resources
Solid Waste - Rotary Kiln Incinerator Permit	PA No. 300501	January 1, 1997	Pennsylvania Department of Environmental Resources
West Point - Permits Not Applicable to the Incineration of Returned Good			
UGTA - Merck Wastewater Contract	Contract	September 30, 1998	Upper Gwynedd Township Authority (UGTA)
Catalytic Oxidizer Plan Approval -	#46-313-117 (previous permit number 46-313-090B)	February 28, 1995	Pennsylvania Department of Environmental Resources
Solid Waste - Waste Crusher Permit	PA No. 300437	None	Pennsylvania Department of Environmental Resources
Wilson, NC			
Wastewater Permit	#8406	June 30, 1996	City of Wilson, Department of Public Works
Air Permit	#4884R9	March 31, 1997	North Carolina Department of Natural Resources & Community Development
Hazardous Waste	NCD980798839	August 31, 2001	North Carolina Department of Environmental Health & Natural Resources

ATTACHMENT III

Tablets Losartan Potassium
Chemical and Pharmaceutical Manufacturing and
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Appendix IV

Material Safety Data Sheet for Losartan Potassium



Tablets Losartan Potassium
 Chemical and Pharmaceutical Manufacturing and
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MENCK SHARP AND BOWNE (IRE) LTD.; BALLINDINE, KILSHICKLAW,
 CLOVELL, COUNTY TIPPERRARY, IRELAND

***** MATERIAL SAFETY DATA SHEET *****

LABEL NAME: LOSARTAN POTASSIUM PLANT MEDS CODE
EA-015
 Emergency Telephone Number: 051-40411

SECTION 1 - MATERIAL IDENTIFICATION

Chemical Name----- 2-n-Butyl-4-chloro-1-(2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-ylethyl)-1H-imidazole-5-methanol, potassium salt
 Synonyms (Common)----- L-158,006; MK-954; DUP-733
 (Chemical)----- Not available
 Material Statistical Number----- 2-48692 (Dry; 2-48693 (milled);
 2-48694 (b'boxed)
 Material Product Number----- SP2240
 Chemical Classification----- Imidazole
 Intended Use----- Highly specific, non-peptide angiotensin II receptor antagonist

SECTION 2 - PRINCIPAL HAZARDOUS COMPONENTS

Component	Molecular Formula	Molecular Weight	CAS Number	Percent (%)
Losartan	C ₂₂ H ₂₂ ClN ₆ OK	461.0	124750-99-8	greater than 98

SECTION 3 - PHYSICAL PROPERTY DATA

Appearance----- White to off white crystalline powder
 Odor/Threshold Level (ppm)----- Not available
 Boiling Point (°C/°F)----- Not applicable
 Freezing Point (°C/°F)----- Not applicable
 Melting Range (°C/°F)----- 265°C (509°F)
 pH ----- 8.2 (10 aqueous solution)
 Solubility in water----- Soluble, greater than 500 mg/ml
 Specific Gravity (Water = 1)----- Not applicable
 Vapor Density (Air=1)----- Not applicable

*** Continued on next page ***

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MERCK SHARP AND DOHME (IREL) LTD.; BALLYDINE, KILSHILLAN,
 CLOONEL, COUNTY ZEPHERARY, IRELAND

***** MATERIAL SAFETY DATA SHEET *****

LABEL NAME: LOSARTAN POTASSIUM

PLANT MARK CODE
 RA-055

Emergency Telephone Number: 051-40411

Vapor Pressure (mm Hg @ °C/°F)---Not applicable

Volatile Components (g w/w)----- 0%

SECTION 4 - FIRE AND EXPLOSION HAZARD DATA

Flash Point (°C/°F)-----Not applicable

Flash Point Test Method-----Not applicable

Autoignition Temperature (°C/°F)-No: available

Flammable Limits -LEL (g)-----Not applicable

-UEL (g)-----Not applicable

Combustibility Information-----Upon application of a match flame, the material blackened in the area of flame impingement, but did not ignite. When subjected to a Makar burner flame application, the material ignited and burned in the area of the Makar burner producing blackish gray smoke and a crusty residue. The fire was not self-supporting.

Dust Explosivity Information-----The unvented pressure was 8 psig. Pressure developed under all venting ratios was less than 1 psig.

Shock Sensitivity Information-----Not known to be shock sensitive

Extinguishing Media-----If material is involved in fire, fight fire with water, dry chemical or CO₂ extinguishers.

Special Fire Fighting Procedures-Firefighters should wear self-contained breathing apparatus and full protective gear.

Fire/Explosion Hazards-----Material may ignite when impinged upon by heat and flames producing blackish gray smoke. Fire was not selfsupporting in tests.

*** Continued on next page ***

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MERCK SHARP AND DOHME (IRE) LTD.; BALLINACRE, KILSHRELLAN,
 CLOSHEL, COUNTY TIPPERARY, IRELAND

***** MATERIAL SAFETY DATA SHEET *****

LAZEL NAME: LOSARTAN POTASSIUM

PLANT MSDS CODE
 BA-055

Emergency Telephone Number: 051-60411

Hazardous Decomposition Products Resulting From A Fire- May release
 nitrogen oxides, CO₂, CO, phosgene and
 smoke.

SECTION 5 - REACTIVITY DATA

Stability (Normal Storage Conditions)- Stable under normal temperatures
 and storage conditions.

Storage Conditions to Avoid-----Not available

Thermal Stability/Instability Information- ARC testing detected a very
 large exotherm initiating at approximately
 225°C with a heat release in excess of
 86 cal/gm. Decomposes with heat.

Incompatibilities (Chemical Entities)- None reasonably foreseeable

Incompatibilities (Materials of Construction)- None reasonably foreseeable

Hazardous Polymerizations-----Will not occur

SECTION 6 - EMERGENCY AND FIRST AID PROCEDURES

Eye Contact-----Immediately flush eyes with plenty of
 water for 15 minutes. Seek medical
 attention immediately.

Skin Contact-----Wash with soap and water. Seek medical
 attention if symptoms appear.

Inhalation-----If inhaled, remove to fresh air. Seek
 medical attention if symptoms appear. If
 not breathing, give artificial
 respiration. If breathing is difficult,
 give oxygen.

Ingestion-----Seek medical attention if symptoms appear.
 Induce vomiting ONLY as directed by
 medical personnel. Never give anything by
 mouth to an unconscious person.

*** Continued on next page ***

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WOCK HAAS AND DOERS (TM) LTD., SAARLUND, GERMANY,
 CLONTEL, CORTEZ YITIMBARI, PERU

***** MATERIAL SAFETY DATA SHEET *****

TABLE NAME: LOSARTAN POTASSIUM TABLET NAME CODE
 BA-055

Emergency Telephone Number: 001-30411

Notes to Physician-----Losartan potassium is under evaluation for use as an antihypertensive agent. Hypotension may be an adverse effect of overexposure. Supportive measures may be considered. No specific antidote for overexposure has been identified.

SECTION 7 - HEALTH HAZARD DATA

Component	OSHA Permissible Exposure Limit (PEL)	NIOSH-1992-93 Threshold Limit Value (TLV)	Health Exposure Control Limit (ECL)
Losartan potassium	Not established	Not established	0.1 mg/m ³ (0-hr TWA)

Carcinogen Designation-----Not listed as a carcinogen by the International Agency for Research on Cancer, the National Toxicology Program, or the Occupational Safety and Health Administration.

Effects of Acute Exposure

Eye Contact-----Severe eye irritant.

Skin Contact-----Vild skin irritant. Mild contact sensitiser in guinea pigs.

Inhalation-----Not available

Ingestion-----Slightly toxic by ingestion. An adverse reaction observed in clinical use in temporary tachycardia (rapid heart rate).

Effects of Chronic Exposure-----Sub-chronic and chronic animal bioassays resulted in observation of a number of clinical, pharmacologically mediated effects (e.g., changes in clinical and arrhythmia parameters, hypotension, gastric mucosal lesions and renal changes). Based upon developmental and reproductive toxicity tests in animals, inadvertent exposure to NG-954

*** Continued on next page ***

NDA 020386

FIRM:

MERCK

10 OF 10

TRADE NAME:

COZAAR (LOSARTAN POTASSIUM) 25/50 MG TAB

GENERIC NAME:

LOSARTAN POTASSIUM

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MECK SHARP AND DUNNE (IHL) LTD., BALLISTINE, KILGERHAN,
 CLOONEL, COUNTY TIPPERRARY, IRELAND

***** MATERIAL SAFETY DATA SHEET *****

LABEL NAME: LOSARTAN POTASSIUM

PLANT MFG CODE
IR-055

Emergency Telephone Number: 081-40411

during the first trimester of pregnancy should not pose increased risk of adverse effects. In a fertility study in rats adverse effects on the fetus/newborn were noted suggesting that late gestation and lactation were critical periods. Losartan, like ACE inhibitors such as enalapril, is not recommended for use during the later stages of pregnancy. Losartan potassium is not considered to be genotoxic.

Reproductive Toxicity Data

SPECIES	ROUTE	TEST	DOSE/NOX/RESULT
Mouse	Oral	LDLo	400 mg/kg
Mouse	Oral	LD50	1287-1890 mg/kg
Rat	Oral	LDLo	200 mg/kg

SECTION 6 - SPILL/LEAK/DISPOSAL PROCEDURES

Steps to be taken in case materials released:

Immediately contact emergency response personnel. Keep unnecessary persons away. If emergency response personnel are unavailable, vacuum, shovel, or sweep up spilled material and place in an appropriate container for disposal. Use suitable protective equipment (Section 9). Follow all fire prevention procedures (Section 4).

For additional assistance in the U.S., CHEMTREC provides a toll-free hotline for chemical emergencies regarding spills, leaks, exposure or accidents: 1-800-424-9300.

Environmental Data-----Compound degrades rapidly in aqueous media under natural light conditions. Hydrolytically and biologically stable in aqueous media. Compound is non-inhibitory to activated sludge or other microbial species representative of the natural

*** Continued on next page ***

Tablets Losartan Potassium
 Chemical and Pharmaceutical Manufacturing and
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 I. Summary
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WENCK PHARM AND BIONE (IND.) LTD., BALLINAGH, KILSHANNON,
 CLONMEL, COUNTY TIPPERARY, IRELAND

***** MANUFACTURE OF WASTE FROM WENCK *****

TABLE NAME: LOSARTAN POTASSIUM

PLANT NAME CODE
 BA-003

Emergency Telephone Number: 031-00411

environment. Has low order of toxicity to representative aquatic organisms including daphnia, fish and algae.

TEST	SPECIES	RESULTS
LC50 (48 hr.)	Daphnia Magna	331 mg/L
LC50 (48 hr.)	Fathead minnow	Greater than 1000 mg/L
EC50 (96 hr.)	Rainbow trout	Greater than 333 mg/L

Waste Disposal Information----- Avoid contact of spilled materials and runoff with soil and surface waterways. Dispose of or treat all spill residues including contaminated soils following all applicable regulations.

SECTION 9 - SPECIAL PROTECTIVE INFORMATION

Respiratory----- An approved and properly fitted, full-face, negative pressure, HEPA filtered respirator or equivalent or greater protection is recommended to control employee exposure below the exposure limit if handling chemical without engineered controls.

Hands/Arms----- Latex gloves for the for the powder. If handling a solution, contact site safety for recommendation of gloves impervious to the solvent used.

Eye/Face----- Wear safety glasses. Full-face protection required if potential exists for direct exposure to dust.

Additional Protective Equipment----- Not available

Ventilation----- Local exhaust ventilation is recommended where chemical may enter the workplace.

SECTION 10 - SPECIAL PRECAUTIONS

Special Precautions to be taken when:

Handling----- Avoid direct contact with skin and eyes.

*** Continued on next page ***

Tablets Losartan Potassium
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WELLS CHEMICAL AND PHARMACEUTICAL CO., INC.; TALENT, CLATSOP COUNTY, OREGON, U.S.A.

***** CRITICAL SAFETY DATA SHEET *****

TABLE NAME: LOSARTAN POTASSIUM

PLANT NAME CODE
22-015

Emergency Telephone Number: 503-464-1111

Storage----- Keep container closed. Store in a cool dry place.

OSHA----- No special recommendations

SECTION 11 - HAZARD IDENTIFICATION DESCRIPTION

U.S. DOT----- Not available

ICAO/IATA----- Not available

IMO----- Not available

Hazardous Substance-Reportable Quantity (RQ)-- Not available.

SECTION 12 - HAZARD STATE CLASSIFICATION

. List all other MSD plants requiring a copy of this MSD: None

SECTION 13 - MSD REVISIONS

W. DuPon

Safety-----Date: August 8, 1993

D. Barry-Walsh

Technical Operations-----Date: August 25, 1993

B. Newman, Ph.D.

Central Safety & Industrial Hygiene-----Date: September 1, 1993

SECTION 14 - MSD DISCUSSION

While this information and recommendations set forth are believed to be accurate as of the date hereof, WELLS & CO., INC. makes no warranty with respect hereto and disclaims all liability from reliance thereon.

END

A handwritten signature in black ink, consisting of several loops and a trailing flourish, positioned above a horizontal line.

J.H.M. RESEARCH & DEVELOPMENT, INC. 5776 SECOND STREET, N.E. WASH. DC 20011

NDA 020386

FIRM:

MERCK

1 OF 1

TRADE NAME: COZAAR (LOSARTAN POTASSIUM) 25/50 MG TAB

GENERIC NAME: LOSARTAN POTASSIUM

Addendum

Summary Basis of Approval
Cover Form

Appl #: 020386

Firm: MERCK

Reviewing Div: 110

Trade Name: COZAAR (LOSARTAN POTASSIUM) 25/50 MG TAB

Generic Name:

LOSARTAN POTASSIUM

Approval Letter: Y

Statistician Review: Y

SBA Form: N

Bio/Dissolution Review: Y

Final Printed Labeling: Y

Microbiologist Review: N

Medical Officer Review: Y

NAS/NRC Review: N

Chemist Review: Y

Pharmacologist Review: Y

Federal Register Notice: N

Completion Date: 13-JUN-96

APPROVAL

LETTER



NDA 20-386/S-001

DEC 29 1995

Merck Research Laboratories
Attention: Larry P. Bell, M.D.
Sumneytown Pike
West Point, PA 19486

Dear Dr. Bell:

Please refer to your June 27, 1995 supplemental new drug application submitted June 28, 1995 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cozaar (losartan potassium) 25 and 50 mg Tablets.

We acknowledge receipt of your amendment dated December 22, 1995.

The supplemental application provides for final printed labeling revised under **CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects** to include information on studies comparing the incidence of cough seen in patients treated with losartan and those treated with lisinopril.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling included in the December 22, 1995 submission. Accordingly, the supplemental application is approved effective on the date of this letter.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Kathleen Bongiovanni
Regulatory Health Project Manager
(301) 594-5334

Sincerely yours,

RJ 12/29/95-

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

LABELING

783202
8368-2

MERCK & CO., INC.
West Point, PA 19486, USA

COZAAR® (LOSARTAN POTASSIUM TABLETS)

USE IN PREGNANCY

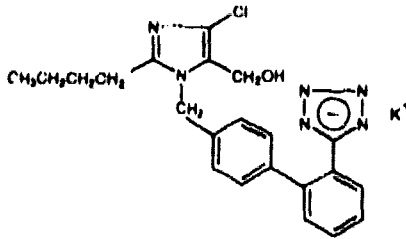
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, COZAAR should be discontinued as soon as possible. See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

COZAAR® (losartan potassium), the first of a new class of antihypertensives, is an angiotensin II receptor (type AT₁) antagonist.

Losartan potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt.

Its empirical formula is C₂₇H₃₂ClKN₄O, and its structural formula is:



Losartan potassium is a white to off-white free-flowing crystalline powder with a molecular weight of 461.01. It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone. Oxidation of the 5-hydroxymethyl group on the imidazole ring results in the active metabolite of losartan.

COZAAR is available for oral administration containing either 25 mg or 50 mg of losartan potassium and the following inactive ingredients: microcrystalline cellulose, lactose hydrate, pregelatinized starch, magnesium stearate, hydroxypropylcellulose, hydroxypropyl methylcellulose, titanium dioxide, D&C yellow No. 10 aluminum lake and FD&C blue No. 2 aluminum lake.

COZAAR 25 mg and 50 mg contain potassium in the following amounts: 2.12 mg (0.054 mEq) and 4.24 mg (0.108 mEq), respectively.

CLINICAL PHARMACOLOGY

Mechanism of Action

Angiotensin II formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kinase II), is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT₁ receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland). There is also an AT₂ receptor found in many tissues but it is not known to be associated with cardiovascular homeostasis. Both losartan and its principal active metabolite do not exhibit any partial agonist activity at the AT₁ receptor and have much greater affinity (about 1000-fold) for the AT₁ receptor than for the AT₂ receptor. *In vitro* binding studies indicate that losartan is a reversible, competitive inhibitor of the AT₁ receptor. The active metabolite is 10 to 40 times more potent by weight than losartan and appears to be a reversible, non-competitive inhibitor of the AT₁ receptor.

Neither losartan nor its active metabolite inhibits ACE (kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin); nor do they bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Pharmacokinetics

General

Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. It is converted, in part, to an active carboxylic acid metabolite that is

COZAAR® (Losartan Potassium Tablets)

responsible for most of the angiotensin II receptor antagonism that follows losartan treatment. The terminal half-life of losartan is about 2 hours and of the metabolite is about 6-9 hours. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan doses up to 200 mg and do not change over time. Neither losartan nor its metabolite accumulate in plasma upon repeated once-daily dosing.

Following oral administration, losartan is well absorbed (based on absorption of radiolabeled losartan) and undergoes substantial first-pass metabolism; the systemic bioavailability of losartan is approximately 33%. About 14% of an orally administered dose of losartan is converted to the active metabolite. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. While maximum plasma concentrations of losartan and its active metabolite are approximately equal, the AUC of the metabolite is about 4 times as great as that of losartan. A meal slows absorption of losartan and decreases its C_{max}, but has only minor effects on losartan AUC or on the AUC of the metabolite (about 10% decreased).

Both losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2% respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed. Following oral and intravenous administration of ¹⁴C-labeled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and its active metabolite. *In vitro* studies indicate that cytochrome P450 2C9 and 3A4 are involved in the biotransformation of losartan to its metabolites. Minimal conversion of losartan to the active metabolite (less than 1% of the dose compared to 14% of the dose in normal subjects) was seen in about one percent of individuals studied.

The volume of distribution of losartan is about 34 liters and of the active metabolite is about 12 liters. Total plasma clearance of losartan and the active metabolite is about 800 mL/min and 50 mL/min, respectively, with renal clearance of about 75 mL/min and 26 mL/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine and about 8% is excreted in urine as active metabolite. Biliary excretion contributes to the elimination of losartan and its metabolites. Following oral ¹⁴C-labeled losartan, about 35% of radioactivity is recovered in the urine and about 60% in the feces. Following an intravenous dose of ¹⁴C-labeled losartan, about 45% of radioactivity is recovered in the urine and 50% in the feces.

Special Populations

Pediatric: Losartan pharmacokinetics have not been investigated in patients <18 years of age.

Geriatric and Gender: Losartan pharmacokinetics have been investigated in the elderly (65-75 years) and in both genders. Plasma concentrations of losartan and its active metabolite are similar in elderly and young hypertensives. Plasma concentrations of losartan were about twice as high in female hypertensives as male hypertensives, but concentrations of the active metabolite were similar in males and females. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).

Race: Pharmacokinetic differences due to race have not been studied.

Renal Insufficiency: Plasma concentrations of losartan are not altered in patients with creatinine clearance above 30 mL/min. In patients with lower creatinine clearance, AUCs are about 50% greater and they are doubled in hemodialysis patients. Plasma concentrations of the active metabolite are not significantly altered in patients with renal impairment or in hemodialysis patients. Neither losartan nor its active metabolite can be removed by hemodialysis. No dosage adjustment is necessary for patients with renal impairment unless they are volume-depleted (see WARNINGS, Hypotension - Volume Depleted Patients and DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-times and about 1.7-times those in young male volunteers. Compared to normal subjects the total plasma clearance of losartan in patients with hepatic insufficiency was about 50% lower and the oral bioavailability was about 2-times higher. A lower starting dose is recommended for patients with a history of hepatic impairment (see DOSAGE AND ADMINISTRATION).

Drug Interactions

Losartan, administered for 12 days, did not affect the pharmacokinetics or pharmacodynamics of a single dose of warfarin. Losartan did not affect the pharmacokinetics of oral or intravenous digoxin. Coadministration of losartan and cimetidine led to an increase of about 18% in AUC of losartan but did not affect the pharmacokinetics of its active metabolite. Coadministration of losartan and phenobarbital led to a reduction of about 20% in the AUC of losartan and that of its active metabolite. There is no pharmacokinetic interaction between losartan and hydrochlorothiazide.

Pharmacodynamics and Clinical Effects

Losartan inhibits the pressor effect of angiotensin II (as well as angiotensin II infusions). A dose of 100 mg inhibits the pressor effect by about 85% at peak with 25-40% inhibition persisting for 24 hours. Removal of the negative feedback of

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angiotensin II causes a 2-3 fold rise in plasma renin activity and consequent rise in angiotensin II plasma concentration in hypertensive patients. Losartan does not affect the response to bradykinin, whereas ACE inhibitors increase the response to bradykinin. Aldosterone plasma concentrations fall following losartan administration. In spite of the effect of losartan on aldosterone secretion, very little effect on serum potassium was observed.

In a single dose study in normal volunteers, losartan had no effects on glomerular filtration rate, renal plasma flow or filtration fraction. In multiple dose studies in hypertensive patients, there were no notable effects on systemic or renal prostaglandin concentrations, fasting triglycerides, total cholesterol or HDL-cholesterol or fasting glucose concentrations. There was a small uricosuric effect leading to a minimal decrease in serum uric acid (mean decrease <0.4 mg/dL) during chronic oral administration.

The antihypertensive effects of COZAAR were demonstrated principally in 4 placebo-controlled 6-12 week trials of dosages from 10 to 150 mg per day in patients with baseline diastolic blood pressures of 95-116. The studies allowed comparisons of two doses (50-100 mg/day) as once-daily or twice-daily regimens, comparisons of peak and trough effects, and comparisons of response by gender, age, and race. Three additional studies examined the antihypertensive effects of losartan and hydrochlorothiazide in combination.

The 4 studies of losartan monotherapy included a total of 1075 patients randomized to several doses of losartan and 334 to placebo. The 10 and 25 mg doses produced some effect at peak (8 hours after dosing) but small and inconsistent trough (24 hour) responses. Doses of 50, 100 and 150 mg once daily gave statistically significant systolic/diastolic mean decreases in blood pressure, compared to placebo in the range of 5.8-10.5/3.8-7.5 mmHg, with the 150 mg dose giving no greater effect than 50-100 mg. Twice-daily dosing at 50-100 mg/day gave consistently larger trough responses than once-daily dosing at the same total dose. Peak (8 hour) effects were uniformly, but moderately, larger than trough effects, with the trough-to-peak ratio for systolic and diastolic responses 50-95% and 60-90%, respectively.

Addition of a low dose of hydrochlorothiazide (12.5 mg) to losartan 50 mg once daily resulted in placebo-adjusted blood pressure reductions of 15.5/9.2 mmHg.

Analysis of age, gender, and race subgroups of patients showed that men and women, and patients over and under 65, had generally similar responses. Black patients, however, had notably smaller responses to losartan monotherapy.

The effect of losartan is substantially present within one week but in some studies the maximal effect occurred in 3-6 weeks. In long term follow-up studies (without placebo control) the effect of losartan appeared to be maintained for up to a year. There is no apparent rebound effect after abrupt withdrawal of losartan. There was essentially no change in average heart rate in losartan-treated patients in controlled trials.

Persistent dry cough (with an incidence of a few percent) has been associated with ACE inhibitor use and in practice can be a cause of discontinuation of ACE inhibitor therapy. Two prospective, parallel-group, double-blind, randomized, controlled trials were conducted to assess the effects of losartan on the incidence of cough in hypertensive patients who had experienced cough while receiving ACE inhibitor therapy. Patients who had typical ACE inhibitor cough when challenged with lisinopril, whose cough disappeared on placebo, were randomized to losartan 50 mg, lisinopril 20 mg, or either placebo (one study, n=97) or 25 mg hydrochlorothiazide (n=136). The double-blind treatment period lasted up to 8 weeks. The incidence of cough is shown below.

Study 1*	HCTZ	Losartan	Lisinopril
Cough	25%	17%	69%

Study 2**	Placebo	Losartan	Lisinopril
Cough	35%	29%	62%

* Demographics = (89% caucasian, 64% female)

** Demographics = (90% caucasian, 51% female)

These studies demonstrate that the incidence of cough associated with losartan therapy, in a population that all had cough associated with ACE inhibitor therapy, is similar to that associated with hydrochlorothiazide or placebo therapy.

INDICATIONS AND USAGE

COZAAR is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

In considering the use of monotherapy with COZAAR, it should be noted that in controlled trials COZAAR had an effect on blood pressure that was notably less in black patients than in non-blacks, a finding similar to the small effect of angiotensin converting enzyme inhibitors in blacks.

CONTRAINDICATIONS

COZAAR is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is

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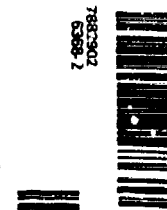


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detected, COZAAR should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester.

Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of COZAAR as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, COZAAR should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Losartan potassium has been shown to produce adverse effects in rat fetuses and neonates, including decreased body weight, delayed physical and behavioral development, mortality and renal toxicity. With the exception of neonatal weight gain (which was affected at doses as low as 10 mg/kg/day), doses associated with these effects exceeded 25 mg/kg/day (approximately three times the maximum recommended human dose of 100 mg on a mg/m² basis). These findings are attributed to drug exposure in late gestation and during lactation. Significant levels of losartan and its active metabolite were shown to be present in rat fetal plasma during late gestation and in rat milk.

Hypotension - Volume Depleted Patients

In patients who are intravascularly volume-depleted (e.g., those treated with diuretics), symptomatic hypotension may occur after initiation of therapy with COZAAR. These conditions should be corrected prior to administration of COZAAR, or a lower starting dose should be used (see DOSAGE AND ADMINISTRATION).

PRECAUTIONS

General

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with impaired liver function (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY, *Pharmacokinetics*).

Hypersensitivity. See ADVERSE REACTIONS, *Post-Marketing Experience*.

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. COZAAR would be expected to behave similarly. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or BUN have been reported. There has been no known use of COZAAR in patients with unilateral or bilateral renal artery stenosis, but a similar effect should be anticipated.

Information for Patients

Pregnancy. Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions

No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, cimetidine and phenobarbital. (See CLINICAL PHARMACOLOGY, *Drug Interactions*.) Potent inhibitors of cytochrome P450 3A4 and 2C9 have not been studied.

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cally but *in vitro* studies show significant inhibition of the formation of the active metabolite by inhibitors of P450 3A4 (ketoconazole, itraconazole, voriconazole, posaconazole), or P450 2C9 (sulfaphenazole) and nearly complete inhibition by the combination of sulfaphenazole and ketoconazole. The pharmacodynamic consequences of concomitant use of losartan and these inhibitors have not been examined.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Losartan potassium was not carcinogenic when administered at maximally tolerated dosages to rats and mice for 105 and 92 weeks, respectively. Female rats given the highest dose (270 mg/kg/day) had a slightly higher incidence of pancreatic acinar adenoma. The maximally tolerated dosages (270 mg/kg/day in rats, 200 mg/kg/day in mice) provided systemic exposures for losartan and its pharmacologically active metabolite that were approximately 160- and 90-times (rats) and 30- and 15-times (mice) the exposure of a 60 kg human given 100 mg per day.

Losartan potassium was negative in the microbial mutagenesis and V79 mammalian cell mutagenesis assays and in the *in vitro* alkaline elution and *in vitro* and *in vivo* chromosomal aberration assays. In addition, the active metabolite showed no evidence of genotoxicity in the microbial mutagenesis, *in vitro* alkaline elution, and *in vitro* chromosomal aberration assays.

Fertility and reproductive performance were not affected in studies with male rats given oral doses of losartan potassium up to approximately 160 mg/kg/day. The administration of toxic dosage levels in females (300/200 mg/kg/day) was associated with a significant ($p < 0.05$) decrease in the number of corpora lutea/female, implants/female, and live fetuses/female at C-section. At 100 mg/kg/day only a decrease in the number of corpora lutea/female was observed. The relationship of these findings to drug-treatment is uncertain since there was no effect at these dosage levels on implants/pregnant female, percent post-implantation loss, or live animals/litter at parturition. In nonpregnant rats dosed at 135 mg/kg/day for 7 days, systemic exposure (AUC) for losartan and its active metabolite were approximately 66 and 26 times the exposure achieved in man at the maximum recommended human daily dosage (100 mg).

Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters). See WARNINGS, *Fetal/Neonatal Morbidity and Mortality*.

Nursing Mothers

It is not known whether losartan is excreted in human milk, but significant levels of losartan and its active metabolite were shown to be present in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Use in the Elderly

Of the total number of patients receiving COZAAR in controlled clinical studies, 391 patients (19%) were 65 years and over, while 37 patients (2%) were 75 years and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

COZAAR has been evaluated for safety in more than 3300 patients treated for essential hypertension and 4058 patients/subjects overall. Over 1200 patients were treated for over 6 months and more than 800 for over one year. In general, treatment with COZAAR was well tolerated. The overall incidence of adverse experiences reported with COZAAR was similar to placebo.

In controlled clinical trials, discontinuation of therapy due to clinical adverse experiences was required in 2.3 percent of patients treated with COZAAR and 3.7 percent of patients given placebo.

The following table of adverse events is based on four 8-12 week placebo controlled trials involving over 1000 patients on various doses (10, 50 mg) of losartan and over 300 patients given placebo. All doses of losartan are grouped because none of the adverse events appeared to have a dose-related frequency. The table includes all adverse events, whether or not attributed to the treatment, occurring in at least 1% of patients treated with losartan and that were more frequent on losartan than placebo.

	Losartan (n=1075) Incidence	Placebo (n=334) Incidence
Digestive		
Diarrhea	2.4	2.1
Dyspepsia	1.3	1.2
Musculoskeletal		
Cramp, muscle	1.1	0.5
Myalgia	1.0	0.9
Pain, back	1.8	1.2
Pain, leg	1.0	0.0
Nervous System/Psychiatric		
Dizziness	3.5	2.1
Insomnia	1.4	0.6



	Losartan (n=1075) Incidence	Placebo (n=334) Incidence
Respiratory		
Congestion, nasal	2.0	1.2
Cough	3.4	3.3
Infection, upper respiratory	7.9	6.9
Sinus disorder	1.5	1.2
Sinusitis	1.0	0.3

The following adverse events were also reported at a rate of 1% or greater in patients treated with losartan, but were as, or more frequent in the placebo group: asthenia/fatigue, edema/swelling, abdominal pain, chest pain, nausea, headache, pharyngitis.

Adverse events occurred at about the same rates in men and women, older and younger patients, and black and non-black patients.

A patient with known hypersensitivity to aspirin and penicillin, when treated with COZAAR, was withdrawn from study due to swelling of the lips and eyelids and facial rash, reported as angioedema, which returned to normal 5 days after therapy was discontinued.

Superficial peeling of palms and hemolysis was reported in one subject.

In addition to the adverse events above, potentially important events that occurred in at least two patients/subjects exposed to losartan or other adverse events that occurred in <1% of patients in clinical studies are listed below. It cannot be determined whether these events were causally related to losartan. **Body as a Whole:** facial edema, fever, orthostatic effects, syncope; **Cardiovascular:** angina pectoris, second degree AV block, CVA, hypotension, myocardial infarction, arrhythmias including atrial fibrillation, palpitation, sinus bradycardia, tachycardia, ventricular tachycardia, ventricular fibrillation; **Digestive:** anorexia, constipation, dental pain, dry mouth, flatulence, gastritis, vomiting; **Hematologic:** anemia; **Metabolic:** gout; **Musculoskeletal:** arm pain, hip pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, fibromyalgia, muscle weakness; **Nervous System/Psychiatric:** anxiety, anxiety disorder, ataxia, confusion, depression, dream abnormality, hypesthesia, decreased libido, memory impairment, migraine, nervousness, paresthesia, peripheral neuropathy, panic disorder, sleep disorder, somnolence, tremor, vertigo; **Respiratory:** dyspnea, bronchitis, pharyngeal discomfort, epistaxis, rhinitis, respiratory congestion; **Skin:** alopecia, dermatitis, dry skin, ecchymosis, erythema, flushing, photosensitivity, pruritus, rash, sweating, urticaria; **Special Senses:** blurred vision, burning/tingling in the eye, conjunctivitis, taste perversion, tinnitus, decrease in visual acuity; **Urogenital:** impotence, nocturia, urinary frequency, urinary tract infection.

Post Marketing Experience

The following adverse reactions have been reported in post-marketing experience: **Hypersensitivity:** Angioedema (involving swelling of the face, lips, and/or tongue) has been reported rarely in patients treated with losartan.

Laboratory Test Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of COZAAR.

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 0.1 percent of patients with essential hypertension treated with COZAAR alone. No patient discontinued taking COZAAR alone due to increased BUN or serum creatinine. (See PRECAUTIONS, Impaired Renal Function.)

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.11 grams percent and 0.09 volume percent, respectively) occurred frequently in patients treated with COZAAR alone, but were rarely of clinical importance. No patients were discontinued due to anemia.

Liver Function Tests: Occasional elevations of liver enzymes and/or serum bilirubin have occurred. In patients with essential hypertension treated with COZAAR alone, one patient (<0.1%) was discontinued due to these laboratory adverse experiences.

OVERDOSAGE

Significant lethality was observed in mice and rats after oral administration of 1000 mg/kg and 2000 mg/kg, respectively, about 44 and 170 times the maximum recommended human dose on a mg/m² basis.

Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan nor its active metabolite can be removed by hemodialysis.

DOSAGE AND ADMINISTRATION

The usual starting dose of COZAAR is 50 mg once daily, with 25 mg used in patients with possible depletion of intravascular volume (e.g., patients treated with diuretics) (see WARNINGS, Hypotension - Volume Depleted Patients) and patients with a history of hepatic impairment (see PRECAUTIONS, General). COZAAR can be administered once or twice daily with total daily doses ranging from 25 mg to 100 mg.

If the antihypertensive effect measured at trough using once-a-day dosing is inadequate, a twice-a-day regimen at the same total daily dose or an increase in dose may give a more satisfactory response.

If blood pressure is not controlled by COZAAR alone, a low dose of a diuretic may be added. Hydrochlorothiazide has been shown to have an additive effect (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects).

No initial dosage adjustment is necessary for elderly patients or for patients with renal impairment, including patients on dialysis.

COZAAR may be administered with other antihypertensive agents.

COZAAR may be administered with or without food.

HOW SUPPLIED

No. 3812 — Tablets COZAAR, 25 mg, are light green, tear drop shaped, film-coated tablets with code MKK on one side and 951 on the other. They are supplied as follows:

NDC 0006-0951-54 unit of use bottles of 90
(6506-01-414-4064, 25 mg 90's)
NDC 0006-0951-58 unit of use bottles of 100
(6506-01-414-4069, 25 mg 100's)

NDC 0006-0951-28 unit dose packages of 100
(6506-01-414-4063, 25 mg individually sealed 100's).

No. 3813 — Tablets COZAAR, 50 mg, are green, teardrop shaped, film-coated tablets with code MKK 952 on one side and COZAAR on the other. They are supplied as follows:

NDC 0006-0952-31 unit of use bottles of 30
(6506-01-414-4082, 50 mg 30's)
NDC 0006-0952-54 unit of use bottles of 90
(6506-01-414-4080, 50 mg 90's)

NDC 0006-0952-58 unit of use bottles of 100
(6506-01-414-4068, 50 mg 100's)

NDC 0006-0952-28 unit dose packages of 100
(6506-01-414-4081, 50 mg individually sealed 100's).

Storage

Store at controlled room temperature, 15-30°C (59-86°F). Keep container tightly closed. Protect from light.

Manufactured by
MERCK & CO., INC., West Point, PA 19486, USA

by:

**DU PONT
PHARMA** Wilmington, DE 19880 USA

Issued December 1995
Printed in USA

211
S-001

RHPM Review of Labeling

NDA: 20-386/S-001 Cozaar (losartan potassium) Tablets

Date of submission: June 27, 1995

Date of receipt: June 28, 1995

Dates of amendments: October 23, 1995 December 22, 1995

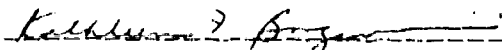
Dates of receipt: October 24, 1995 December 26, 1995

Applicant: Merck Research Laboratories

Background: Merck submitted a supplement that provides for draft labeling revised under **CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects** to include information on studies comparing the incidence of cough seen in patients treated with losartan and those treated with lisinopril. We issued an approvable letter dated August 29, 1995, asking for final printed labeling identical to the enclosed draft. Merck submitted a counter-proposal in an amendment dated October 23, 1993. Drs. Ganley and Lipicky reviewed the counter-proposal and agreed that the firm could delete information on the blood pressure lowering effect from the cough trials from the labeling, but they should retain the numbers derived from a per-protocol rather than an all-patients-treated analysis. We issued a second approvable letter on December 19, 1995. Merck has responded with final printed labeling.

Review: I have reviewed the submitted final printed labeling. The only differences from the previously approved labeling are the changes that are identical in content to the marked-up draft that was enclosed with the December 19, 1995, approvable letter (additions to the end of the CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects subsection).

Recommendation: I will prepare an approval letter for this supplement. This supplement falls under 21 CFR 314.70 (b), supplements requiring FDA approval before the change is made.


Kathleen F. Bongiovanni 12-27-95

cc: 20-386/S-001
HFD-110
HFD-111/KBongiovanni
HFD-111/SBenton
kb/12/27/95.

21.1
S-001

RHPM Review of Labeling

NDA: 20-386/S-001 Cozaar (losartan potassium) Tablets

Date of submission: June 27, 1995

Date of receipt: June 28, 1995

Date of amendment: October 23, 1995

Date of receipt: October 24, 1995

Applicant: Merck Research Laboratories

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Review: I revised the draft labeling that was included in the August 29, 1995 approvable letter to delete "the observed decrease in supine diastolic blood pressure" and the parts of the table labeled SDBP. Dr. Ganley reviewed the revised labeling and found it acceptable.

Recommendation: I will prepare an approvable letter for this supplement. This supplement falls under 21 CFR 314.70 (b), supplements requiring FDA approval before the change is made.

Kathleen F. Bongiovanni
Kathleen F. Bongiovanni 12/19/95

cc: 20-386/S-001
HFD-110
HFD-111/KBongiovanni
HFD-111/SBenton
kb/12/19/95.

Larry P. Bell, M.D.
Director
Regulatory Affairs

Merck & Co., Inc.
BLA-30
West Point PA 19486
Fax 610 397 2335
Tel 610 397 2310
215 652 5000

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not work copies.

December 22, 1995

NDA SUPPL AMEND

SE4-001
(AF)



Raymond J. Lipicky, M.D. - Director
Division of Cardio-Renal Drug Products
HFD-110, WOC2, Room 5039
Office of Drug Evaluation I (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Dear Dr. Lipicky:

FINAL PRINTED LABELING
NDA 20-386/S-001: COZAAR™ Tablets (Losartan Potassium)

Please refer to the above referenced Supplemental New Drug Application submitted June 27, 1995 and to the FDA Approvable Letters dated August 29, 1995 and December 19, 1995.

Pursuant to Section 505(b) of the Food, Drug and Cosmetic Act, we are submitting Final Printed Labeling for approved SNDA 001.

As indicated on the attached Form FDA 356h, this supplemental application provides for changes in Item 3(c)ii of the approved Supplemental New Drug Application for COZAAR Tablets.

Enclosed is the following:

- Printed Package Circular #7882902

As required by §306(k)(1) of the Generic Drug Enforcement Act [21 U.S.C. 335a(k)(1)], we hereby certify that, in connection with this application, Merck & Co., Inc. did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

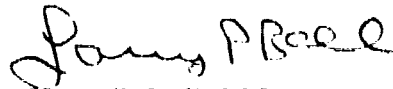
ORIGINAL

Raymond J. Lipicky, M.D. - Director
NDA 20-386/S-001: COZAAR™ Tablets (Losartan Potassium)
Page 2

We consider the filing of this Supplemental New Drug Application to be a confidential matter and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission from Merck & Co., Inc.

Questions regarding this information should be addressed to Larry P. Bell, M.D. (610/397-2310) or, in my absence, Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely yours,



Larry P. Bell, M.D.
Director
Regulatory Affairs

Enclosures

Federal Express:

qAbellMrsMpt1222.doc

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Within 10 days after the date of this letter, you are required to amend this supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw this supplemental application.

These changes may not be implemented until you have been notified in writing that this supplemental application is approved.

Should you have any questions, please contact:

Ms. Kathleen Bongiovanni
Regulatory Health Project Manager
Telephone: (301) 594-5300

Sincerely yours,

R J 12/19/95

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

CURRENT CIRCULAR WITH REVISIONS

COZAAR® (Losartan Potassium Tablets)

The effect of losartan is substantially present within one week but in some studies the maximal effect occurred in 3-6 weeks. In long-term follow-up studies (without placebo control) the effect of losartan appeared to be maintained for up to a year. There is no apparent rebound effect after abrupt withdrawal of losartan. There was essentially no change in average heart rate in losartan-treated patients in controlled trials.

~~Because persistent non-productive cough has been reported with all ACE inhibitors (presumably due to the inhibition of the degradation of endogenous bradykinin), two prospective randomized studies were conducted to assess the incidence of cough in patients who experienced cough while receiving ACE inhibitor therapy. In these studies, patients were challenged with the ACE inhibitor lisinopril to confirm the existence of cough. Patients who were positive for cough were then treated with one of the following: losartan 50 mg, lisinopril 20 mg, hydrochlorothiazide 25 mg, or placebo. The first study (n=135) used hydrochlorothiazide as a control; the second study (n=97) used placebo as a control. In the first study, dry cough occurred in 34.1% of patients treated with hydrochlorothiazide; 29.2% of patients treated with losartan; and 71.7% of patients treated with lisinopril. In the second study, dry cough occurred in 31.4% of patients treated with placebo; 36.7% of patients treated with losartan; and 87.5% of patients treated with lisinopril. These studies demonstrate that the incidence of cough with losartan in a population who had cough associated with ACE inhibitor therapy is comparable to that observed with hydrochlorothiazide or placebo.~~

INDICATIONS AND USAGE

COZAAR is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

In considering the use of monotherapy with COZAAR, it should be noted that in controlled trials COZAAR had an effect on blood pressure that was notably less in black patients than in non-blacks, a finding similar to the small effect of angiotensin converting enzyme inhibitors in blacks.

COMMENTS/SUPPORT

7882900

6368

Persistent dry cough (with an incidence of a few percent) has been associated with ACE inhibitor use and in practice can be a cause of discontinuation of ACE inhibitor therapy. Two prospective, parallel-group, double-blind, randomized, controlled trials were conducted to assess the effects of losartan on the incidence of cough in hypertensive patients who had experienced cough while receiving ACE inhibitor therapy. Patients who had typical ACE inhibitor cough when challenged with lisinopril, whose cough disappeared on placebo, were randomized to losartan 50 mg, lisinopril 20 mg, or either placebo (one study, n=97) or 25 mg hydrochlorothiazide (n=135). The double-blind treatment period lasted up to 8 weeks. The incidence of cough is

shown

below.

Study 1*	HCTZ	Losartan	Lisinopril
Cough	25%	17%	69%
Study 2**	Placebo	losartan	Lisinopril
Cough	35%	29%	62%

* Demographics = (89% caucasian, 64% female)

** Demographics = (90%caucasian, 51% female)

These studies demonstrate that the incidence of cough associated with losartan therapy, in a population that all had cough associated with ACE inhibitor therapy, is similar to that associated with hydrochlorothiazide or placebo therapy.

MEDICAL OFFICER REVIEW

NDA #: 20-386/S-001
NDA Volume: 20.1
DRUG NAME: losartan
SPONSOR: Merck
TYPE OF DOCUMENT: Comments on Draft Labeling
DATE RECEIVED: 10/24/95
DATE REVIEW COMPLETED: 11/1/95
MEDICAL OFFICER: Charles J. Ganley, M.D.

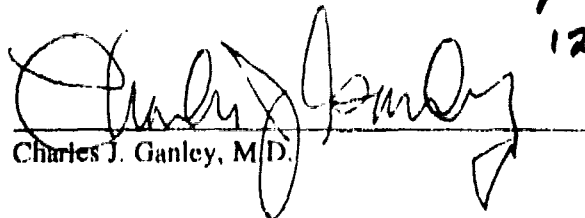
Merck submits labeling in response to an FDA approvable letter (Re: the cough study labeling) dated August 29, 1995. They have made 2 major labeling revisions. First, they have eliminated the blood pressure data that was measured in the study because it was not obtained consistently at the same time of day in relation to drug ingestion (e.g. trough). Second, they changed the percentage of patients with a positive cough back to their "all patients treated" analysis (see attached).

Impression:

The exclusion of blood pressure data from the table appears to be justified based on the explanation provided by the sponsor. However, the changes in the percentage of patients who developed cough is not justified. The sponsor is somewhat disingenuous in their comparison of their "all patients treated" analysis versus the FDA "per protocol" analysis. The FDA numbers utilized all patients but relied the definition of cough provided in the protocol (see attached table from Study 80 as an example). Merck has not followed the protocol definition of cough as described in the primary reviews of those studies. The Merck analysis may be more accurately described as the "all patients treated not described in the protocol" approach.

Conclusion:

- (1) The blood pressure data can be removed from the label as Merck has proposed.
- (2) The percentage of patients developing cough should not be changed.

} Agree
Kipichy
12/12/95

Charles J. Ganley, M.D.

cc: orig.
HFD-110
HFD-110 / CSO / C. GANLEY / S.CHEN

FDA TEXT OF 8/29/95 WITH MRL REVISIONS

COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

7882000
6368

Persistent dry cough (with an incidence of a few percent) has been associated with ACE inhibitor use and in practice can be a cause of discontinuation of ACE inhibitor therapy. Two prospective, parallel-group, double-blind, randomized, controlled trials were conducted to assess the effects of losartan on the incidence of cough in hypertensive patients who had previously experienced cough while receiving ACE inhibitor therapy. Patients who had typical ACE inhibitor cough when challenged with lisinopril, whose cough disappeared subsequently while on placebo, were randomized to losartan 50 mg, lisinopril 20 mg, or either placebo (one study, n=97) or 25 mg hydrochlorothiazide (HCTZ) (n=135). The double-blind treatment period lasted up to 8 weeks. The incidence of cough and the observed decreases in supine diastolic blood pressure are shown below.

Study 1* (n=135)	Losartan (n=48)	Lisinopril (n=46)	HCTZ (n=41)
Cough	17.2%	17.7%†	14.1%
SDBP	-5.2	-8.5	-4.7
Study 2** (n=97)	Losartan (n=30)	Lisinopril (n=32)	Placebo (n=35)
Cough	36.7%	37.5%††	31.4%
SDBP	-8.2	-9.0	-1.6

NOTE: Order of treatment groups has been revised so that losartan appears first. See attachment for rationale for exclusion of blood pressure data and retention of MRL incidence of cough.

* Demographics = (89% caucasian, 64% female)

** Demographics = (90% caucasian, 51% female)

† Statistically significantly different versus losartan and HCTZ, p<0.01

†† Statistically significantly different versus losartan and placebo,

p<0.001

These studies demonstrate that the incidence of cough associated with losartan therapy, in a population that all had cough associated with ACE inhibitor therapy, is similar to that associated with hydrochlorothiazide or placebo therapy.

**Table 5. Patient Listing ** of Cough Outcome During Phase III.
(Medical Reviewer's All Patients Treated Analysis)**

Placebo	Losartan	Lisinopril
Yes - 10 1090, 1019, 1046 ⁴ , 1051, 1109, 1118, 1121, 1152, 1155, 1143	Yes - 9 1088 ³ , 1020, 1032, 1060, 1120, 1151, 1154, 1026, 1144	Yes - 20 1003, 1005, 1011, 1033, 1037, 1041, 1050, 1057, 1074, 1080, 1102, 1105, 1119, 1127, 1131, 1148, 1153, 1156, 1159, 1025
No - 25 1001, 1006, 1007, 1070 ¹ , 1012, 1030, 1031, 1036, 1038, 1042, 1055, 1059 ⁵ , 1075, 1078, 1081 ⁵ , 1083, 1087 ⁶ , 1101 ^{5,3} , 1104, 1108, 1128, 1132, 1147, 1150, 1027 ^{5,3}	No - 21 1002, 1004, 1009, 1072, 1010, 1029, 1034, 1039, 1040, 1047, 1056 ⁵ , 1073, 1076, 1079, 1100, 1103, 1122, 1129, 1130, 1145, 1149	No - 12 1008*, 1071* ² , 1089*, 1015, 1021, 1035, 1058*, 1077, 1082, 1123, 1146, 1142*

* During phase III, patient did not have ≥ 3 days between final 2 visits (not positive response for this reason; listed as positive by sponsor).

** Three patients (1028 (lisinopril), 1106 (lisinopril), 1158 (Losartan)) were withdrawn without phase III data and are not included in this listing.

- 1 = Did not have "no cough" at screening visit.
- 2 = Did not have 2 consecutive visits in phase II.
- 3 = Did not have ≥ 3 days between visits in phase II.
- 4 = Did not have ≥ 3 days between visits in phase I.
- 5 = Dropout during phase III.
- 6 = Did not have positive cough response in phase I.

MEDICAL OFFICER REVIEW

NOV - 3 1995

NDA #: 20-386/S-001

NDA Volume: 20.1

DRUG NAME: losartan

SPONSOR: Merck

TYPE OF DOCUMENT: Comments on Draft Labeling

DATE RECEIVED: 10/24/95

DATE REVIEW COMPLETED: 11/1/95

MEDICAL OFFICER: Charles J. Ganley, M.D.

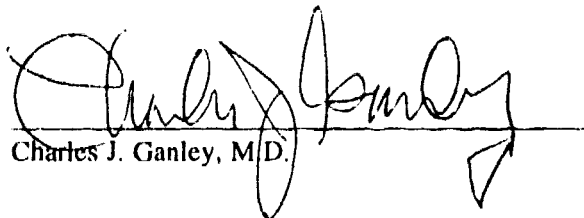
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Charles J. Ganley, M.D.

cc: orig.
HFD-110
HFD-110 / CSO / C. GANLEY / S.CHEN

FDA TEXT OF 8/29/95 WITH MRL REVISIONS

COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

7882900
6368

Persistent dry cough (with an incidence of a few percent) has been associated with ACE inhibitor use and in practice can be a cause of discontinuation of ACE inhibitor therapy. Two prospective, parallel-group, double-blind, randomized, controlled trials were conducted to assess the effects of losartan on the incidence of cough in hypertensive patients who had previously experienced cough while receiving ACE inhibitor therapy. Patients who had typical ACE inhibitor cough when challenged with lisinopril, whose cough disappeared subsequently while on placebo, were randomized to losartan 50 mg, ~~lisinopril 20 mg, or either placebo (one study, n=97) or 25 mg hydrochlorothiazide (HCTZ) (n=135).~~ The double-blind treatment period lasted up to 8 weeks. The incidence of cough and the observed decreases in supine diastolic blood pressure are is shown below.

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Cough	1728.2%	6971.7%†	2534.1%
SDBP	-5.2	-8.6	-4.7
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Cough	2936.7%	6287.5%††	3531.4%
SDBP	-8.2	-8.9	-1.6

NOTE: Order of treatment groups has been revised so that losartan appears first. See attachment for rationale for exclusion of blood pressure data and retention of MRL incidences of cough.

* Demographics = (89% caucasian, 64% female)

** Demographics = (90% caucasian, 51% female)

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Larry P. Bell, M.D.
Director
Regulatory Affairs

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Merck & Co., Inc.
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West Point PA 19486
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215 652 5000

October 23, 1995

Raymond J. Lipicky, M.D., Director
Division of Cardio-Renal Drug Products
HFD-110, WOC2, Room 5039
Office of Drug Evaluation I (CDER)
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852



NDA SUPPL AMEND (AL)

→ 34-001

Dear Dr. Lipicky:

NDA 20-386/S-001: Tablets COZAAR™ (Losartan Potassium)

Reference is made to the above New Drug Application. Specific reference is made a Supplemental New Drug Application submitted June 27, 1995, and to an approvable letter dated August 29, 1995 from the FDA, which contained the Agency's comments on the submitted draft labeling.

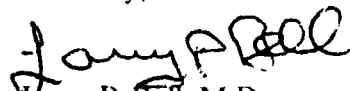
By copy of this letter we are submitting a revised draft package circular. To facilitate review the left hand column provides the draft labeling text as revised by the Agency in the August 29, 1995 approvable letter. Deletions to this draft are shown by strike-through and additions are shown in underline. The right hand column provides Merck Research Laboratories (MRL) comments.

It is apparent upon review that there is close agreement on the draft package circular. While MRL has accepted most of the Agency's modifications to the original package circular, minor modifications and editorial changes have been made. Specifically, we have eliminated the blood pressure data previously added by the Agency for the following reasons: blood pressure data was specified as a safety measurement, blood pressure was not measured at standard times during the dosing interval, final blood pressure values were determined at various times on treatment therapy.

MRL has also retained the original values for incidence of cough. These data were obtained using an "all-patients-treated" analysis and have been retained to ensure consistency with other MRL labels, including the current COZAAR™ label, and manuscripts that have utilized an "all-patients-treated" analysis.

After review of the material provided, we request a meeting to resolve any remaining issues concerning the draft package circular. We trust this information is helpful. If you have any questions or need additional information please contact Larry P. Bell, M.D. (610/397-2310) or, in my absence, Bonnie J. Goldman, M.D. (610/397-2383).

Sincerely,


Larry P. Bell, M.D.

Attachments
Federal Express #1:

ORIGINAL

Desk Copies w/Attach: Kathleen Bongiovanni, HFD-111, WOC2, Room 5023
Federal Express #2:
Dr. Charles Ganley, HFD-110, WOC2, Room 5074
Federal Express #1:

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Larry P. Bell, M.D.
Director
Regulatory Affairs

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not desk copies.

Merck & Co., Inc.
BLA-30
West Point PA 19486
Fax 610 397 2335
Tel 610 397 2310
215 652 5000

September 7, 1995



Raymond J. Lipicky, M.D. - Director
Division of Cardio-Renal Drug Products
HFD-110, Room 16B-45
Office of Drug Evaluation I (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



SUPPL NEW CORRESP

Dear Dr. Lipicky:

NDA 20-386/S-001
COZAAR Tablets

Please refer to the above referenced Supplemental New Drug Application submitted June 28, 1995 and to the FDA Approvable Letter dated August 29, 1995.

The purpose of this letter is to notify the Agency of our intent to file an amendment.

Questions regarding this information should be addressed to Larry P. Bell, M.D. (610/397-2310) or, in my absence, Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely yours,

A handwritten signature in black ink, appearing to read "Larry P. Bell for LPB".

Larry P. Bell, M.D.
Director
Regulatory Affairs

LPB\gm\ys

Federal Express

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ORIGINAL

Food and Drug Administration
Rockville MD 20857

NDA 20-386/S-001

AUG 29 1995

Merck Research Laboratories
Attention: Larry P. Bell, M.D.
Sumneytown Pike
West Point, PA 19486

Dear Dr. Bell:

Please refer to your June 27, 1995 supplemental new drug application submitted June 28, 1995 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cozaar (losartan potassium) 25 and 50 mg Tablets.

The supplemental application provides for draft labeling revised under **CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects** to include information on studies comparing the incidence of cough seen in patients treated with losartan and those treated with lisinopril.

We have completed the review of this supplemental application as submitted with draft labeling and it is approvable. Before this supplement may be approved, however, it will be necessary for you to submit final printed labeling (FPL). The labeling should be identical in content to the enclosed marked-up draft. In addition, all previous revisions as reflected in the most recently approved package insert must be included. To facilitate review of your submission, please provide a highlighted or marked-up copies that show the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the FPL may be required.

Please submit fifteen copies of the printed labeling ten of which are individually mounted on heavy weight paper or similar material.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend this supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw this supplemental application.

These changes may not be implemented until you have been notified in writing that this supplemental application is approved.

Should you have any questions, please contact:

Ms. Kathleen Bongiovanni
Regulatory Health Project Manager
Telephone: (301) 594-5300

Sincerely yours,

RJL 8/29/95

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

CURRENT CIRCULAR WITH REVISIONS

COZAAR® (Losartan Potassium Tablets)

The effect of losartan is substantially present within one week but in some studies the maximal effect occurred in 3-6 weeks. In long-term follow-up studies (without placebo control) the effect of losartan appeared to be maintained for up to a year. There is no apparent rebound effect after abrupt withdrawal of losartan. There was essentially no change in average heart rate in losartan-treated patients in controlled trials.

~~Because persistent non-productive cough has been reported with all ACE inhibitors (presumably due to the inhibition of the degradation of endogenous bradykinin), two prospective randomized studies were conducted to assess the incidence of cough in patients who experienced cough while receiving ACE inhibitor therapy. In these studies, patients were challenged with the ACE inhibitor lisinopril to confirm the existence of cough. Patients who were positive for cough were then treated with one of the following: losartan 50 mg, lisinopril 20 mg, hydrochlorothiazide 25 mg, or placebo. The first study (n=135) used hydrochlorothiazide as a control; the second study (n=97) used placebo as a control. In the first study, dry cough occurred in 34.1% of patients treated with hydrochlorothiazide; 29.2% of patients treated with losartan; and 71.7% of patients treated with lisinopril. In the second study, dry cough occurred in 31.4% of patients treated with placebo; 36.7% of patients treated with losartan; and 87.5% of patients treated with lisinopril. These studies demonstrate that the incidence of cough with losartan in a population who had cough associated with ACE inhibitor therapy is comparable to that observed with hydrochlorothiazide or placebo.~~

INDICATIONS AND USAGE

COZAAR is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

In considering the use of monotherapy with COZAAR, it should be noted that in controlled trials COZAAR had an effect on blood pressure that was notably less in black patients than in non-blacks, a finding similar to the small effect of angiotensin converting enzyme inhibitors in blacks.

COMMENTS/SUPPORT

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Persistent dry cough (with an incidence of a few percent) has been associated with ACE inhibitor use and in practice can be a cause of discontinuation of ACE inhibitor therapy. Two prospective, parallel-group, double-blind, randomized, controlled trials were conducted to assess the effects of losartan on the incidence of cough in hypertensive patients who had experienced cough while receiving ACE inhibitor therapy. Patients who had typical ACE inhibitor cough when challenged with lisinopril, whose cough disappeared on placebo, were randomized to losartan 50 mg, lisinopril 20 mg, or either placebo (one study, n=97) or 25 mg hydrochlorothiazide (n=135). The double-blind treatment period lasted up to 8 weeks. The incidence of cough and the observed decrease in supine diastolic blood pressure are shown below.

Study 1*	HCTZ	Losartan	Lisinopril
Cough	25%	17%	69%
SDBP	-4.7	-5.2	-8.5
Study 2**	Placebo	Losartan	Lisinopril
Cough	35%	29%	62%
SDBP	-1.6	-8.2	-9.0

* Demographics = (89% caucasian, 64% female)

** Demographics = (90% caucasian, 51% female)

These studies demonstrate that the incidence of cough associated with losartan therapy, in a population that all had cough associated with ACE inhibitor therapy, is similar to that associated with hydrochlorothiazide or placebo therapy.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION
Division of Cardio-Renal Drug Products

AUG 29 1995

Memorandum

DATE :
FROM : Director, Division of Cardio-Renal Drug Products, HFD-110
SUBJECT: NDA 20-386/SE4-001, Losartan/Cough, Merck
TO : NDA File

Lipinsky

Merck has submitted the results of two adequate and well-controlled trials in support of a claim that losartan is not associated with the cough that is attributable to ACE inhibitors. Indeed the results of these two trials demonstrate that the incidence of cough is not greater in the groups taking losartan than in those taking hydrochlorothiazide or placebo, and that the incidence of cough was substantially (statistically significantly) higher in the groups receiving lisinopril. Neither I nor Dr. Ganley, the medical reviewer, have any doubt that the trials show that losartan does not produce cough.

Lisinopril was the only ACE inhibitor studied. Lisinopril produced a numerically greater blood pressure lowering than did losartan (not the first time that Merck has shown that other antihypertensive agents produce numerically greater blood pressure lowering effects than losartan). These were relatively short duration studies. Only 60-70% of the subjects that had typical ACE inhibitor cough (100% of subjects enrolled, had to have) had the cough recur when lisinopril was started and/or continued. So there are small nags and questions that remain unanswered, but it is clear enough that, with respect to cough, losartan is not lisinopril. It also seems entirely reasonable to generalize the lisinopril result to all ACE inhibitors.

The supplement is therefore approvable. The blood pressure results should appear in labelling. A draft to be sent to Merck is appended.

MEDICAL REVIEW

NDA #: 20-386/SE4-001
 NDA Volume: 19.1
 DRUG NAME: losartan
 SPONSOR: MERCK
 TYPE OF DOCUMENT: Labeling supplement
 DATE RECEIVED: 6/28/95
 DATE REVIEW COMPLETED: 7/27/95
 MEDICAL OFFICER: Charles J. Ganley, M.D.

This submission includes labeling for the inclusion of information obtained from two cough studies (Study 80 and 56). The reviews of those studies have been completed. Investigation of several centers in study 80 have been or will be completed shortly. Assuming that DSI's report gives them a clean bill of health, this information should be included in the labeling. Until DSI's final report is received, the discussion regarding final labeling should proceed. The proposed labeling describing these studies are attached.

The following revisions are suggested.

1. Some mention of the demographics (gender, race) of the populations studied in both trials should be included.

Table 1. Demographics

	Study 56	Study 80
Male	35%	49%
Female	64%	51%
Caucasian	89%	90%

2. The percent of patients who developed cough as reported in the proposed label depends on the analysis. Merck's analysis is somewhat biased because they used a slightly different definition than specified in the protocol. In addition, there are two analysis performed for each trial, an all patients treated and a per protocol analysis. Table 2 lists the Medical Reviewer's per protocol analysis compared to that in the labeling.

Table 2. Percentage of Patients with Positive Cough Response for Cough (Medical Reviewer's Per Protocol Analysis)

Study 80*	Placebo	Losartan	Lisinopril
Medical Reviewer's Analysis	35%	29%	62%
Merck's Proposed Label	31.4%	36.7%	87.5%
Study 56**	HCTZ	Losartan	Lisinopril
Medical Reviewer's Analysis	25%	17%	69%
Merck's Proposed Label	34.1%	29.2%	71.7%

* Differs from the sponsors per protocol analysis in that five lisinopril patients did not fulfill the protocol specified criteria for cough (≥ 3 days between 2 final visits).

** Differs from the sponsors per protocol analysis in that nine lisinopril, 2 HCTZ and three losartan patients did not fulfill the protocol specified criteria for cough (> 1 day between 2 final visits).

3. There should be some mention of the changes in blood pressure between treatments. The mean change in diastolic blood pressures are listed in table 3. In study 56, it appears that lisinopril had are larger (but no significant) antihypertensive effect.

Table 3. Mean Change in Diastolic Blood Pressure.

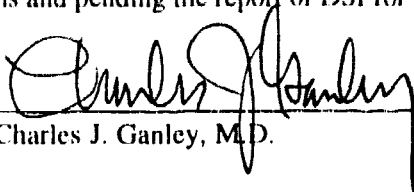
Study 80	Placebo	Losartan	Lisinopril
Change in DBP from baseline (mmHg)*	-1.6	- 8.2	- 9.0
Study 56	HCTZ	Losartan	Lisinopril
Change in sitting DBP from baseline (mmHg)	- 4.7	- 5.2	- 8.5

* Incomplete information was provided regarding baseline and position of the patients at the time DBP measurement.

4. There trial description should note that the double-blind treatment periods lasted 8 weeks. It is not clear that longer follow-up would have yielded similar results.

Conclusion:

The labeling should be approved with revisions and pending the report of DSI for study 80.



Charles J. Ganley, M.D.

cc: orig.
HFD-110
HFD-110 / CSO / C. GANLEY / S.CHEN

CURRENT CIRCULAR WITH REVISIONS

COZAAR® (Losartan Potassium Tablets)

The effect of losartan is substantially present within one week but in some studies the maximal effect occurred in 3-6 weeks. In long-term follow-up studies (without placebo control) the effect of losartan appeared to be maintained for up to a year. There is no apparent rebound effect after abrupt withdrawal of losartan. There was essentially no change in average heart rate in losartan-treated patients in controlled trials.

Because persistent non-productive cough has been reported with all ACE inhibitors (presumably due to the inhibition of the degradation of endogenous bradykinin), two prospective randomized studies were conducted to assess the incidence of cough in patients who experienced cough while receiving ACE inhibitor therapy. In these studies, patients were challenged with the ACE inhibitor lisinopril to confirm the existence of cough. Patients who were positive for cough were then treated with one of the following: losartan 50 mg, lisinopril 20 mg, hydrochlorothiazide 25 mg, or placebo. The first study (n=135) used hydrochlorothiazide as a control; the second study (n=97) used placebo as a control. In the first study, dry cough occurred in 34.1% of patients treated with hydrochlorothiazide; 29.2% of patients treated with losartan; and 71.7% of patients treated with lisinopril. In the second study, dry cough occurred in 31.4% of patients treated with placebo; 36.7% of patients treated with losartan; and 87.5% of patients treated with lisinopril. These studies demonstrate that the incidence of cough with losartan in a population who had cough associated with ACE inhibitor therapy is comparable to that observed with hydrochlorothiazide or placebo.

INDICATIONS AND USAGE

COZAAR is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

In considering the use of monotherapy with COZAAR, it should be noted that in controlled trials COZAAR had an effect on blood pressure that was notably less in black patients than in non-blacks, a finding similar to the small effect of angiotensin converting enzyme inhibitors in blacks.

COMMENTS/SUPPORT

7882988
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Based on the Cough Study (Protocol 056) included in the NDA (submitted 12/3/93) and the Cough II Study (Protocol 080) (submitted 2/14/95).

Larry P. Bell, M.D.
Director
Regulatory Affairs

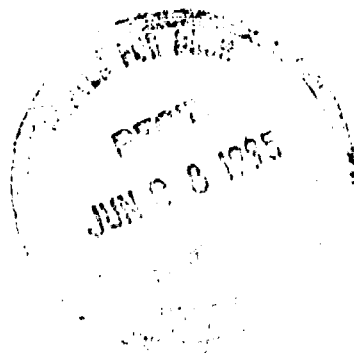
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Merck & Co., Inc.
BLA-30
West Point PA 19486
Fax 610 397 2335
Tel 610 397 2310
215 652 5000

June 27, 1995



Raymond J. Lipicky, M.D. - Director
Division of Cardio-Renal Drug Products
HFD-110, Room 16B-45
Office of Drug Evaluation I (CDER)
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852



Dear Dr. Lipicky:

NDA NO. 20-386 SUPP. NO. S-001

NDA SUPP. NO. SE4

NDA 20-386: COZAAR Tablets (Losartan Potassium)

Pursuant to Section 505(b) of the Food Drug and Cosmetic Act and in accordance with 21 CFR 314.70(b), we submit, for your approval, a supplement to NDA 20-386.

As indicated on the attached Form FDA 356h, the supplemental application provides for changes in Item 4c(i) of the approved New Drug Application for COZAAR Tablets.

Please refer to our submission on February 14, 1995 of the clinical study report for the Cough study (protocol 080) and to the FDA Approval letter of April 14, 1995 in which it is stated that MRL agreed to submit a supplemental NDA to address this issue.

Enclosed as Draft Labeling for Approval is a paste-up of the circular, annotated for revisions. The circular has been revised under CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects (page 8) to include the results of the cough studies. Additions are shown in double-underline.

In accordance with the Prescription Drug user Fee Act of 1992, a check (Check No. _____, was sent to the Food and Drug Administration, Philadelphia, PA on June 26, 1995. The User Fee I.D. number is _____

ORIGINAL

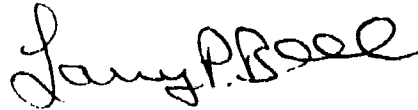
Dr. Raymond Lipicky
NDA 20-386
Page 2

As required by Section 306(k)(1) of the Generic Drug Enforcement Act [21 U.S.C. 335a (k)(1)], we hereby certify that, in connection with this application, Merck & Co., Inc. did not and will not use in any capacity the services of any person debarred under subsections 306 (a) or (b) of the Act.

We consider the filing of this Supplemental New Drug Application to be a confidential matter, and request the Food and Drug Administration not to make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this supplemental application should be directed to Larry P. Bell, M.D. (215/397-2310) or, in my absence, to Bonnie J. Goldmann, M.D. (215/397-2383).

Sincerely,



Larry P. Bell, M.D.
Director
Regulatory Affairs

Attachments

Federal Express

Q:/Slonaker/McHugh/20-386/SNDA1

END

MD

J.H.M. Research & Development, Inc., 5776 Second Street, N.E., Washington, D.C. 20011

N 20386 PI Ap 11/22/95

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AP 11/22/95



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MERCK & CO., INC.
West Point, PA 19486, USA

COZAAR®
(LOSARTAN POTASSIUM TABLETS)

USE IN PREGNANCY

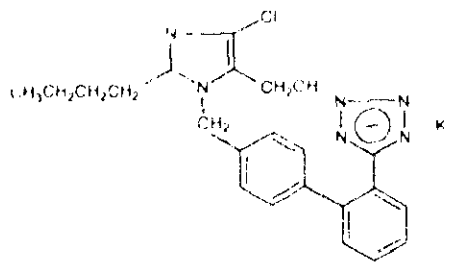
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, COZAAR should be discontinued as soon as possible. See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

COZAAR® (losartan potassium), the first of a new class of antihypertensives, is an angiotensin II receptor (type AT₁) antagonist.

Losartan potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]imidazole 5-methanol monopotassium salt.

Its empirical formula is C₂₇H₃₂ClKN₄O, and its structural formula is



Losartan potassium is a white to off-white free-flowing crystalline powder with a molecular weight of 461.01. It is freely soluble in water, soluble in alcohols, and slightly soluble in certain organic solvents, such as acetone and methyl ethyl ketone. Oxidation of the 5-hydroxymethyl group on the imidazole ring results in the active metabolite of losartan.

COZAAR is available for oral administration containing either 25 mg or 50 mg of losartan potassium and the following inactive ingredients: microcrystalline cellulose, lactose, hydroxypropylcellulose, hydroxypropylmethylcellulose, titanium dioxide, D&C yellow No. 10 aluminum lake and FD&C blue No. 2 aluminum lake.

COZAAR 25 mg and 50 mg contain potassium in the following amounts: 2.12 mg (0.054 mEq) and 4.24 mg (0.108 mEq) respectively.

CLINICAL PHARMACOLOGY

Mechanism of Action

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kinase III). It is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT₁ receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland). There is also an AT₂ receptor found in many tissues but it is not known to be associated with cardiovascular homeostasis. Both losartan and its principal active metabolite do not exhibit any partial agonist activity at the AT₁ receptor and have much greater affinity (about 1000-fold) for the AT₁ receptor than for the AT₂ receptor. *In vitro* binding studies indicate that losartan is a reversible, competitive inhibitor of the AT₁ receptor. The active metabolite is 10 to 40 times more potent by weight than losartan and appears to be a reversible, non-competitive inhibitor of the AT₁ receptor.

Neither losartan nor its active metabolite inhibit ACE (kininase II), the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin. Neither bind to or block other hormone receptors or other receptors known to be important in cardiovascular regulation.

Pharmacokinetics

General

Losartan potassium is a drug that undergoes substantial first-pass metabolism by cytochrome P450 2C9. Its elimination is partly from an active, carboxylic acid, metabolite that is

COZAAR® (Losartan Potassium Tablets)

responsible for most of the angiotensin II receptor antagonism that follows losartan treatment. The terminal half-life of losartan is about 2 hours and of the metabolite is about 6.9 hours. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan doses up to 200 mg and do not change over time. Neither losartan nor its metabolite accumulate in plasma upon repeated once-daily dosing.

Following oral administration, losartan is well absorbed (based on absorption of radiolabeled losartan) and undergoes substantial first-pass metabolism; the systemic bioavailability of losartan is approximately 33%. About 14% of an orally administered dose of losartan is converted to the active metabolite. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. While maximum plasma concentrations of losartan and its active metabolite are approximately equal, the AUC of the metabolite is about 4 times as great as that of losartan. A meal slows absorption of losartan and decreases its C_{max}, but has only minor effects on losartan AUC or on the AUC of the metabolite (about 10% decreased).

Both losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.7% respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Losartan metabolites have been identified in human plasma and urine, in addition to the active carboxylic acid metabolite, several inactive metabolites are formed. Following oral and intravenous administration of ¹⁴C-labeled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and its active metabolite. *In vitro* studies indicate that cytochrome P450 2C9 and 3A4 are involved in the biotransformation of losartan to its metabolites. Minimal conversion of losartan to the active metabolite (less than 1% of the dose compared to 14% of the dose in normal subjects) was seen in about one percent of individuals studied.

The volume of distribution of losartan is about 34 liters and of the active metabolite is about 12 liters. Total plasma clearance of losartan and the active metabolite is about 600 mL/min and 50 mL/min, respectively, with renal clearance of about 75 mL/min and 25 mL/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% is excreted in urine as active metabolite. Biliary excretion contributes to the elimination of losartan and its metabolites. Following oral ¹⁴C-labeled losartan, about 55% of radioactivity is recovered in the urine and about 60% in the feces. Following an intravenous dose of ¹⁴C-labeled losartan, about 45% of radioactivity is recovered in the urine and 50% in the feces.

Special Populations

Pediatric: Losartan pharmacokinetics have not been investigated in patients < 18 years of age.

Geriatric and Gender: Losartan pharmacokinetics have been investigated in the elderly (55-75 years) and in both genders. Plasma concentrations of losartan and its active metabolite are similar in elderly and young hypertensives. Plasma concentrations of losartan were about twice as high in female hypertensives as male hypertensives, but concentrations of the active metabolite were similar in males and females. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).

Race: Pharmacokinetic differences due to race have not been studied.

Renal Insufficiency: Plasma concentrations of losartan are not altered in patients with creatinine clearance above 30 mL/min. In patients with lower creatinine clearance, AUC's are about 50% greater and t_{1/2}'s are doubled in hemodialysis patients. Plasma concentrations of the active metabolite are not significantly altered in patients with renal impairment or in hemodialysis patients. Neither losartan nor its active metabolite can be removed by hemodialysis. No dosage adjustment is necessary for patients with renal impairment unless they are volume depleted (see WARNINGS, Hypotension - Volume Depleted Patients and DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5 times and about 1.7 times those in young male volunteers. Compared to normal subjects the total plasma clearance of losartan in patients with hepatic insufficiency was about 50% lower and the oral bioavailability was about 2 times higher. A lower starting dose is recommended for patients with a history of hepatic impairment (see DOSAGE AND ADMINISTRATION).

Drug Interactions

Losartan, administered for 12 days, did not affect the pharmacokinetics or pharmacodynamics of a single dose of warfarin. Losartan did not affect the pharmacokinetics of oral or intravenous digoxin. Coadministration of losartan and cimetidine led to an increase of about 18% in AUC of losartan but did not affect the pharmacokinetics of its active metabolite. Coadministration of losartan and phenobarbital led to a reduction of about 20% in the AUC of losartan and that of its active metabolite. There is no pharmacokinetic interaction between losartan and hydrochlorothiazide.

Pharmacodynamics and Clinical Effects

Losartan inhibits the pressor effect of angiotensin II (as well as angiotensin I) in humans. A dose of 100 mg inhibits the pressor effect by about 50% at 1 hour with 25-40% inhibition persisting for 24 hours. Because of the negative feedback of

Losartan is a registered trademark of Merck & Co., Inc. © 1997 Merck & Co., Inc. All rights reserved. Merck & Co., Inc., West Point, PA 19486, USA. Losartan potassium is a registered trademark of Merck & Co., Inc.

COZAAR® (Losartan Potassium Tablets)

angiotensin II causes a 2-3 fold rise in plasma renin activity and consequent rise in angiotensin II plasma concentration in hypertensive patients. Losartan does not affect the response to bradykinin, whereas ACE inhibitors increase the response to bradykinin. Aldosterone plasma concentrations fall following losartan administration. In spite of the effect of losartan on aldosterone secretion, very little effect on serum potassium was observed.

In a single-dose study in normal volunteers, losartan had no effects on glomerular filtration rate, renal plasma flow or filtration fraction. In multiple dose studies in hypertensive patients, there were no notable effects on systemic or renal prostaglandin concentrations, fasting triglycerides, total cholesterol or HDL-cholesterol or fasting glucose concentrations. There was a small uricosuric effect leading to a minimal decrease in serum uric acid (mean decrease -0.4 mg/dL) during chronic oral administration.

The antihypertensive effects of COZAAR were demonstrated principally in 4 placebo-controlled 6-12 week trials of dosages from 10 to 150 mg per day in patients with baseline diastolic blood pressures of 95-115. The studies allowed comparisons of two doses (50-100 mg/day) as once daily or twice daily regimens, comparisons of peak and trough effects, and comparisons of response by gender, age, and race. Three additional studies examined the antihypertensive effect of losartan and hydrochlorothiazide in combination.

The 4 studies of losartan monotherapy included a total of 1075 patients randomized to several doses of losartan and 334 to placebo. The 10 and 25 mg doses produced some effect at peak (6 hours after dosing) but small and inconsistent trough (24 hour) responses. Doses of 50, 100 and 150 mg once daily gave statistically significant systolic/diastolic mean decreases in blood pressure, compared to placebo in the range of 5.5-10.5/3.5-7.5 mmHg, with the 150 mg dose giving no greater effect than 50-100 mg. Twice daily dosing at 50-100 mg/day gave consistently larger trough responses than once daily dosing at the same total dose. Peak (6 hour) effects were uniformly, but moderately, larger than trough effects, with the trough to peak ratio for systolic and diastolic responses 50-95% and 60-90%, respectively.

Addition of a low dose of hydrochlorothiazide (12.5 mg) to losartan 50 mg once daily resulted in placebo adjusted blood pressure reductions of 15.5/9.2 mmHg.

Analysis of age, gender, and race subgroups of patients showed that men and women, and patients over and under 65, had generally similar responses. Black patients, however, had not only smaller responses to losartan monotherapy.

The effect of losartan is substantially present within one week but in some studies the maximal effect occurred in 3-6 weeks. In long term follow up studies (without placebo control) the effect of losartan appeared to be maintained for up to a year. There is no apparent rebound effect after abrupt withdrawal of losartan. There was essentially no change in average heart rate in losartan treated patients in controlled trials.

INDICATIONS AND USAGE

COZAAR is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

In considering the use of monotherapy with COZAAR, it should be noted that in controlled trials COZAAR had an effect on blood pressure that was notably less in black patients than in non blacks, a finding similar to the small effect of angiotensin converting enzyme inhibitors in blacks.

CONTRAINDICATIONS

COZAAR is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin or renin enzyme inhibitors. When pregnancy is detected, COZAAR should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function. Oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformities, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus, have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intravascular drug exposure that has been limited to the last trimester.

Mothers whose embryos and fetuses are exposed to ACE inhibitors should be so informed. Nonetheless, when patients become pregnant physicians should have the patient discontinue the use of COZAAR as soon as possible.

Rarely, probably less often than once in 1000, fetuses and newborns have been found to be anuric after birth. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and neonatal anuria and complications should be carefully monitored.

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(LOSARTAN POTASSIUM TABLETS)**

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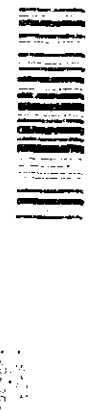


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If oligohydramnios is observed, COZAAR should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Losartan potassium has been shown to produce adverse effects in rat fetuses and neonates, including decreased body weight, delayed physical and behavioral development, mortality and renal toxicity. With the exception of neonatal weight gain (which was affected at doses as low as 10 mg/kg/day), doses associated with these effects exceeded 25 mg/kg/day (approximately three times the maximum recommended human dose of 100 mg on a mg/m² basis). These findings are attributed to drug exposure in late gestation and during lactation. Significant levels of losartan and its active metabolite were shown to be present in rat fetal plasma during late gestation and in rat milk.

Hypotension - Volume Depleted Patients

In patients who are intravascularly volume depleted (e.g., those treated with diuretics), symptomatic hypotension may occur after initiation of therapy with COZAAR. These conditions should be corrected prior to administration of COZAAR, or a lower starting dose should be used (see DOSAGE AND ADMINISTRATION).

PRECAUTIONS

General

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in anuric patients, a lower dose should be considered for patients with impaired liver function (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY, Pharmacokinetics).

Hypersensitivity. See ADVERSE REACTIONS, Post-Marketing Experience.

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and death. COZAAR would be expected to behave similarly in studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or BUN have been reported. There has been no known use of COZAAR in patients with unilateral or bilateral renal artery stenosis, but a similar effect should be anticipated.

Information for Patients

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions

No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, cimetidine and phenobarbital. (See CLINICAL PHARMACOLOGY, Drug Interactions.) Potent inhibitors of cytochrome P450 3A4 and 2C9 have not been studied clinically, but *in vitro* studies show significant inhibition of the formation of the active metabolite by inhibitors of P450 3A4 (ketoconazole, itraconazole, gestodene, or P450 2C9 (itraconazole) and clearly complete inhibition by the combination of sulfaphenazole and ketoconazole. The pharmacodynamic consequences of concomitant use of losartan and these inhibitors have not been examined.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Losartan potassium was not carcinogenic when administered at maximally tolerated dosages to rats and mice for 105 and 52 weeks, respectively. Female rats given the highest dose (270 mg/kg/day) had a slightly higher incidence of pituitary adenoma. The maximally tolerated dosage (270 mg/kg/day) in rats, 200 mg/kg/day in mice provided systemic exposures to losartan and its pharmacologically active metabolite that were approximately 16x and 90 times that of 30- and 15- times (m) of the exposure of a 90 kg human given 100 mg per day.

Losartan potassium was negative in the *in vitro* dominant pathway and V-79 mammalian cell mutagenesis assays and in the *in vitro* alkaline elution and *in vivo* micronucleus induction assays. In addition, the active metabolite showed no evidence of genotoxicity in the *in vitro* mutagenesis assays, alkaline elution, and *in vivo* micronucleus induction assays.

Fertility and reproductive performance were not affected in studies with male rats given oral doses of losartan potassium up to approximately 150 mg/kg/day. The administered doses were approximately 1.5 times (150 mg/kg/day) the maximum recommended human daily dose.

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ciated with a significant (p<0.05) decrease in the number of corpora lutea/female, implants/female and live fetuses/female at C-section. At 100 mg/kg/day, a decrease in the number of corpora lutea/female was observed. The relationship of these findings to drug-treatment is uncertain since there was no effect at these dosage levels on implants/pregnant female, percent post implant losses, or live animals/litter at parturition. In nonpregnant rats dosed at 135 mg/kg/day for 7 days, systemic exposure (AUCs) for losartan and its active metabolite were approximately 66 and 26 times the exposure achieved in man at the maximum recommended human daily dosage (100 mg).

Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters). See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers

It is not known whether losartan is excreted in human milk, but significant levels of losartan and its active metabolite were shown to be present in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Use in the Elderly

Of the total number of patients receiving COZAAR in controlled clinical studies, 39% patients (19%) were 65 years and over, while 37 patients (2%) were 75 years and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

COZAAR has been evaluated for safety in more than 3300 patients treated for essential hypertension and 4056 patients/subjects overall. Over 1200 patients were treated for over 6 months and more than 800 for over one year. In general, treatment with COZAAR was well tolerated. The overall incidence of adverse experiences reported with COZAAR was similar to placebo.

In controlled clinical trials, discontinuation of therapy due to clinical adverse experiences was required in 2.3 percent of patients treated with COZAAR and 3.7 percent of patients given placebo.

The following table of adverse events is based on four 6-12 week placebo controlled trials involving over 1000 patients on various doses (10-150 mg) of losartan and over 300 patients given placebo. All doses of losartan are grouped because none of the adverse events appeared to have a dose related frequency. The table includes all adverse events, whether or not attributed to the treatment, occurring in at least 1% of patients treated with losartan and that were more frequent on losartan than placebo.

	Losartan (n= 1075) Incidence	Placebo (n= 334) Incidence
Upper Respiratory		
Coryza	2.4	2.1
Pharyngitis	1.3	1.2
Musculoskeletal		
Cramp, muscle	1.1	0.7
Myalgia	1.0	0.8
Pain, back	1.8	1.2
Pain, leg	1.0	0.0
Nervous System (Other)		
Dizziness	2.5	2.1
Insomnia	1.4	0.6
Respiratory		
Congestion, nasal	2.0	1.2
Cough	2.4	3.3
Infection, upper respiratory	1.9	0.8
Sinus disorder	1.5	1.2
Sore throat	1.0	0.3

The following adverse events were also reported at a rate of 1% or greater in patients treated with losartan, but were not reported in the placebo group: asthenia/fatigue, edema, headache, abdominal pain, chest pain, nausea, headache, pharyngitis.

Adverse events occurred at about the same rates in men and women, older and younger patients, and black and non-black patients.

A patient with known hypersensitivity to aspirin and penicillin, when treated with COZAAR, was withdrawn from study due to swelling of the lips and eyelids and facial rash, reported as angioedema, which returned to normal 5 days after therapy was discontinued.

Upper extremity paresthesias and hemolysis was reported in a patient.

In addition to the adverse events above, potentially important events that occurred in at least two patients/subjects reported to losartan or other adverse events that occurred in 1% of patients in our studies are listed below. It cannot be determined whether these events were causally related to losartan therapy as a whole, facial edema, fever, otitis media, sinusitis, conjunctivitis, ear infection, peritonitis, second degree atrial block, S-V-A block, myocardial infarction.



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COZAAR® (Losartan Potassium Tablets)

NDC 0006-0952-28 unit dose package of 100
(6505 01-414-4061, 50 mg individually sealed 100's)

Storage

Store at controlled room temperature, 15-30°C (59-86°F).
Keep container tightly closed. Protect from light.

Made by
MERCK & CO., INC., West Point, PA 19486, USA

by:



Wilmington, DE 19860 USA

Issued September 1995
Printed in USA

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arrhythmias including atrial fibrillation, palpitation, sinus bradycardia, tachycardia, ventricular tachycardia, ventricular fibrillation; *Digestive*: anorexia, constipation, dental pain, dry mouth, flatulence, gastritis, vomiting; *Hematologic*: anemia; *Metabolic*: gout; *Musculoskeletal*: arm pain, hip pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, fibromyalgia, muscle weakness; *Nervous System/Psychiatric*: anxiety, anxiety disorder, ataxia, confusion, depression, dream abnormality, hyposthesia, decreased libido, memory impairment, migraine, nervousness, paresthesia, peripheral neuropathy, panic disorder, sleep disorder, somnolence, tremor, vertigo; *Respiratory*: dyspnea, bronchitis, pharyngeal discomfort, epistaxis, rhinitis, respiratory congestion; *Skin*: alopecia, dermatitis, dry skin, eczema, erythema, flushing, photosensitivity, pruritus, rash, sweating, urticaria; *Special Senses*: blurred vision, burning/stinging in the eye, conjunctivitis, taste perversion, tinnitus, decrease in visual acuity; *Urogenital*: impotence, nocturia, urinary frequency, urinary tract infection.

Post-Marketing Experience

The following adverse reactions have been reported in post-marketing experience: *Hypersensitivity*: Angioedema (involving swelling of the face, lips, and/or tongue) has been reported rarely in patients treated with losartan.

Laboratory Test Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of COZAAR.

Creatinine, Blood Urea Nitrogen. Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 0.1 percent of patients with essential hypertension treated with COZAAR alone. No patient discontinued taking COZAAR alone due to increased BUN or serum creatinine (see PRECAUTIONS, *Impaired Renal Function*).

Hemoglobin and Hematocrit. Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.33 grams percent and 0.09 volume percent, respectively) occurred frequently in patients treated with COZAAR alone but were rarely of clinical importance. No patients were discontinued due to anemia.

Liver Function Tests. Occasional elevations of liver enzymes and/or serum bilirubin have occurred. In patients with essential hypertension treated with COZAAR alone, one patient was discontinued due to these laboratory adverse experiences.

OVERDOSAGE

Toxicity and lethality was observed in mice and rats after oral administration of 1000 mg/kg and 2000 mg/kg, respectively (about 44 and 170 times the maximum recommended human dose on a mg/m² basis).

Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan nor its active metabolite can be removed by hemodialysis.

DOSAGE AND ADMINISTRATION

The usual starting dose of COZAAR is 50 mg once daily with 25 mg used in patients with possible depletion of intravascular volume (e.g., patients treated with diuretics) (see WARNINGS, *Hypotension - Volume Depleting Patients*) and patients with a history of hepatic impairment (see PRECAUTIONS, *Concomitant Use*). COZAAR can be administered once or twice daily, with total daily doses ranging from 25 mg to 160 mg.

If the antihypertensive effect measured at trough using once-a-day dosing is inadequate, a twice-a-day regimen at the same total daily dose or an increase in dose may give a more satisfactory response.

If blood pressure is not controlled by COZAAR alone, a low dose of a diuretic may be added. Hydrochlorothiazide has been shown to have an additive effect (see CLINICAL PHARMACOLOGY, *Pharmacokinetics and Clinical Effect*).

No dosage adjustment is necessary for elderly patients or for patients with renal impairment, including patients on dialysis.

COZAAR may be administered either as an oral suspension or as tablets.

COZAAR may be administered either with or without food.

HOW SUPPLIED

COZAAR 25 mg Tablets (NDC 0006-0952-28) are supplied in a unit dose package of 100 individually sealed 100's and in a 100 mg unit dose package of 100 individually sealed 100's. They are supplied as follows:

- NDC 0006-0952-28 unit of use bottles of 100 (6505 01-414-4064, 25 mg 90's)
- NDC 0006-0952-58 unit of use bottles of 100 (6505 01-414-4063, 25 mg 100's)
- NDC 0006-0952-28 unit dose package of 100 (6505 01-414-4063, 25 mg individually sealed 100's)
- NDC 0006-0952-58 unit dose package of 100 (6505 01-414-4064, 25 mg individually sealed 100's)
- NDC 0006-0952-28 unit of use bottles of 100 (6505 01-414-4062, 50 mg 30's)
- NDC 0006-0952-58 unit of use bottles of 100 (6505 01-414-4061, 50 mg 90's)
- NDC 0006-0952-28 unit of use bottles of 100 (6505 01-414-4061, 50 mg 100's)

APPROVED

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

N 20386

COZAAR

APPROVAL LETTER



Bongiovanni

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-386

APR 14 1995

Merck Research Laboratories
Attention: Larry P. Bell, M.D.
Sumneytown Pike
West Point, PA 19486

Dear Dr. Bell:

Please refer to your December 3, 1993 new drug application submitted on December 3, 1993 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cozaar (losartan potassium) 25 and 50 mg Tablets.

We acknowledge receipt of your amendments dated March 1, 7, 13, 14, 17 and 22, and April 5, 7 and 14, 1995.

The information contained in your amendment dated February 14, 1995 is currently under review. We note that you have agreed to submit a supplemental NDA to address this issue.

This new drug application provides for the use of Cozaar (losartan potassium) Tablets in the treatment of hypertension.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit fifteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-386. Approval of this labeling by FDA is not required before it is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any deficiencies that may occur.

Page 2 - NDA 20-386

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Kathleen Bongiovanni
Consumer Safety Officer
(301) 594-5300

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

cc:

Original NDA

HFD-2/MedWatch (with labeling)

HFC-130/JAllen

HFD-2/MLumpkin

HFD-5/THassall (If user fee application)

HFD-80 (with labeling)

HFD-100 (with labeling)

HFD-110

HFD-110/CSO

HFD-240 (with labeling)

HFD-613 (with labeling)

HFD-735/DBarash (with labeling)

HFD-110/KBongiovanni

sb/4/12/95;4/13/95;4/14/95

R/D: RMittal

RWolters/4/13/95

GJagadeesh

AProakis/4/13/95

CResnick/4/13/95

APPROVAL

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MRL COMMENTS/SUPPORT

 **MERCK & CO., INC.**
West Point, PA 19486, USA

XXXXXXX

COZAAR®

(LOSARTAN POTASSIUM TABLETS)

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, COZAAR should be discontinued as soon as possible. See WARNINGS: *Fetal/Neonatal Morbidity and Mortality.*

Agreement with FDA (Teleconference 4/4/95) to retain parenthesis placement following "Tablets".

DESCRIPTION

COZAAR® (losartan potassium), the first of a new class of antihypertensives, is an angiotensin II receptor (type AT₁) antagonist.

Losartan potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt.

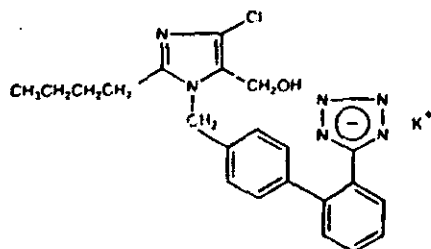
Its empirical formula is C₂₂H₂₂ClKN₆O, and its structural formula is:

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COZAAR® (Losartan Potassium Tablets)



Losartan potassium is a white to off-white free-flowing crystalline powder with a molecular weight of 461.01. It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone. Oxidation of the 5-hydroxymethyl group on the imidazole ring results in the active metabolite of losartan.

COZAAR is available for oral administration containing either 25 mg or 50 mg of losartan potassium and the following inactive ingredients: microcrystalline cellulose, lactose hydrous, pregelatinized starch, magnesium stearate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, titanium dioxide, D&C yellow No. 10 aluminum lake and FD&C blue No. 2 aluminum lake.

COZAAR 25 mg and 50 mg contain potassium in the following amounts: 2.12 mg (0.054 mEq) and 4.24 mg (0.108 mEq), respectively.

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COZAAR® (Losartan Potassium Tablets)

CLINICAL PHARMACOLOGY

Mechanism of Action

Angiotensin II [formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II)], is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT₁ receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland). There is also an AT₂ receptor found in many tissues but it is not known to be associated with cardiovascular homeostasis. Both losartan and its principal active metabolite do not exhibit any partial agonist activity at the AT₁ receptor and have much greater affinity (about 1000-fold) for the AT₁ receptor than for the AT₂ receptor. *In vitro* binding studies indicate that losartan is a reversible, competitive inhibitor of the AT₁ receptor. The active metabolite is 10 to 40 times more potent by weight than losartan and appears to be a reversible, non-competitive inhibitor of the AT₁ receptor.

Accepted.

Neither losartan nor its active metabolite inhibits ACE (kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin); nor do they bind to or block other hormone receptors, or ion channels known to be important in cardiovascular regulation.

Accepted.

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Pharmacokinetics
General
~~*Pharmacokinetics*~~

Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. It is converted, in part, to an active carboxylic acid metabolite which contributes significantly to that is responsible for most of the angiotensin II receptor antagonism that follows losartan treatment. The terminal half-life of losartan is about 2 hours and of the metabolite is about 6-9 hours. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan doses up to 200 mg and do not change over time. Neither losartan nor its metabolite accumulate in plasma upon repeated once-daily dosing.

Agreement with FDA (Teleconference 4/4/95) to retain FDA-requested wording.

Following oral administration, losartan is well absorbed (based on absorption of radiolabeled losartan) and undergoes substantial first-pass metabolism; the systemic bioavailability of losartan is approximately 33%. About 14% of an orally administered dose of losartan is converted to the active metabolite. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. While maximum plasma concentrations of losartan and its active metabolite are approximately equal, the AUC of the metabolite is about 4 times greater than as great as that of losartan. A meal slows absorption of losartan and decreases its C_{max} but has only minor effects on losartan AUC or on the AUC of the metabolite (about 10% decreased).

Accepted

Both losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2% respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

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Losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed. Following oral and intravenous administration of ¹⁴C-labeled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and its active metabolite. *In vitro* studies indicate that cytochrome P450 2C9 and 3A4 are involved in the biotransformation of losartan to its metabolites. Minimal conversion of losartan to the active metabolite (less than 1% of the dose compared to 14% of the dose in normal subjects) was seen in about one percent of individuals studied.

The volume of distribution of losartan is about 34 liters and of the active metabolite is about 12 liters. Total plasma clearance of losartan and the active metabolite is about 600 mL/min and 50 mL/min, respectively, with renal clearance of about 75 mL/min and 25 mL/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% is excreted in urine as active metabolite. Biliary excretion contributes to the elimination of losartan and its metabolites. Following oral ¹⁴C-labeled losartan, about 35% of radioactivity is recovered in the urine and about 60% in the feces. Following an intravenous dose of ¹⁴C-labeled losartan, about 45% of radioactivity is recovered in the urine and 50% in the feces.

Special Populations

Pediatric: Losartan pharmacokinetics have not been investigated in patients < 18 years of age.

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Geriatric and Gender: Losartan pharmacokinetics have been investigated in the elderly (65-75 years) and in both genders. Plasma concentrations of losartan and its active metabolite are similar in elderly and young hypertensives. Plasma concentrations of losartan were about twice as high in female hypertensives as male hypertensives, but concentrations of the active metabolite were similar in males and females. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).

Race: Pharmacokinetic differences due to race have not been studied.

Renal Insufficiency: Plasma concentrations of losartan are not altered in patients with creatinine clearance above 30 mL/min. AUCs below that creatinine clearance appear to be in patients with lower creatinine clearance, AUCs are about 50% greater and they are doubled in hemodialysis patients. Plasma concentrations of the active metabolite are not significantly altered in patients with renal impairment or in hemodialysis patients. Neither losartan nor its active metabolite can be removed by hemodialysis. No dosage adjustment is necessary for patients with renal impairment unless they are volume-depleted (see WARNINGS, *Hypotension - Volume-Depleted Patients* and DOSAGE AND ADMINISTRATION).

Accepted.

Accepted.

Accepted.

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Hepatic Insufficiency: Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-times and about 1.7-times those in young male volunteers. Compared to normal subjects the total plasma clearance of losartan in patients with hepatic insufficiency was about 50% lower and the oral bioavailability was about 2-fold times higher. A lower starting dose is recommended for patients with a history of hepatic impairment (see DOSAGE AND ADMINISTRATION).

Accepted.

Accepted.

Drug Interactions

Losartan, administered for 12 days, did not affect the pharmacokinetics or pharmacodynamics of a single dose of warfarin. Losartan did not affect the pharmacokinetics of oral or intravenous digoxin. Coadministration of losartan and cimetidine led to an increase of about 18% in AUC of losartan but did not affect the pharmacokinetics of its active metabolite. Coadministration of losartan and phenobarbital led to a reduction of about 20% in the AUC of losartan and that of its active metabolite. There is no pharmacokinetic interaction between losartan and hydrochlorothiazide.

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COZAAR® (Losartan Potassium Tablets)

Pharmacodynamics and Clinical Effects

Losartan inhibits the pressor effect of angiotensin II (as well as angiotensin I) infusions. A dose of 100 mg inhibits the pressor effect by about 85% at peak with 25-40% inhibition persisting for 24 hours. Removal of the negative feedback of angiotensin II causes a 2-3 fold rise in plasma renin activity and consequent rise in angiotensin II plasma concentration in hypertensive patients. Losartan does not affect the response to bradykinin, whereas an ACE inhibitor increased the response to bradykinin. Aldosterone plasma concentrations fall following losartan administration. In spite of the effect of losartan on aldosterone secretion, very little effect on serum potassium was observed.

In a single-dose study in normal volunteers, losartan had no effects on glomerular filtration rate, renal plasma flow or filtration fraction. In multiple dose studies in hypertensive patients, there were no notable effects on systemic or renal prostaglandin concentrations, fasting triglycerides, total cholesterol or HDL-cholesterol or fasting glucose concentrations. There was a small uricosuric effect leading to a minimal decrease in serum uric acid (mean decrease < 0.4 mg/dL) during chronic oral administration.

The antihypertensive effects of COZAAR were demonstrated principally in 4 placebo-controlled 6-12 week trials of dosages from 10 to 150 mg per day in patients with baseline diastolic blood pressures of 95-115. The studies allowed comparisons of two doses (50 and 100 mg/day) as once-daily or twice-daily regimens, comparisons of peak and trough effects, and comparisons of response by gender, age, and race. Three additional studies examined the antihypertensive efficacy effects of losartan and hydrochlorothiazide in combination.

Accepted.

Editorial revision for clarity and accuracy and for consistency with twice-daily dosing range mentioned in next paragraph (i.e., "Twice-daily dosing at 50-100 mg/day").

Accepted.

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MRL COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

~~The 4 studies of losartan monotherapy included a total of 1076 patients randomized to losartan and 334 to placebo. The 10 and 25 mg doses of losartan produced some effect at peak (6 hours after dosing) but small and inconsistent trough (24 hour) responses. The blood pressure response of losartan in the range of 50 to 150 mg once daily was statistically significant compared to placebo. However, there was little additional effect when the dose was increased above 50 mg. The range of placebo-adjusted systolic and diastolic antihypertensive responses in these four studies at doses of 50-150 mg once daily were 5.5-10.6/3.4-7.8 mmHg, respectively. Although peak (6 hours) effects were uniformly larger than trough effects following once-daily dosing, the reductions at trough were not the result of excessive reductions at peak; the trough to peak ratios for systolic and diastolic blood pressure were 50-95% and 60-90% at doses of 50-100 mg, respectively. Twice-daily dosing at total daily doses of 50-100 mg generally gave larger numerical placebo-adjusted reductions in blood pressure when compared to once-daily dosing.~~

MRL text submitted to FDA 3/14/95.

The 4 studies of losartan monotherapy included a total of 1075 patients randomized to several doses of losartan and 334 to placebo. The 10 and 25 mg doses produced some effect at peak (6 hours after dosing) but small and inconsistent trough (24 hour) responses. Doses of 50, 100, and 150 mg once daily gave statistically significant systolic/diastolic mean decreases in blood pressure compared to placebo in the range of 6.9-5/4.6 5.5-10.5/3.5-7.5 mmHg, with the 150 mg dose giving no greater effect than 50-100 mg. Twice-daily dosing at 50-100 mg/day gave consistently larger trough responses than once daily dosing at the same total dose. Peak (6 hour) effects were uniformly, but moderately larger than trough effects, with the trough to peak ratio for systolic and diastolic responses 45-70% 50-95% and 60-90% respectively.

Agreement with FDA (Teleconference 4/4/95) to accept FDA-requested language with MRL numbers (see attached for supporting documentation).

Addition of a low dose of hydrochlorothiazide (12.5 mg) to losartan 50 mg once daily resulted in placebo-adjusted blood pressure reductions of 15.5/9.2 mmHg.

**MRL TEXT SUBMITTED 3/14/95 WITH
FDA-REQUESTED REVISIONS OF 4/3/95**

COZAAR® (Losartan Potassium Tablets)

Analysis of age, gender, and race subgroups of patients showed that men and women, and patients over and under 65, had generally similar responses. Black patients, however, had notably smaller responses to losartan monotherapy; ~~generally less than 50% of the effect in whites, with no detectable effect in two of the three studies where this could be assessed.~~

The effect of losartan is substantially present within one week and but in some studies the maximal effect occurred in 3-8 weeks. In long-term follow-up studies (without placebo control) the effect of losartan appeared to be maintained for up to a year. There is no apparent rebound effect after abrupt withdrawal of losartan. There was essentially no change in average heart rate in losartan-treated patients in controlled trials.

MRL COMMENTS/SUPPORT

Agreement with FDA (Teleconference 4/4/95) to reword section as shown.

Agreement with FDA (Teleconference 4/4/95) to accept FDA-requested wording.

**MRL TEXT SUBMITTED 3/14/95 WITH
FDA-REQUESTED REVISIONS OF 4/3/95**

COZAAR® (Losartan Potassium Tablets)

INDICATIONS AND USAGE

COZAAR is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

~~In controlled clinical trials, monotherapy with COZAAR had less effect on blood pressure in black patients than in non-black patients.~~

In considering the use of COZAAR monotherapy with COZAAR, it should be noted that in controlled trials COZAAR had an effect on blood pressure that was notably less in black patients than in non-blacks, sometimes showing no effect at all; a finding similar to the small effect of angiotensin converting enzyme inhibitors in blacks.

CONTRAINDICATIONS

COZAAR is contraindicated in patients who are hypersensitive to any component of this product.

MRL COMMENTS/SUPPORT

MRL text submitted to FDA 3/14/95.

Agreement with FDA (Teleconference 4/4/95) to accept FDA wording with modification as shown.

**MRL TEXT SUBMITTED 3/14/95 WITH
FDA-REQUESTED REVISIONS OF 4/3/95**

MRL COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

WARNINGS:

Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, COZAAR should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester.

Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of COZAAR as soon as possible.

**MRL TEXT SUBMITTED 3/14/95 WITH
FDA-REQUESTED REVISIONS OF 4/3/95**

MRL COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, COZAAR should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Losartan potassium has been shown to produce adverse effects in rat fetuses and neonates, including decreased body weight, delayed physical and behavioral development, mortality and renal toxicity. With the exception of neonatal weight gain (which was affected at doses as low as 10 mg/kg/day), doses associated with these effects exceeded 25 mg/kg/day (approximately three times the maximum recommended human dose of 100 mg on a mg/m² basis). These findings are attributed to drug exposure in late gestation and during lactation. Significant levels of losartan and its active metabolite were shown to be present in rat fetal plasma during late gestation and in rat milk.

**MRL TEXT SUBMITTED 3/14/95 WITH
FDA-REQUESTED REVISIONS OF 4/3/95**

MRL COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

Hypotension – Volume-Depleted Patients

In patients who are intravascularly volume-depleted (e.g., those treated with high-dose diuretics), symptomatic hypotension may occur after initiation of therapy with COZAAR. These conditions should be corrected prior to administration of COZAAR, or a lower starting dose should be used (see DOSAGE AND ADMINISTRATION).

Agreement with FDA (Teleconference 4/4/95) to delete "high dose" from statement.

PRECAUTIONS

General

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with impaired liver function (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY, Pharmacokinetics).

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. COZAAR would be expected to behave similarly. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or BUN have been reported. There has been no known use of COZAAR in patients with unilateral or bilateral renal artery stenosis, but a similar effect should be anticipated.

**MRL TEXT SUBMITTED 3/14/95 WITH
FDA-REQUESTED REVISIONS OF 4/3/95**

MRL COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

Information for Patients

Pregnancy. Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions

~~Compounds that have been studied in clinical pharmacokinetic trials include~~ No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, cimetidine and phenobarbital. (See CLINICAL PHARMACOLOGY, Drug Interactions.) Significant Potent inhibitors of cytochrome P450 3A4 and 2C9 have not been studied clinically but *in vitro* studies show significant inhibition of the formation of the active metabolite by inhibitors of P450 3A4 (ketoconazole, itraconazole, voriconazole, posaconazole, isavuconazole, troleanomycin, gestodene), or P450 2C9 (sulfaphenazole) and nearly complete inhibition by the combination of sulfaphenazole and ketoconazole. The pharmacodynamic consequences of concomitant use of losartan and these inhibitors have not been examined

Agreement with FDA (Teleconference 4/4/95) to revise section as shown.

**MRL TEXT SUBMITTED 3/14/95 WITH
FDA-REQUESTED REVISIONS OF 4/3/95**

MRL COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

Carcinogenesis, Mutagenesis, Impairment of Fertility

Losartan potassium was not carcinogenic when administered at maximally tolerated dosages to rats and mice for 105 and 92 weeks, respectively. Female rats given the highest dose (270 mg/kg/day) had a slightly higher incidence of pancreatic acinar adenoma. The maximally tolerated ~~These~~ dosages (270 mg/kg/day in rats, 200 mg/kg/day in mice) provided systemic exposures for losartan and its pharmacologically active metabolite that were approximately 160- and 90-times (rats) and 30- and 15-times (mice) the exposure of a 50 kg human given 100 mg per day.

Agreement with FDA (Teleconference 4/4/95) to retain FDA statement regarding pancreatic acinar adenoma in female rats with commitment from FDA to look again at MRL data.

Losartan potassium was negative in the microbial mutagenesis and V-79 mammalian cell mutagenesis assays and in the *in vitro* alkaline elution and *in vitro* and *in vivo* chromosomal aberration assays. In addition, the active metabolite showed no evidence of genotoxicity in the microbial mutagenesis, *in vitro* alkaline elution, and *in vitro* chromosomal aberration assays.

Fertility and reproductive performance were not affected in studies with male rats given oral doses of losartan potassium up to approximately 150 mg/kg/day. The administration of toxic dosage levels in females (300/200 mg/kg/day) was associated with a significant ($p < 0.05$) decrease in the number of corpora lutea/female, implants/female, and live fetuses/female at C-section. At 100 mg/kg/day only a decrease in the number of corpora lutea/female was observed. The relationship of these findings to drug-treatment is uncertain since there was no effect at these dosage levels on implants/pregnant female, percent post-implantation loss, or live animals/litter at parturition. In nonpregnant rats dosed at 135 mg/kg/day for 7 days, systemic exposure (AUCs) for losartan and its active metabolite were approximately 68 and 26 times the exposure achieved in man at the maximum recommended human daily dosage (100 mg).

**MRL TEXT SUBMITTED 3/14/95 WITH
FDA-REQUESTED REVISIONS OF 4/3/95**

MRL COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters).

See WARNINGS, *Fetal/Neonatal Morbidity and Mortality*.

Nursing Mothers

It is not known whether losartan is excreted in human milk, but significant levels of losartan and its active metabolite were shown to be present in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

**MRL TEXT SUBMITTED 3/14/95 WITH
FDA-REQUESTED REVISIONS OF 4/3/95**

MRL COMMENTS/SUPPORT

4/13/95

Use in the Elderly

Of the total number of patients receiving COZAAR in controlled clinical studies, 391 patients (19%) were 65 years and over, while 37 patients (2%) were 75 years and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

COZAAR has been evaluated for safety in more than 3300 patients treated for essential hypertension and 4058 patients/subjects overall. Over 1200 patients were treated for over 6 months and more than 800 for over one year. In general, treatment with COZAAR was well tolerated. The overall incidence of adverse experiences reported with COZAAR was similar to placebo.

In controlled clinical trials, discontinuation of therapy due to clinical adverse experiences was required in 2.3 percent of patients treated with COZAAR and 3.7 percent of patients given placebo.

The following table of adverse events is based on four 6-12 week placebo controlled trials involving over 1000 patients on various doses (10-150 mg) of losartan and over 300 patients given placebo. All doses of losartan are grouped because none of the adverse events appeared to have a dose-related frequency. The table includes all adverse events, whether or not attributed to the treatment, occurring in at least 1% of patients treated with losartan (or at a lower rate for selected events) and that were more frequent on losartan than placebo.

Agreement with FDA (Teleconference 4/4/95) to delete text as shown.

**MF EXT SUBMITTED 3/14/95 WITH
FDA-REQUESTED REVISIONS OF 4/3/95**

MRL COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

	Losartan (n=1075) Incidence	Placebo (n=334) Incidence
<i>Digestive</i>		
Diarrhea	2.4	2.1
Dyspepsia	1.3	1.2
<i>Musculoskeletal</i>		
Cramp, muscle	1.1	0.3
Myalgia	1.0	0.9
Pain, back	1.8	1.2
Pain, leg	1.0	0.0
<i>Nervous System/Psychiatric</i>		
Dizziness	3.5	2.1
Insomnia	1.4	0.6
<i>Respiratory</i>		
Congestion, nasal	2.0	1.2
Cough	3.4	3.3
Infection, upper respiratory	7.9	6.9
Sinus disorder	1.5	1.2
Sinusitis	1.0	0.3

Agreement with FDA (Teleconference 4/4/95) to retain table as shown.

The following adverse events were also reported at a rate of 1% or greater in patients treated with losartan, but were as, or more frequent, in the placebo group: asthenia/fatigue, edema/swelling, abdominal pain, chest pain, nausea, headache, pharyngitis.

Adverse events occurred at about the same rates in men and women, older and younger patients, and black and non-black patients.

REVISION OF PARAGRAPH AS REQUESTED BY FDA ON 4/14/95.

Relocated per FDA Teleconference 4/13/95.

**N TEXT SUBMITTED 3/14/95 WITH
FDA REQUESTED REVISIONS OF 4/3/95**

MRL COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

A patient with known hypersensitivity to aspirin and penicillin, when treated with COZAAR, was withdrawn from study due to swelling of the lips and eyelids and facial rash, reported as angioedema, which returned to normal 5 days after therapy was discontinued.

Relocated per FDA Teleconference 4/13/95.

Superficial peeling of palms and possible hemolysis was reported in one subject.

Relocated per FDA Teleconference 4/13/95.

~~The following adverse events occurred without regard to causality, at ≥0.5% in patients treated with losartan: Body as a Whole: abdominal pain, asthenia/fatigue, chest pain, edema/swelling, fever, orthostatic effects; Cardiovascular: palpitation, tachycardia; Digestive: anorexia, constipation, dental pain, nausea, vomiting; Metabolic: gout; Musculoskeletal: arm pain, hip pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness; Nervous System/Psychiatric: anxiety, depression, headache, libido decreased, paresthesia, vertigo; Respiratory: dyspnea, bronchitis, epistaxis, pharyngeal discomfort, pharyngitis, rhinitis, respiratory congestion; Skin: flushing, pruritus, rash; Special Senses: tinnitus; Urogenital: impotence, urinary frequency, urinary tract infection.~~

**No. ... TEXT SUBMITTED 3/14/95 WITH
FDA-REQUESTED REVISIONS OF 4/3/95**

MRL COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

In addition to the adverse events in the table above, potentially important events, without regard to causality, that occurred in at least twice in the two patients/subjects exposed to losartan or other adverse events that occurred in <1% of patients in clinical studies are listed below. It cannot be determined whether these events were causally related to losartan. Body as a Whole: facial edema, fever, orthostatic effects, syncope; Cardiovascular: angina pectoris, second degree AV block, CVA, hypotension, myocardial infarction, arrhythmias including atrial fibrillation, palpitation, sinus bradycardia, tachycardia, ventricular tachycardia, ventricular fibrillation; Digestive: anorexia, constipation, dental pain, dry mouth, flatulence, gastritis, vomiting; Hematologic: anemia; Metabolic: gout; Musculoskeletal: arm pain, hip pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, fibromyalgia, muscle weakness; Nervous System/Psychiatric: anxiety, anxiety disorder, ataxia, confusion, depression, dream abnormality, hypesthesia, decreased libido, memory impairment, migraine, nervousness, paresthesia, peripheral neuropathy, panic disorder, sleep disorder, somnolence, tremor, vertigo; Respiratory: dyspnea, bronchitis, pharyngeal discomfort, epistaxis, rhinitis, respiratory congestion; Skin: alopecia, dermatitis, dry skin, ecchymosis, erythema, flushing, photosensitivity, pruritus, rash, sweating, urticaria; Special Senses: blurred vision, burning/stinging in the eye, conjunctivitis, taste perversion, tinnitus, decrease in visual acuity; Urogenital: impotence, nocturia, urinary frequency, urinary tract infection.

Laboratory Test Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of COZAAR.

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 0.1 percent of patients with essential hypertension treated with COZAAR alone. No patient discontinued taking COZAAR alone due to increased BUN or serum creatinine. (See PRECAUTIONS, Impaired Renal Function.)

Agreement with FDA (Teleconference 4/4/95 and request 4/7/95) to revise paragraph as shown. Paragraph has been revised to include those adverse events that were previously included on page 19, as well as those potentially important events from all studies. Those four adverse events that FDA had requested be included (orthostatic effects, vertigo, epistaxis, tinnitus) are included in this section since they meet the incidence criteria.

Agreement with FDA (Teleconference 4/4/95) to revise subsection as shown.

**TEXT SUBMITTED 3/14/95 WITH
FDA-REQUESTED REVISIONS OF 4/3/95**

MRL COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.11 grams percent and 0.09 volume percent, respectively) occurred frequently in patients treated with COZAAR alone, but were rarely of clinical importance. No patients were discontinued due to anemia.

Liver Function Tests: Occasional elevations of liver enzymes and/or serum bilirubin have occurred. In patients with essential hypertension treated with COZAAR alone, one patient (<0.1%) was discontinued due to these laboratory adverse experiences.

OVERDOSAGE

Significant lethality was observed in mice and rats after oral administration of 1000 mg/kg and 2000 mg/kg, respectively, about 44 and 170 times the maximum recommended human dose on a mg/m² basis.

**MRL TEXT SUBMITTED 3/14/95 WITH
FDA-REQUESTED REVISIONS OF 4/3/95**

COZAAR® (Losartan Potassium Tablets)

Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan nor its active metabolite can be removed by hemodialysis.

MRL COMMENTS/SUPPORT

**MRL TEXT SUBMITTED 3/14/95 WITH
FDA-REQUESTED REVISIONS OF 4/3/95**

MRL COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

DOSAGE AND ADMINISTRATION

~~The usual starting dose for most patients is 50 mg once daily. The dosage range is 25 to 100 mg. For patients with possible depletion of intravascular volume (e.g., those treated with high dose diuretics) (see WARNINGS, Hypotension—Intravascular Volume Depletion) and for patients with a history of hepatic impairment (see PRECAUTIONS, General), a starting dose of 25 mg is recommended. Some patients may receive an additional benefit by an increase in the dose (100 mg). If blood pressure is not controlled by COZAAR alone, a low dose of a diuretic may be added. Hydrochlorothiazide has been shown to have an additive effect (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects).~~

~~COZAAR can be administered once or twice daily with total daily doses ranging from 25 mg to 100 mg. The usual starting dose is 50 mg once daily, with 25 mg used in patients with possible depletion of intravascular volume (e.g., patients treated with diuretics) (see PRECAUTIONS, General) and patients with a history of hepatic impairment (see PRECAUTIONS, General).~~

~~If the antihypertensive effect measured at trough using once-a-day dosing is inadequate, a twice-a-day regimen may give a more satisfactory response.~~

~~Some patients may receive an additional benefit by an increase in the dose (100 mg). If blood pressure is not controlled by COZAAR alone, a low dose of a diuretic may be added. Hydrochlorothiazide has been shown to have an additive effect (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects).~~

MRL text submitted to FDA 3/14/95.

FDA-requested text of 4/3/95.

**MRL TEXT SUBMITTED 3/14/95 WITH
FDA-REQUESTED REVISIONS OF 4/3/95**

MRL COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

The usual starting dose of COZAAR is 50 mg once daily, with 25 mg used in patients with possible depletion of intravascular volume (e.g., patients treated with diuretics) (see WARNINGS, Hypotension - Volume-Depleted Patients) and patients with a history of hepatic impairment (see PRECAUTIONS, General). COZAAR can be administered once or twice daily with total daily doses ranging from 25 mg to 100 mg.

If the antihypertensive effect measured at trough using once-a-day dosing is inadequate, a twice-a-day regimen at the same total daily dose or an increase in dose may give a more satisfactory response.

If blood pressure is not controlled by COZAAR alone, a low dose of a diuretic may be added. Hydrochlorothiazide has been shown to have an additive effect (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects).

No initial dosage adjustment is necessary for elderly patients or for patients with renal impairment, including patients on dialysis.

COZAAR may be administered with other antihypertensive agents.

COZAAR may be administered with or without food.

HOW SUPPLIED

No. 3612 — Tablets COZAAR, 25 mg, are light green, teardrop-shaped, film-coated tablets with code MRK on one side and 851 on the other. They are supplied as follows:

- NDC 0008-0951-54 unit of use bottles of 90
- NDC 0006-0951-58 unit of use bottles of 100
- NDC 0006-0951-28 unit dose packages of 100.

Text agreed to by FDA and MRL at teleconference 4/4/95.

**MRL TEXT SUBMITTED 3/14/95 WITH
FDA-REQUESTED REVISIONS OF 4/3/95**

MRL COMMENTS/SUPPORT

COZAAR® (Losartan Potassium Tablets)

No. 3613 — Tablets COZAAR, 50 mg, are green, teardrop-shaped, film-coated tablets with code MRK 952 on one side and COZAAR on the other. They are supplied as follows:

NDC 0006-0952-31 unit of use bottles of 30

NDC 0006-0952-54 unit of use bottles of 90

NDC 0006-0952-58 unit of use bottles of 100

NDC 0006-0952-28 unit dose packages of 100.

Storage

Store at controlled room temperature, 15-30°C (59-86°F).
Keep container tightly closed. Protect from light.

Manuf for:

☉ MERCK & CO., INC., West Point, PA 19486, USA

by:



Wilmington, DE 19880, USA

Issued XXXXX.
Printed in U.S.A.

ldaann46.doc

CSO OVERVIEW OF NDA REVIEW PACKAGE
NDA 20-386 Cozaar (losartan potassium) Tablets
Merck Research Laboratories

1S

CSO: Kathleen Bongiovanni

Chemistry

Primary reviewer: Carl Berninger, Ph.D.; Ram Mittal, Ph.D.

Issues: Environmental Assessment: response submitted 3-13-95. Under review (Nancy Sager)

EER: Acceptable 3-7-95.

Methods Validation: on-going

Labeling: Merck has sent in a counterproposal for labeling 3-14-95.

Conclusion: approvable.

Pharmacology

Primary reviewer: Anthony Proakis, Ph.D., and G. Jagadeesh, Ph.D.

Labeling: see pgs 165-6 of 12-7-94 review.

Conclusion: approvable. Labeling changes included in Dr. Lipicky's mark-up.

Biostatistics (pre-clinical)

Primary reviewer: Mohammad Rahman, Ph.D.

Conclusion: approvable:

Medical

Primary reviewer: Charles Ganley, M.D.

Conclusion: approvable. Labeling changes included in Dr. Lipicky's mark-up.

Biostatistics (clinical)

Primary reviewer: Walid Nuri, Ph.D

Conclusion: approvable.

Biopharm

Primary reviewer: Emmanuel Fadiran, Ph.D.

Conclusion: approvable. Labeling changes included in Dr. Lipicky's mark-up.

Safety Updates: dated 4-4-94 and 1-31-95.

Labeling: See Dr. Lipicky's marked-up draft (in package)

Patent info: included in package

Debarment Certification: included in package

Labeling & Nomenclature Committee: review Feb 9, 1994. Some minor concerns.

Overview revised 3-23-95

AE

LTR



Food and Drug Administration
Rockville MD 20857

NDA 20-386

MAR 2 1995

Merck Research Laboratories
Attention: Larry P. Bell, M.D.
Sumneytown Pike
West Point, PA 19486

Dear Dr. Bell:

Please refer to your December 3, 1993 new drug application submitted on December 3, 1993 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cozaar (losartan potassium) 25 and 50 mg Tablets.

We acknowledge receipt of your amendments and correspondence dated December 10, 1994; January 6 and 31, February 9, 23 and 28, March 25, April 4, 11, 12, 14 and 15, May 2, 4 (two), 18 and 20, June 17, 29 and 30, July 15, 21, 25 (two), 26 (two), and 28 (two), August 12, 17, 18, 19 and 26, September 1, 13 and 19, October 3, 5 (two), 7, and 21 (two), and December 8 and 21, 1994; and January 11, 25, 27 and 31 and February 7, 8, 9, 10, 14 (two), 16 and 23, 1995.

We have completed the review of this application as submitted with draft labeling. Before the application may be approved, however, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed marked-up draft. If additional information relating to the safety or effectiveness of this drug becomes available, revision of the FPL may be required.

Please submit fifteen copies of the printed labels and other labeling, ten of which are individually mounted on heavy weight paper or similar material.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Cardio-Renal Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

We remind you that a satisfactory inspection of your manufacturing facilities for conformance with current good manufacturing practices (CGMP) is required before this application may be approved.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any deficiencies that may occur.

We note that you have responded to our letter of December 9, 1994 that asked for additional information on the Environmental Assessment portion of this application with two amendments, dated January 30 and February 8, 1995. We have completed our review and have the following requests:

The following information should be provided. It is not necessary to provide a complete update of your confidential and non-confidential environmental assessments as the requested information may be submitted in an addendum to your environmental assessments dated February 1, 1995. The two addenda should be titled:

Confidential Addendum to February 1, 1995
Environmental Assessment for Cozaar

Non-Confidential Addendum to February 1, 1995
Environmental Assessment for Cozaar

The Non-Confidential Addendum should be self explanatory since it will be attached directly to your non-confidential environmental assessment of February 1, 1995 and made available for public inspection once the application is approved.

1. The following information should be included in the non-confidential EA Addendum:
 - a. The contract packaging sites including specific addresses;
 - b. Information in Appendix 1, sections 1 and 2 (nomenclature and description); and
 - c. Site permit information (Attachment 3).
2. The basis (detailed calculations) for the estimated concentrations from production at the _____ facilities should be provided.
3. The request for information regarding the methods used in the *Daphnia magna* and *Pimephales promelas* studies was not adequately addressed. The testing information provided does not, for example, report the no observed effects level, if observed, the length and weight of the fathead minnows, etc. Please review the reporting requirements for these tests which are located in either 40 CFR § 797, parts 1300 and 1400 or Environmental Assessment Technical Assistance Documents 4.08 and 4.11 and provide the missing information.

Please change the dissolution specifications from "not less than _____ of the labeled amount of losartan potassium dissolved in 45 minutes" to "not less than _____ of the labeled amount of losartan potassium dissolved in 30 minutes."

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

Under section 736(a)(1)(B)(ii) of the Prescription Drug User Fee Act of 1992, this letter triggers the remaining 50% of the fee assessed for this application. You will receive an invoice for the amount due within the next month. Payment will be due within 30 days of the date of the invoice.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Ms. Kathleen Bongiovanni
Consumer Safety Officer
Telephone: (301) 594-5300

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Draft Labeling

cc:

Original NDA

HF-2/Medwatch (with draft labeling)

HFC-130/JAllen

HFD-2/MLumpkin

HFD-5/THassall (if user fee application)

HFD-80

HFD-100

HFD-110

HFD-110/CSO

HFD-240 (with draft labeling)

HFD-638 (with draft labeling)

HFD-735/DBarash (with draft labeling)

HFD-110/KBongiovanni

sb/1/31/95;2/8/95;2/14/95

R/D: RMittal/2/9/95

RWolters/2/9/95

AProakis

GJagadeesh

CResnick/2/10/95

EFadirian/2/10/95

WNuri/2/13/95

CGanley/2/13/95

NMorgenstern/2/13/95

APPROVABLE

**COZAAR
(LOSARTAN POTASSIUM TABLETS)
USE IN PREGNANCY**

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death in the developing fetus. When pregnancy is detected, COZAAR should be discontinued as soon as possible. See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

COZAAR* (losartan potassium), the first of a new class of antihypertensives, is an angiotensin II receptor (type AT1) antagonist. Losartan potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[*p*-(*o*-1 *H*-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt.

Its empirical formula is C₂₂H₂₂ClKN₆O, and its structural formula is:

Losartan potassium is a white to off-white free-flowing crystalline powder with a molecular weight of 461.01. It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone. Oxidation of the 5-hydroxymethyl group on the imidazole ring results in the active metabolite of losartan.

COZAAR is available for oral administration containing either 25 mg or 50 mg of losartan potassium and the following inactive ingredients: microcrystalline cellulose, lactose hydrous, pregelatinized starch, magnesium stearate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, titanium dioxide, D&C yellow No. 10 aluminum lake and FD&C blue No. 2 aluminum lake.

COZAAR 25 mg and 50 mg contain potassium in the following amounts: 2.12 mg (0.054 mEq) and 4.24 mg (0.108 mEq), respectively.

CLINICAL PHARMACOLOGY

Mechanism of Action

Angiotensin II [formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase I)], is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system and an important component in the pathophysiology of renin-related hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting

effects of angiotensin II by interfering with the binding of angiotensin II to the AT₁ receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland). There is also an AT₂ receptor found in many tissues but it is not known to be associated cardiovascular homeostasis. Both losartan and its principal active metabolite do not exhibit any partial agonist activity of the AT₁ receptor and have much greater affinity (about 1000-fold for the AT₁ receptor than for the AT₂ receptor). *In-vitro* binding studies indicate that losartan is a reversible, competitive inhibitor of the AT₁ receptor. The active metabolite is 10 to 40 times more potent by weight than losartan and appears to be a reversible, non-competitive inhibitor of the AT₁ receptor.

Neither losartan nor its active metabolite inhibits ACE (kininase I), the enzyme that converts angiotensin I to angiotensin II, and degrades bradykinin, other hormone receptors, or ion channels known to be important in cardiovascular regulation.

Pharmacokinetics

Losartan is an orally active agent that undergoes substantial first pass metabolism by cytochrome P-450 enzymes. It is converted, in part, to an active carboxylic acid metabolite that is responsible for most of the angiotensin II receptor antagonism that follows losartan treatment. The terminal half life of losartan is about 1-2 hours and of the metabolite is about 6-9 hours. The pharmacokinetics of losartan and its metabolite are generally dose-proportional and constant over time and neither the drug nor its metabolite accumulate on replicated dosing.

Following oral administration, losartan is well absorbed (based on absorption of radiolabelled losartan) and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and several inactive metabolites. The absolute bioavailability of losartan is approximately 33%. Losartan's low bioavailability is due to its high presystemic first pass metabolism. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours respectively. Maximum plasma concentrations of losartan and its metabolite are approximately equal, but because of the longer half life, the exposure (AUC) of the metabolite is about 5 times as great as that of losartan. A meal slows absorption of losartan and decreases its C_{max} but has only minor effects on losartan AUC or on the AUC of the metabolite (about 10% decreased).

Both losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2% respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed. Following oral and intravenous administration of ¹⁴C-labeled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and its active metabolite. *In vitro* studies indicate that cytochrome P450C9 and 3A4 are involved in the biotransformation of losartan to its

metabolites. Minimal conversion of losartan to the active metabolite (less than 1% of the dose compared to 14% of the dose in normal subjects) was seen in about one percent of individuals studied.

The volume of distribution of losartan is about 47 liters and of the active metabolite is about 12 liters. Total plasma clearance of losartan and the active metabolite is about 600 ml/min and 50 ml/min, respectively, with renal clearance of about 75 ml/min and 25 ml/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% excreted in urine as active metabolite. Biliary excretion contributes to the elimination of losartan and its metabolites. Following oral ¹⁴C-labeled losartan, about 35% of radioactivity is recovered in the urine and about 60% in the feces. Following an intravenous dose of ¹⁴C-labeled losartan, about 45% of radioactivity is recovered in the urine and 50% in the feces.

Special Populations

Pediatric

Losartan pharmacokinetics have not been investigated in patients < 18 years of age.

Geriatric and Gender

Losartan Pharmacokinetics have been investigated in the elderly (65-75 years) and in both genders. Renal clearance of losartan is decreased by about 50% in elderly male hypertensives when compared to young healthy males, but clearance of the active metabolite is little altered. The AUC of the metabolite is about 50% greater in elderly men and women than in young males. Plasma concentrations of losartan were about twice as high in female hypertensives as male hypertensives, but concentrations of the active metabolite were similar in males and females.

Race

Pharmacokinetic differences due to race have not been studied.

Renal Insufficiency

Plasma concentrations of losartan are not altered in patients with creatinine clearance above 30 ml/min. Below that clearance, AUCs are increased by about 50% and are doubled in hemodialysis patients. Plasma concentrations of the active metabolite are not significantly altered in patients with renal impairment or in hemodialysis patients. Neither losartan nor its active metabolite can be removed by hemodialysis.

Hepatic Insufficiency

Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were respectively, 5-times and about 1.7-times those in young male volunteers. Compared to normal subjects the volume of distribution of losartan in patients with hepatic insufficiency decreased by about 50% but the oral bioavailability increased by about 100%.

Drug Interactions

Losartan, administered for 12 days, did not affect the pharmacokinetics of a single dose of warfarin. This does not rule out the possibility of a pharmacodynamic interaction of losartan and warfarin and there is no chronic experience with co-administration of the two drugs. Losartan did not affect the pharmacokinetics of oral or intravenous digoxin. Coadministration of losartan and cimetidine led to an increase of about 23% in AUC of losartan but did not affect the pharmacokinetics of its active metabolite. Coadministration of losartan and phenobarbital led to a reduction of about 20% in the AUC of losartan and that of its active metabolite. There is no interaction between losartan and hydrochlorothiazide.

Pharmacodynamics and Clinical Effects

Losartan inhibits the pressor effect of angiotensin II (as well as angiotensin I) infusions. A dose of 100 mg inhibits the pressor effect by about 85% at peak with 25-40% inhibition persisting for 24 hours. Aldosterone plasma concentrations fall. Removal of the negative feedback of angiotensin II causes a rise in plasma renin activity and consequent rise in angiotensin II plasma concentration. Losartan does not affect the response to bradykinin, whereas an ACE inhibitor increased the response to bradykinin. In spite of its effect on aldosterone secretion, very little effect on serum potassium was observed.

Losartan has no effects on glomerular filtration rate, renal plasma flow or filtration fraction. There were no notable effects on systemic prostaglandin concentrations, fasting triglycerides, total cholesterol or HDL-cholesterol or fasting glucose concentrations. There was a clear, but small uricosuric effect leading to a small decrease in serum uric acid (mean decrease < 0.4 mg/dL) during chronic oral administration. [Address possibility of flank pain, renal failure syndrome - suprofen, ticrynafen, etc.]

[NOTE: Plasma concentration data, effects on proteinuria and effects of hemodynamics in heart failure have been left out deliberately, pending further data.]

The antihypertensive effects of Cozaar were demonstrated principally in 4 placebo-controlled 6-12 week trials of dosages from 10 to 150 mg per day in patients with baseline diastolic blood pressures of 95-115. The studies allowed comparisons of two doses (50 and 100 mg) as once daily or twice daily regimens, comparisons of peak and trough effects, and comparisons of response by gender, age, and race. Three studies examined the interaction of losartan and diuretic.

The 4 studies of losartan monotherapy included a total of 1075 patients randomized to several doses of losartan and 334 to placebo. The 10 and 25 mg doses produced some effect at peak (6 hours after dosing) but small and inconsistent trough (24 hour) responses. Doses of 50, 100, and 150 mg once daily gave decreases in blood pressure, compared to placebo, of 5-9.5/4-6 mmHg, with the 150 mg dose giving no greater effect than 50-100 mg. Twice daily dosing at 50-100 mg/day gave consistently larger trough responses, 8.5-9.5/6-6.3 mmHg, than once daily dosing at the same total dose. Peak (6 hour) effects were uniformly larger than trough effects, with the trough to peak ratio for systolic and diastolic responses 45-70% and 60-90% respectively.

[Describe, briefly, the losartan/HCTZ data.]

Analysis of age, gender, and race subgroups of patients showed that men and women, and patients over and under 65, had generally similar responses. Black patients, however, had notably smaller responses, generally less than 50% of the effect in whites, and with no detectable effect in two of the 3 studies where this could be assessed.

The effect of losartan is substantially present within one week but in some studies the maximal effect occurred in 3-6 weeks. In long-term follow-up studies (without placebo control) the effect of losartan appeared to be maintained for up to a year. There is no apparent rebound effect after abrupt withdrawal of losartan. There was essentially no change in average heart rate in losartan-treated patients in controlled trials.

INDICATIONS AND USAGE

COZAAR is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

In considering the use of COZAAR monotherapy, it should be noted that in controlled trials COZAAR had an effect on blood pressure that was less in black patients than in non-blacks, sometimes showing no effect at all, a finding similar to the small effect of angiotensin converting enzyme inhibitors in blacks.

CONTRAINDICATIONS

COZAAR is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS:

Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, COZAAR should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester.

Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of losartan potassium as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, losartan potassium should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Losartan potassium has been shown to produce adverse effects in rat fetuses and neonates, including decreased body weight, delayed physical and behavioral development, mortality and renal toxicity. These findings are attributed to drug exposure in late gestation and during lactation. With the exception of neonatal weight gain (which was affected at doses as low as 10 mg/kg/day), doses associated with these effects exceeded 20 mg/kg/day (approximately twice the maximum recommended human dose of 100 mg on a mg/m² basis). Significant levels of losartan and its active metabolite were shown to be present in rat fetal plasma and rat milk.

Hypotension-Patients on Diuretic Therapy

Patients receiving diuretic therapy or who are salt and volume depleted from other causes can be expected to have a greater antihypertensive effect from any dose of losartan. Therapy with COZAAR should be initiated at no greater than 25 mg in such patients and patients should be monitored for 4 to 6 hours after the first dose of COZAAR.

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. COZAAR would be expected to behave similarly. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increased in serum creatinine or BUN were observed in 20% of patients. There has been no known use of COZAAR in patients with unilateral or bilateral renal artery stenosis, but a similar effect should be anticipated.

PRECAUTIONS

General

In patients who are intravascularly volume-depleted (e.g., those treated with high-dose diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of COZAAR, or a lower starting dose should be used (see DOSAGE AND ADMINISTRATION).

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with impaired liver function (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY, Pharmacokinetics).

Information for Patients

Pregnancy. Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions

Compounds that have been studied in clinical pharmacokinetic trials include hydrochlorothiazide, digoxin, warfarin, cimetidine and phenobarbital. (See CLINICAL PHARMACOLOGY: Drug Interactions.) Significant inhibitors of cytochrome P4503A4 (ketoconazole, for example) have not been studied clinically but *in vitro* studies of ketoconazole, troleandomycin and gestodene have shown substantial inhibition of formation of the active metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Losartan potassium was not carcinogenic when administered at maximally tolerated dosages to rats and mice for 105 and 92 weeks, respectively. Female rats given the highest dose (270 mg/kg/day) had a slightly higher incidence of pancreatic acinar adenoma. The maximally tolerated dosages (270 mg/kg/day in rats, 200 mg/kg/day in mice) provided systemic exposures for losartan and its pharmacologically active metabolite that were approximately 110- and 90-times (rats) and 30- and 7-times (mice) the exposure of a 50 kg human given 100 mg per day.

Losartan potassium was negative in the microbial mutagenesis and V-79 mammalian cell mutagenesis assays and in the *in vitro* alkaline elution, and *in vitro* and *in vivo* chromosomal aberration assays. In addition, the active metabolite showed no evidence of genotoxicity in the microbial mutagenesis, *in vitro* alkaline elution, and *in vitro* chromosomal aberration assays.

Fertility and reproductive performance were not affected in studies with male rats given oral doses of losartan potassium up to approximately 150 mg/kg/day. Doses of 300/200 mg/kg/day in females resulted in significantly ($p \leq 0.05$) fewer corpora lutea/female,

implants/female and live fetuses/female. In the 100 mg/kg/day group there was a slight but significant effect on the number of corpora lutea/female. In nonpregnant rats dosed at 135 mg/kg/day for 7 days, systemic exposure (AUCs) for losartan and its active metabolite were approximately 66 and 26 times the exposure achieved in man at the maximum recommended human daily dosage (100 mg).

Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters).
See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers

It is not known whether losartan is excreted in human milk, but significant levels of losartan and its active metabolite were shown to be present in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Use in the Elderly

Of the total number of patients receiving COZAAR in controlled clinical studies, 391 patients (19%) were 65 years and over, while 37 patients (2%) were 75 years and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

COZAAR has been evaluated for safety in more than 2500 [UPDATE] patients treated for essential hypertension and ___ patients overall. ___ patients were treated for over 6 months and ___ for over one year. In general, treatment with COZAAR was well tolerated. The overall incidence of adverse experiences reported with COZAAR was similar to placebo. In controlled clinical trials, discontinuation of therapy due to clinical adverse experiences was required in 2.3 percent of patients, treated with COZAAR and 3.7% of patients given placebo. Although angioedema was not reported by name, one patient treated with COZAAR was withdrawn from study because of swelling of the lips and eyelids, which returned to normal 5 days after therapy was discontinued.

The following table of adverse events is based on four 6-12 week placebo controlled trials [011, 050, 065, 021] involving over 1000 patients on various doses (10-150 mg) of losartan and over 300 given placebo. All doses of losartan are grouped because none of the adverse events appeared to have a dose-related frequency. The table includes all adverse events, whether or not attributed to the treatment, occurring in at least 0.5% of losartan patients and that were numerically more frequent on losartan than placebo.

Event (by body system)	Losartan n=1075	Placebo n=334
Event 1		
Event 2		
Etc.		

The following adverse events occurred at $\geq 0.5\%$ but were at least as frequent on placebo: headache, asthenia/fatigue, etc.

Adverse events occurred at about the same rates in men and women, older and younger patients, and black and non-black patients.

Lab Findings:

Vital Signs:

In addition to the events in the table above, the following potentially important events were observed at least twice in the (total exposure) patients exposed to losartan in all studies. It cannot be determined whether these events were casually related to losartan.

[List by body system; omit if they are already in the table or in the paragraph that follows the table. Leave out anything not occurring at least twice, anything too vague (pain, thyroid disorder, arrhythmia) or very improbable (cancer early in treatment). Also include brief discussion of the single case of hemolytic anemia and exfoliation of the palms.]

OVERDOSAGE

Significant lethality was observed in mice and rats after oral administration of 1000 mg/kg and 2000 mg/kg, respectively, about 44 and 170 times the maximum recommended human dose on a mg/m² basis.

Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan nor its active metabolite can be removed by hemodialysis.

DOSAGE AND ADMINISTRATION

COZAAR can be administered once or twice daily with total daily doses ranging from 25 to 100 mg. The usual starting dose is between 25 and 50 mg once daily, with 25 mg preferred for patients with possible depletion of intravascular volume because of preceding diuretic therapy (see PRECAUTIONS, General) and patients with a history of hepatic impairment (see PRECAUTIONS, General). The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy.

If the antihypertensive effect measured at trough using once-a-day dosing is inadequate, a twice-a-day regimen may give a more satisfactory response.

HOW SUPPLIED

No. 3612 - Tablets COZAAR, 25 mg, are light green, teardrop-shaped, film-coated tablets with code MRK on one side and 951 on the other. They are supplied as follows:

- NDC 0006-0951-31 unit of use bottles of 30
- NDC 0006-0951-54 unit of use bottles of 90
- NDC 0006-0951-58 unit of use bottles of 100
- NDC 0006-0951-28 unit dose packages of 100
- NDC 0006-0951-82 bottles of 1000.

No. 3613 - Tablets COZAAR, 50 mg, are green, teardrop-shaped, film-coated tablets with code MRK on one side and 952 on the other. They are supplied as follows:

- NDC 0006-0952-31 unit of use bottles of 30
- NDC 0006-0952-54 unit of use bottles of 90
- NDC 0006-0952-58 unit of use bottles of 100
- NDC 0006-0952-28 unit dose packages of 100
- NDC 0006-0952-82 bottles of 1000.

Page 11 - COZAAR LABELING

Storage¹⁹⁰

Store at temperatures below 30°C (86°F). Keep container tightly closed. Protect from light

Manuf by:

MERCK & CO., INC., West Point, PA 19486, USA

by:

Wilmington, DE 19880, USA

Issued XXXXX

Printed in U.S.A.

** Based on a patient weight of 50 kg.

COZAAR (Losartan Potassium)

DIVISION
DIRECTOR
AND

OFFICE
DIRECTOR
MEMOS

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: MAR 2 1995

FROM: Director, Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: NDA 20-386, Cozaar (losartan potassium)

TO: Director, Office of Drug Evaluation I, HFD-100

We are returning losartan for final signature on the approvable letter. We have incorporated all revisions to the labeling noted on your marked-up draft and memorandum of February 27, 1995 and those discussed at our March 1, 1995 internal meeting into a clean draft.

The approvable letter contains Dr. Vincent's latest environmental assessment deficiencies.

The firm has been informed that some type of phase IV study regarding the effect of 3A4 inhibitors on the effectiveness of losartan may be forthcoming.

Raymond J. Lipicky, M.D.

cc

Orig.

HFD-110

HFD-110/GBuehler

sb/3/1/95

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: FEB 27 1995
FROM: Director, Office of Drug Evaluation I, HFD-100
SUBJECT: Losartan (Cozaar, NDA 20-386)
TO: Dr. Raymond Lipicky, HFD-110

Losartan clearly is an antihypertensive agent with an effect size, over the 50-100 mg range, that is typical of what we have seen with other agents (ACEI's, beta-blockers), net diastolic change of 4-8 mmHg, and 5-9 mmHg systolic. It was pretty similar to enalapril 10-20 where these were studied, although generally a little behind enalapril. Trough/peak rates were variable, 50-90%, showing some drop-off; it is therefore not too surprising that the b.i.d. regimens were better than the same dose o.d. and labeling should make that clear. There is little effect in blacks and it does not seem to be a good monotherapy candidate in blacks.

I have only a few issues to raise:

1. Cough

The "less-cough than ACEIs" is a critical claim and should be a replicated finding. Study 056 is reasonably convincing as far as cough goes but the pooled trials analysis (MOR p. 19) doesn't really show a significant difference (I would have accepted this approach as a second study, I believe). I also believe any comparison should have a valid estimate of antihypertensive effect size; that's important to define implications of any difference. For example, if cough is less but BP effect is also much less (as suggested by 056), then L could be important for people with intolerable cough but might not be a good first choice (or again, it might be if you were willing to add a second drug or switch if effect was inadequate).

2. Interactions/metabolism

It is important to see just what the effect of 3A4 inhibitors is on the effectiveness of losartan. Given 30 x potency of E3174 and at least 4 times greater half life (and steady state plasma peak concentration after 40 mg of 180 ng/ml E3174 vs 30 ng/ml parent), not forming E3174 could lead to lack of effect (just as codeine doesn't work in poor 2D6 metabolizers because they don't form morphine). This should at least be determined post-marketing. The cimetidine results probably give an adequate answer for weak 3A4 antagonists (erythromycin, grapefruit

juice), but not for the antifungals.

3. Trough/Peak

Systolic pressure should "count" too. For potentially pertinent doses, the following table gives these results:

Sup D. Syst/Diast T/P Ratio (%)					
	25	50	100 + Others	150	Enal 20
Study 111	35/23	66/60	44/72	54/49	61/47
Study 050	--	/78	(50-100 mg) /73	--	--
Study 065	84/85	73/87	25 b.i.d. 68/90		

I calculated systolic values from means given in the review. This gives somewhat different values from MOR calculations, which only use people with both peak and trough measurements (p. 42, 65 of MOR). Despite the somewhat better b.i.d. results in study 065, the trough/peak ratio is not really higher for the b.i.d., as one might have expected. All in all, these results are not so bad.

4. Biopharm

I am puzzled by the absolute bio figure of 30%. If I understand study 022, where the absolute bio of losartan was 23%, the absolute bio of E3174 was about 100%. That suggest to me that considerable E3174 is formed and absorbed in the gut.

Perhaps, however, I don't understand the calculations/normalization. This is how I reach the above conclusion. Figures given are:

	L		E 3174	
	100 mg Tablet	30 mg IV	100 mg Tablet	30 mg IV
Cmax	486.2	--	584	112.5
AUC	722.4	925.6	3561	1066

Cmax and AUC are said to be normalized to nominal doses of 100 mg and 30 mg but those were the doses given, so I don't follow this. If you take 30% of the L AUC (216.7), which is "normalizing" to a 30 mg dose, 216.7 is 23% of 925.6, the calculated absolute bioavailability. A similar

procedure for E3174 would give 30% of AUC (.3 x 3561) or 1068, which is almost identical to the AUC for the metabolite after IV, suggesting an absolute bioavailability of about 100%. As the bioavailability of L itself is considerably less than 100%, this would imply gut metabolism to E3174 and absorption of E 3174. What's wrong with what I did?

5. Labeling

I worked from the latest Division mark-up, noting some of Merck's proposals as well. Apart from what is obvious on the text:

- a. I presume the 2nd/3rd trimester warning is to be boxed.
- b. Pharmacokinetics needs a short introduction. How's this:

Pharmacokinetics

Losartan is an orally active agent that undergoes substantial first pass metabolism by cytochrome P-450 enzymes. It is converted, in part, to an active carboxylic acid metabolite that is responsible for most of the angiotensin II receptor antagonism that follows losartan treatment. The terminal half life of losartan is about 1-2 hours and of the metabolite is about 6-9 hours. The pharmacokinetics of losartan and its metabolite are generally dose-proportional and constant over time and neither the drug nor its metabolite accumulate on replicated dosing.

- c. Labeling says that E-3417 is, by binding studies, 20-40 x as potent as L (p. 2, paragraph 2) and 5-10 x as potent (p. 2, paragraph 6). We will need to decide.
- d. I have substantially rewritten PK. The ADME format is not very useful (it caused you to omit the half-life, for example) and forces inclusion of lots of not too helpful stuff. See what you think.
- e. I have a suggested revision of the clinical Studies section.

The antihypertensive effects of COZAAR were demonstrated principally in 4 placebo-controlled 6-12 week trials of dosages from 10 to 150 mg per day in patients with baseline diastolic blood pressures of 95-115. The studies allowed comparisons of two doses (50 and 100 mg) as once daily or twice daily regimens, comparisons of peak and trough effects, and comparisons of response by gender, age, and race. _____ studies examined the interaction of losartan and diuretic.

The 4 studies of losartan monotherapy included a total of 1075 patients randomized to several doses of losartan and 334 to placebo. The 10 and 25 mg doses produced some effect at peak (6 hours after dosing) but small and inconsistent trough (24 hour) responses. Doses of 50, 100, and 150 mg once daily gave decreases in blood pressure, compared to placebo, of 5-9.5/4-6 mmHg, with the 150 mg dose giving no greater effect than 50-100 mg. Twice daily dosing at 50-100 mg/day gave consistently larger trough responses, 8.5-9.5/6-6.3 mmHg, than once daily dosing at the same total dose. Peak (6 hour) effects were uniformly larger than trough effects, with the trough to peak ratio for systolic and diastolic responses 45-70% and 60-90%, respectively, [I have omitted the blood pressure comparison data for the present. I would consider putting in the comparative data, but probably if any goes in, at all goes in, as you have done in the draft, although it would be possible to include only the enalapril comparison, which is probably best studied. Most of the other studies are really too small to merit inclusion.]

[Describe, briefly, the losartan/HCTZ data]

Analysis of age, gender, and race subgroups of patients showed that men and women, and patients over and under 65, had generally similar responses. Black patients, however, had notably smaller responses, generally less than 50% of the effect in whites, and with no detectable effect in two of the 3 studies where this could be assessed.

The effect of losartan is substantially present within one week but in some studies the maximal effect occurred in 3-6 weeks. In long-term follow-up studies (without placebo control) the effect of losartan appeared to be maintained for up to a year. There is no apparent rebound effect after abrupt withdrawal of losartan. The average change in heart rate in controlled trials was _____.

- f. Is the warning on Impaired Renal Function based on losartan data or carried over from ACEI's? If the latter, it should say so; I've assumed this was the case and changed it.
- g. The effects of major 3A4 inhibitors should be studied. You would expect little or no active metabolite and increased losartan parent in the presence of, say, ketoconazole.
- h. Adverse reactions (version, starting on p. 9)

The following table of adverse events is based on four 6-12

week placebo controlled trials [011, 050, 065, 021] involving over 1000 patients on various doses (10-150 mg) of losartan and over 300 given placebo (this is similar to Dr. Ganley's table on p. 13, but I see no reason not to include study 021 also). All doses of losartan are grouped because none of the adverse events appeared to have a dose-related frequency. The table includes all adverse events, whether or not attributed to the treatment, occurring in at least 0.5% of losartan patients and that were numerically more frequent on losartan than placebo.

Event (by body system)	Losartan n=1075	Placebo n=334
Event 1		
Event 2		
Etc.		

The following adverse events occurred at $\geq 0.5\%$ but were at least as frequent on placebo: headache, asthenia/fatigue, etc.

Adverse events occurred at about the same rates in men and women, older and younger patients, and black and non-black patients.

Lab findings:

Vital Signs:

In addition to the events in the table above, the following potentially important events were observed at least twice in the (total exposure) patients exposed to losartan in all studies. It cannot be determined whether these events were causally related to losartan.

[List by body system; omit if they are already in the table or in the paragraph that follows the table. Leave out anything not occurring at least twice, anything too vague (pain, thyroid disorder, arrhythmia) or very improbable (cancer early in treatment).]



Robert Temple, M.D.

Bongiovanni

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION **Public Health Service**
Division of Cardio-Renal Drug Products

Memorandum

DATE : ~~MAR 2 1995~~ Feb 15, 1995

FROM : Director, Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: Approval (approvable) of NDA 20-386, Cozaar (losartan potassium) Tablets,
Merck Research Laboratories

TO : Director, Office of Drug Evaluation I, HFD-100

Introduction

Losartan is the first of a new class of angiotensin receptor blockers that has been developed, initially for use as an antihypertensive therapy. The NDA, in addition to acute and chronic animal toxicology, manufacturing and controls, environmental assessment and patient information, contained the results of 26 clinical pharmacology studies, 5 active-control trials, 9 open-label studies, 2 studies in patients with congestive heart failure and 6 placebo-controlled trials of up to 12 weeks in duration. The initial submission contained data obtained from 3628 losartan-treated patients and periodic safety updates have increased that number to a final (as of 6/30/94) number to a total of 4,753 losartan-treated patients. This is among the largest data bases I have seen (if not the largest) from the point of view of total exposure and contains a wealth of information.

In addition to the many controlled trials of as long as three months duration, the dose of losartan was varied over a 15-fold range (10 to 150 mg), it was studied in both once-a-day and twice-a-day regimens, and black and white patients in 2 trials were stratified by race so a clean analysis of effect by race could be performed. There was even one trial where not only was there stratification by race but also by severity of hypertension. There is no question that losartan is an antihypertensive drug. It is antihypertensive in both once-a-day and twice-a-day regimens, its safety profile is as reasonable as any we have seen and all-in-all, it is not a very interesting matter. Consequently, even though this is a new chemical entity, considering the work load of the Cardio-Renal Drugs Advisory Committee and the timing of its regular meetings, in order to meet user fee deadlines and conform to project management goals, I have elected not to take this to the Advisory Committee. There are more important issues for them to devote their time to.

The reviews in the attached documentation are complete, are comprehensive and well written. Therefore, in this transmittal memorandum (and secondary review) I will only touch upon highlights and can offer no new insights.

Major Placebo Controlled Trials

All of the placebo-controlled trials were randomized, parallel-group, double-blind trials where casual cuff blood pressure (except for the ABPM trial; study 021) was the principal measurement. Blood pressure was measured at trough (before the next dose was taken) and sometimes at peak (e.g., sometime arbitrarily defined) also. The crude features are summarized in the following table. The Number of Patients column is listed as Number of Patients Randomized/Number of patients completing the trial.

<u>Trial Number</u>	<u>Duration</u>	<u>Number Patients</u>	<u>Major Endpoints</u>	<u>Special Features</u>
005	5 days	100/96	Diastolic Blood Pressure	Withdrawal Blood Pressures, All White
011	8 Weeks	576/521	10,25, 50, 100, 150, Enal	Stratified on basis of race
050	12 Weeks	366/322	50, 50 to 100	Peak and Trough, Race Stratified
065	12 Weeks	428/365	bid vs qd	Stratified by race
021	6 Weeks	122/91	bid vs qd	ABPM

The overall results, trough blood pressures, as a function of dose are shown in Figures 1 and 2 (attached). The lines connecting the points connect results obtained within the same trial.

All decreases in diastolic or systolic blood pressure were statistically significantly different from placebo (p values ranging from 0.024 to <0.001) except for the 25 mg, once-a-day dose in study 011 for either systolic or diastolic blood pressure. It is reasonably clear that the trough blood pressure response is a function of dose, that for a given dose (e.g., 25 or 50 mg) the response to bid is greater than qd (even though within each individual trial there was no statistically significant difference between qd and bid (with reasonable sample sizes, about 30 for study 021 and about 80 for study 065), and that both systolic and diastolic blood pressures are affected by treatment.

The shape of the curve that relates change of trough blood pressure to dose is not so clear. If one considers only the results of study 011, a 7-arm, parallel-group trial (placebo and 5 doses losartan (and enalapril, not shown)), the plateau occurs between 50 and 100 mg, when administered once-a-day. Study 021, also a parallel-group trial, shows that there is still a dose response going from 50 to 100 mg once-a-day. Although study 050 did not show an increasing effect going from 50 to 100 mg, the group that went from 50 to 100 mg got to 100 by titration if 50 did not change blood pressure. In sum, it appears to me that the apparent plateau from 50 onward is only apparent and not real. Indeed the logistic model (Figure 3 of Dr. Nuri's review) appears to give the best fit and would predict that the next increment in dose that would produce a clearly differentiable effect would be in the range of several hundred mg, so this is another example where varying the dose by 50% (e.g., 100 to 150 mg) is not very useful. Retrospectively, doses that should have delineated the shape of the dose-response curve would have been 5, 15, 50, 150 and 500 mg.

The effect of losartan in blacks and whites is clearly described by the results. Blacks and whites were stratified, so one can take these results as pretty definitive and not just tentative or suggestive. The dose response for these two populations are shown in Figure 3 (attached).

It is clear that over the entire range of doses studied, blacks have less of a response to losartan than do whites. Bid dosing in whites sticks out rather prominently with respect to its greater effect on trough, diastolic blood pressure in whites and less clearly in blacks.

Other demographic features, such as age or sex (each being analyzed for each study) showed less obvious differences in response, although patients over the age of 65 appear to have a little less of an effect. None of the differences observed as a function of age or sex are as consistent, as obvious nor as great as the black/white difference observed. The best summary of these data are found on pages 4 through 6 in Dr. Ganley's review.

Some Pharmacology and Clinical Pharmacology

General. Losartan (MK-954, DuP 753) is an angiotensin II receptor blocking agent (about 10,000 more

selective for AT₁ angiotensin receptors than for AT₂ angiotensin receptors). Judging from experiments in pithed rats, isolated aortic strips, and receptor binding techniques, its mechanism of action is that of competitive antagonism. In receptor binding studies the IC₅₀ was about 20 nanoMolar. Of passing note is that it inhibits platelet aggregation at concentration of 40 microMolar (2000 times that of the IC₅₀ for the AT₁ receptor).

An active metabolite (E-3174, L 158,641, EXP3174, a carboxylic acid metabolite, formed via an oxidative pathway) is known to be formed, presumably in the liver (at least human liver slices produce it, in both animals and man; P450, CYP2C9 AND CYP3A4). E-3174, in contrast to losartan, shows features of non-competitive antagonism (non-parallel shifts in dose-response curves in the same animal systems that losartan shifts in parallel fashion) and is about 30 times as potent as losartan. About 14% of administered losartan is converted to the E-3174 metabolite, so most of the effect comes from E-3174.

There were 29 studies that described various aspects of the clinical pharmacology of losartan. The absolute bioavailability of losartan is about 30% (estimates range from 22.9 to 32.6%); C_{Max}, AUC, etc. are dose proportional over a range of 10 to 300 mg administered orally, reach peak concentrations about 1 hour after dosing; it has a volume of distribution of about 47 Liters and shows a plasma half-life of about between 1 and 2 hours. Less than 4% of an administered dose, in man, is recovered in the urine. Not surprisingly, the pharmacokinetic constants which describe losartan are unaffected by renal insufficiency, except for AUC.

The absolute bioavailability of E-3174 has not been determined; following oral administration of losartan C_{Max}, AUC, etc. of E-3174 are dose proportional over a range of 10 to 300 mg losartan administered orally, reach a peak 3 to 4 hours after administration; it has a volume of distribution of about 16 Liters and has a plasma half-life of 6 to 9 hours. About 50% of an intravenously administered dose is recovered in the urine. The pharmacokinetic description of E-3174 seems to change as function of renal disease, as shown in Figure 4 (attached).

The study (012) that defined effects of renal disease was not large and the variability was great so this is not well defined, but it seems reasonable to conclude that losartan is little affected and that E-3174 has a longer half-life as the creatine clearance decreases. Overall not much happens.

The effects of food and hepatic disease.

Food delays and decreases the absorption of losartan. The production of the E-3174 metabolite is also delayed and very slightly decreased. Since the metabolite is the major player, the effect of food is not very important.

Hepatic insufficiency increases the absolute bioavailability of losartan from about 33% to about 65% with AUC and C_{Max} increasing about 5 fold, decreases its clearance (without much change in t_{1/2}) because a smaller volume of distribution is apparently also present (n=9 Protocol 067). Although the formation of E-3174 is also affected, it is not affected much. It is difficult to know what one would predict, but I predict very little change in effect as a function of hepatic disease.

Time course of drug action and interval between dose. The time course of drug action appears longer than a few hours, which is all it should be if losartan were the molecule responsible for its principal antihypertensive effects (a competitive, reversible antagonist with a half-life of a couple of hours). So, E-3174 must be important to the antihypertensive effects in man and animals. E-3174 is complicated in that it appears to be a non-competitive antagonist and its reversibility has not been well characterized. Prediction of the effects of orally administered losartan seems difficult, based upon the description of basic properties of either losartan or E-3174.

Protocol 069 (a placebo-controlled, 4-hour IV infusion of E-3174) did a reasonable job of characterizing the relationship between plasma concentration and antihypertensive effect. That relationship is shown in the accompanying Figure labelled Protocol 069 (Figure 5). There is a very broad, clock-wise hysteresis. Peak antihypertensive effects occurred about 3 hours after peak plasma concentrations.

It is clear that neither losartan nor E-3174 have agonist or partial agonist properties; these have been carefully looked for in man and animals and do not appear to be present. It is also clear that upon discontinuing losartan after weeks of therapy, the antihypertensive effect decreases over the course of a day or so.

Dosing regimens of once-a-day (studies 005, 011 and 050) as well as once-a-day and twice-a-day (studies 065 and 0210) show a larger effect on trough blood pressure for the bid regimens (when analyzed for all patients by intent-to-treat or completers, or when looked at for black patients or white patients), partially depicted in the figures of dose-response (Figures A and B). Additionally, although there is no formal analysis (only graphs to look at, pages 72 and 73 of Dr. Ganley's review), I see two humps in the bid regimen (each at its peak at about the number 1 on the time axis) and cannot see anything like that in the once-a-day regimens. So, although once-a-day regimens clearly are superior to placebo at trough, have reasonable peak/trough ratios and exhibit dose-response, twice-a-day administration is a superior regimen. Labelling should indicate that once or twice-a-day regimens are acceptable but that, before adding other drugs, twice-a-day should be tried.

Safety

General.

Overall, the 5 placebo-controlled trials randomized 1592 patients and 1395 (88%) completed the trials (the bulk of which were 8 to 12 weeks duration). Of the 1592 randomized patients, 357 were randomized to placebo, so 1235 were randomized to losartan. Drop outs due to adverse effects were (number dropped and in parentheses the %) 7 (1.96%), 1 (0.53%), 3 (0.83%), 8 (3.07%), 3 (2.88%), 3 (2.88%) and 1 (3.2%) in the placebo, 10, 25, 50, 100, 150 mg qd and 25, 50 mg bid groups, respectively. The pattern of adverse effects (incidence of any adverse event) were similarly relatively evenly distributed involving 54.06%, 47.50%, 52.63%, 47.51%, 54.81%, 56.60% and 45.16% in the placebo, 10, 25, 50, 100 150 mg qd and 25 and 50 mg bid groups, respectively. There were no overall statistically significant differences between placebo and any of the randomized losartan groups with respect to drop-outs nor to overall incidence of any side effect. After review of tables constructed by Dr. Ganley and by the sponsor (in their integrated summary of safety and efficacy), I cannot tell what side effects are drug related (meaning, highly likely to be due to losartan) and which are not.

Of note in the lists (pages 211-216 of Dr. Ganley's review) are, alphabetically, burning/stinging of the eye (0.3%, placebo = 0.0%), congestion, nasal (2.0%, placebo = 1.3%), congestion, pulmonary (0.2%, placebo = 0.0%), congestion, respiratory (0.65, placebo = 0.7%), conjunctivitis (0.1%, placebo = 0.0%), edema eyelid (0.1%, placebo = 0.0%), edema, facial (0.1%, placebo = 0.0%), inflammation, eyelid (0.2%, placebo = 0.3%), laryngitis (0.2%, placebo = 0.3%), obstruction, airway, upper (0.1%, placebo = 0.0%), pharyngitis (1.8%, placebo = 3.0%), urticaria (0.2%, placebo = 0.7%), wheezing (0.1%, placebo = 0.0%). The word angioedema appears not once anywhere I have looked. It is hard to make a case for any of the immediately preceding being angioedema but not diagnosed. It is also hard to make the case for edema, facial, edema, eyelid not being angioedema by another name. General concept has angioedema and bradykininase inhibition by ACE inhibitors going hand in hand. So an angiotensin receptor blocker that has no bradykininase inhibition properties should not cause angioedema. One patient was withdrawn from a study because of swelling of the lips and eyelids (which were gone 2 days after losartan was withdrawn). I am not sure that angioedema was not observed, am not sure that it was and do not know what action to take. I suggest that the labelling make the assertion that swelling of the lips, face and

eyelids, reversible upon discontinuation of losartan have been reported, and were a cause of one study withdrawal, but that the diagnosis of angioedema has not been reported.

As a consequence of angiotensin blockade (AT₁), circulating plasma renin activity increases and angiotensin II increases (both, about an order of magnitude and their increase is dose-related) and aldosterone decreases or remains normal. Plasma ACE activity is unchanged. Losartan appears to be uricosuric, for unknown reasons. This phenomenon had no clinical consequences recognized.

Alkaline phosphatase, AST and ALT elevations were sporadically reported more often (not statistically significantly) for losartan treated patients than for those receiving placebo. One of these patients had a proven viral hepatitis. Tracking down those patients that had both AST and ALT elevations (not one alone) led to no obvious hepatic injury being present (some had sporadic elevations, some had elevations persist long after drug was withdrawn, etc.). Red cells in the urine (hematuria, measured several different ways) similarly did not lead to finding cases where it appeared that losartan had induced any renal disease.

Cough. As a consequence of mechanism of action, like angioedema, one would not expect cough to be a part of losartan's effects. We specified that such a claim would require 2 studies that clearly demonstrated the lack of cough as a side effect. The current application contains the results of one study (protocol 056, page 156 of Dr. Ganley's review), the second study is in progress. Protocol 056 recruited patients who had ACE type cough while being treated with 20 mg lisinopril, orally, once-a-day. The study was well designed and found a greater incidence of cough ($p < 0.01$) in patients randomized to lisinopril than in patients randomized to losartan or HCTZ. Although it is reasonably clear that losartan and lisinopril are distinguishable with respect to the incidence of cough, almost 30% of patients receiving losartan redeveloped cough after losartan was started (having been cough free on placebo) and the blood pressure reduction produced by lisinopril was greater than that produced by losartan (so the two therapies were not at equieffective doses). This single study should not be considered sufficient to allow a claim of "no cough" associated with losartan therapy.

Renal Cell Carcinoma.

In the entire data-base (this NDA and the Losartan/HCTZ NDA), including open-label follow-on long term use, there were 6 cases of renal cell carcinoma observed, occurring in patients receiving losartan (2 others were observed in patients receiving control agents; 1 placebo and 1 captopril/HCTZ). At the time of NDA filing (see table SS.9, page 20 of Dr. Ganley's review), only one patient with renal cell carcinoma was reported; the remaining 5 on losartan or losartan/HCTZ (2 losartan alone, 3 losartan/HCTZ, 1 losartan/HCTZ/felodipine) became known during the review as a consequence of Merck's careful follow-up and reporting system; because documents were submitted during the course of review (and our review documents were restricted to the time period of documents as they were submitted), numbers of cases vary depending upon where one looks. At the time of constructing table SS.9 there were 12 other malignancies reported in addition to the one renal cell carcinoma. Of the 13 reported malignancies, one (intestinal) was observed while the patient was receiving placebo. Of the 12 patients receiving losartan, one was receiving HCTZ, losartan and felodipine, and 6 were receiving HCTZ and losartan. So, there were 5 patients receiving losartan alone.

I do not think the incidence of renal cell carcinoma would have been noticed at all during the course of our review, except that very early in the development of losartan an investigator (Dr. Remuzzi, independent of Merck, to whom Merck had supplied losartan) reported that rats treated with streptozotocin appeared to have a high incidence of grossly detected renal cell tumors. This finding suggested that losartan might act as a tumor promoter (streptozotocin is a known tumorigen) and therefore the index of suspicion (on our part) was very high.

It is clear (see reviews by Drs. Jagadeesh and Proakis, our Pharmacology reviewers; Dr. Fahman, our

statistical consultant, and the Carcinogenicity Assessment Committee meeting minutes) that there is no reasonable suggestion of carcinogenicity (other than pancreatic acinar adenoma in female rats, 3/75 in the high dose group vs 0/75 to 0/130 in each of the other 3 groups) in standard mouse and rat assays that were adequately designed, implemented and analyzed, nor any suggestion of mutagenicity in standard tests. Thus, in standard testing systems, losartan would not be regarded as a tumorigen (although including the pancreatic acinar adenoma in female rats will be included in labelling to conform to the wishes of the Carcinogenicity Assessment Committee, I do not regard that finding as a signal).

Moreover, at the suggestion of the Division, Merck undertook an extensive battery of animal tumorigenicity testing (in addition to the standard assays) in an attempt to evaluate the tumor promoter suggestion of the Remuzzi study. In short, the original observation could not be repeated and extensive tests (well beyond that conducted by Dr. Remuzzi; this effort was subject to a laboratory field inspection that Dr. Proakis participated in) failed to suggest any tumor promoting potential of losartan. It is worth noting that evaluating the notion of evaluating tumor promotion is not something that anyone requires of any drug. We suggested doing it because of the original Remuzzi observations. The results of the Merck extensive laboratory evaluation were not known until December, 1994. Thus, the clinical cases of renal cell carcinoma and the Remuzzi study were heavy influences on degree of suspicion.

As it turns out, with respect to the clinical data (see review by Dr. Burkhart, our epidemiology consultant), there are 4 things one may regard as fact. The incidence of renal cell carcinoma in a hypertensive patient population is greater than that in a non-hypertensive population. The incidence of renal cell carcinoma in the patient population studied in NDAs 20-386 and 20-387 and receiving losartan is greater than any incidence reported in the literature in hypertensive patients. The relative risk for developing renal cell carcinoma estimated from the losartan data-base and the relative risk for developing renal cell carcinoma in hypertensive patients receiving enalapril or lisinopril (the latter data coming from the Merck who have a sophisticated follow-up and data reporting system) are not differentiable and the point estimates are similar. The relative risk for developing renal cell carcinoma in patients with congestive heart failure taking enalapril (data also from the same data collection and reporting system) does not even suggest that enalapril alters the risk of development of renal cell carcinoma in a congestive heart failure population. In sum, there is no theoretical (or empirical human, animal or *in-vitro*) data that are persuasive and require the conclusion that losartan is tumorigenic or a tumor promoter. Although its use was associated with a high incidence of renal cell carcinoma, the observations must be considered to be a function of the increased incidence of such tumors in patients who have hypertension and the more competent than usual Merck system of data collection and reporting. The data do not support a conclusion that losartan is related to renal cell carcinoma.

Dr. Knudsen in his review (dated 12/20/94), of NDA 20-387 (losartan/HCTZ) reaches another conclusion. Unfortunately, as a consequence of lack of communication within the Division, Dr. Knudsen apparently was unaware of the Division's activities regarding this matter and formulated a different point of view. In his review, he rejects the rationale of the immediately preceding paragraph. He thinks the only fact that matters is that the high incidence of renal cell carcinoma in the patient population studied in NDAs 20-386 and 20-387. I, and all other reviewers of this matter disagree with his reasoning.

Rat and Rabbit Reproduction

In the attached review package is a letter that the Division sent to each angiotensin receptor blocking agent developers, stating that the angiotensin converting enzyme Inhibitor class labelling for pregnancy would be needed unless that animal reproduction studies differentiated angiotensin receptor blocking agents from angiotensin converting enzyme inhibitors in this regard. Since there is no current animal model for the effects of ACE inhibitors on the human fetus during the late stages of pregnancy and since the submitted animal studies showed fetal harm from administration of losartan to pregnant animals, the ACE inhibitor warning should appear. There is no way of knowing that the effects of losartan would be the

same as ACE inhibitors in pregnant humans, but it is reasonable to assume that the known deleterious effects in pregnant women are mediated through interference with the renin-angiotensin system and that losartan does interfere with the renin-angiotensin system. The warning is avoid empirical confirmation of the suspicion that losartan would produce the same effects.

Summary

It is clear that losartan lowers blood pressure over the dose ranges studied and that its use is relatively side-effect free. Consequently, losartan is approvable. Although one can argue that the doses studied show that increasing dose beyond 100 mg is of no value, the argument rests heavily upon not differentiating between doses of 100 and 150 mg (there were only 129 patients who received doses of 150 mg for 30 days or longer; table D-69, page D157 of Merck's 5/6/94 submission of clinical efficacy and safety summary, volume 1.101). I do not regard that as a very adequate argument (although it has sufficed in the past) particularly since there is no evidence that increasing dose is limited by the occurrence of dose-dependent side effects.

The antihypertensive effect of 50 mg of losartan was compared to that of 5 mg of felodipine ER, 20 mg of enalapril, 20 of lisinopril, 50 mg of captopril, and to HCTZ, all being administered once -a-day, in controlled trials. The antihypertensive effect of 50 mg of losartan was greater than that of 50 mg of captopril given once-a-day (the usual dose, in the treatment of hypertension, being 50 mg tid) and also greater than that of 12.5 mg HCTZ. Otherwise, the other comparators produced diastolic blood pressure effect 2 to 3 mm Hg greater than that seen with losartan (always not statistically significantly less; but reproducibly less). So, it is not clear to me whether an angiotensin receptor blocking agent is inherently less effective or the dosing has not been well enough worked out. In any event, although clearly able to lower blood pressure (in those with mild hypertension or those with severe hypertension; two protocols clearly show that), the performance of losartan does not appear to be as good as that able to be produced by other agents.



Raymond J. Lipicky, M.D.

cc:
NDA 20-386
HFD-110
HFD-110/CGanley/CResnick/AProakis/GJagadeesh
HFD-426/AParekh/EFadiran
HFD-713/GChi/WNuri
HFD-111/KBongiovanni

Table 2, Dr. Nuri' s statistical review

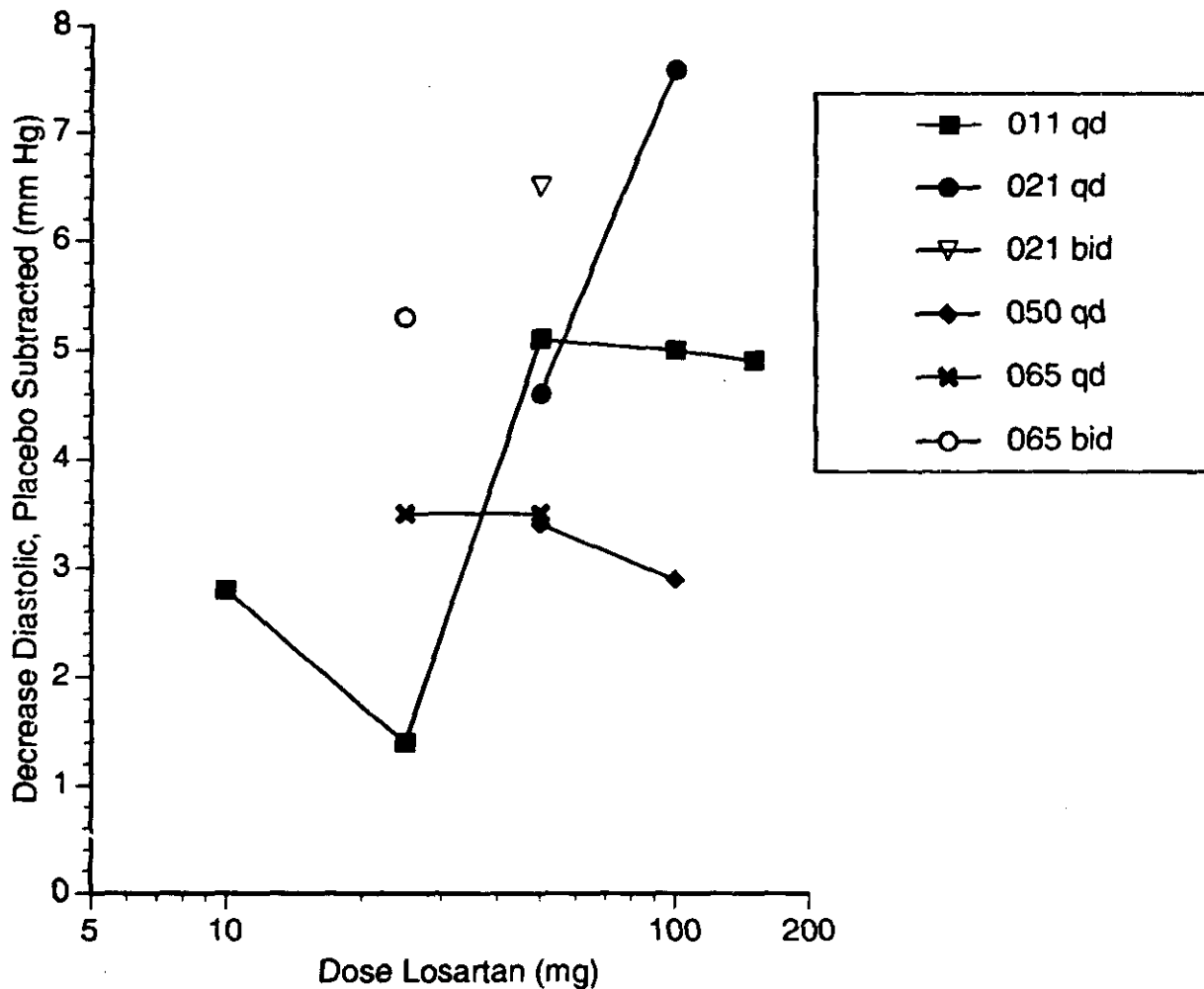


FIGURE 1. Losartan, trough, diastolic blood pressure, all placebo controlled trials.

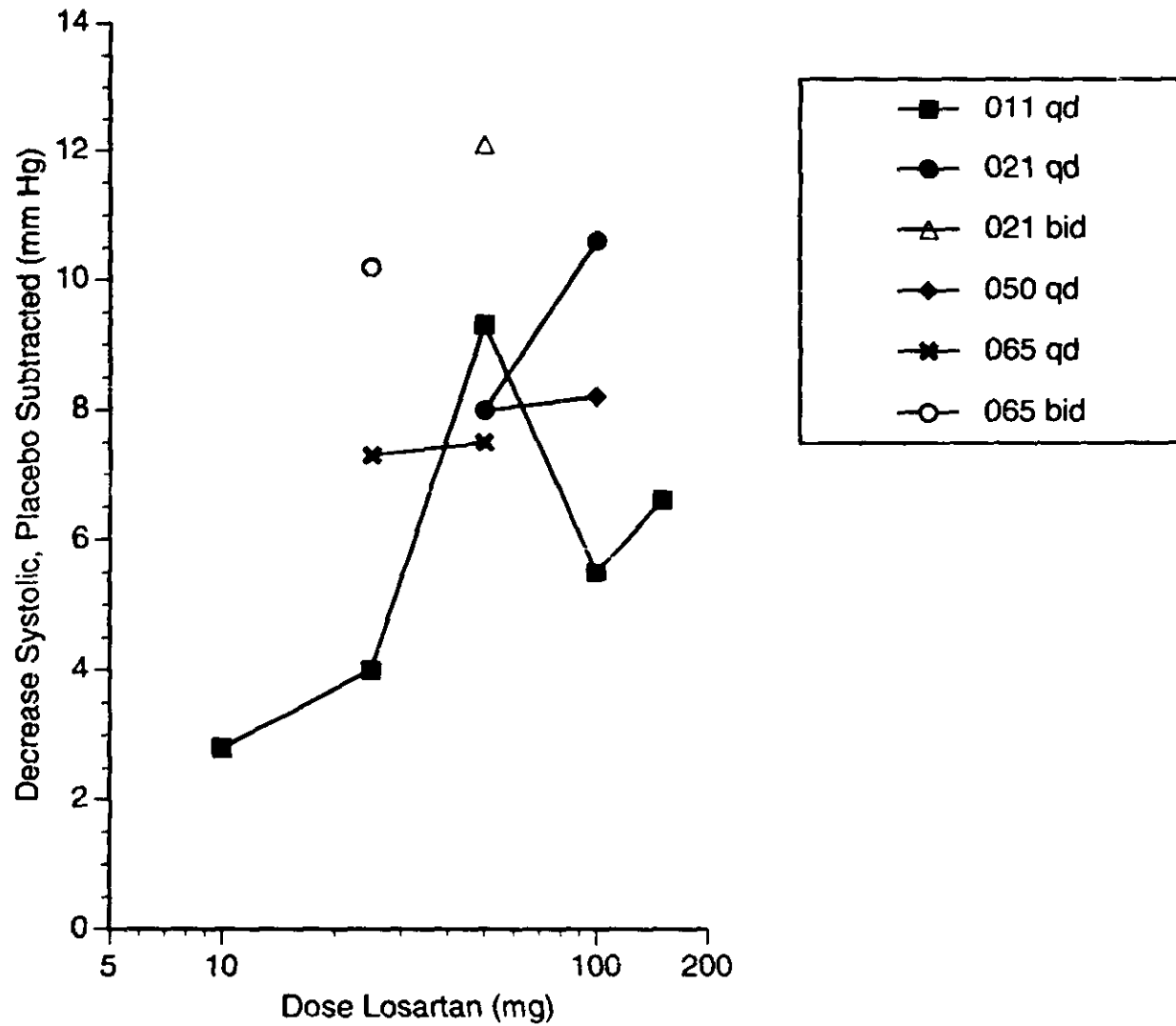


FIGURE 2. Losartan, trough, systolic blood pressure, all placebo controlled trials.

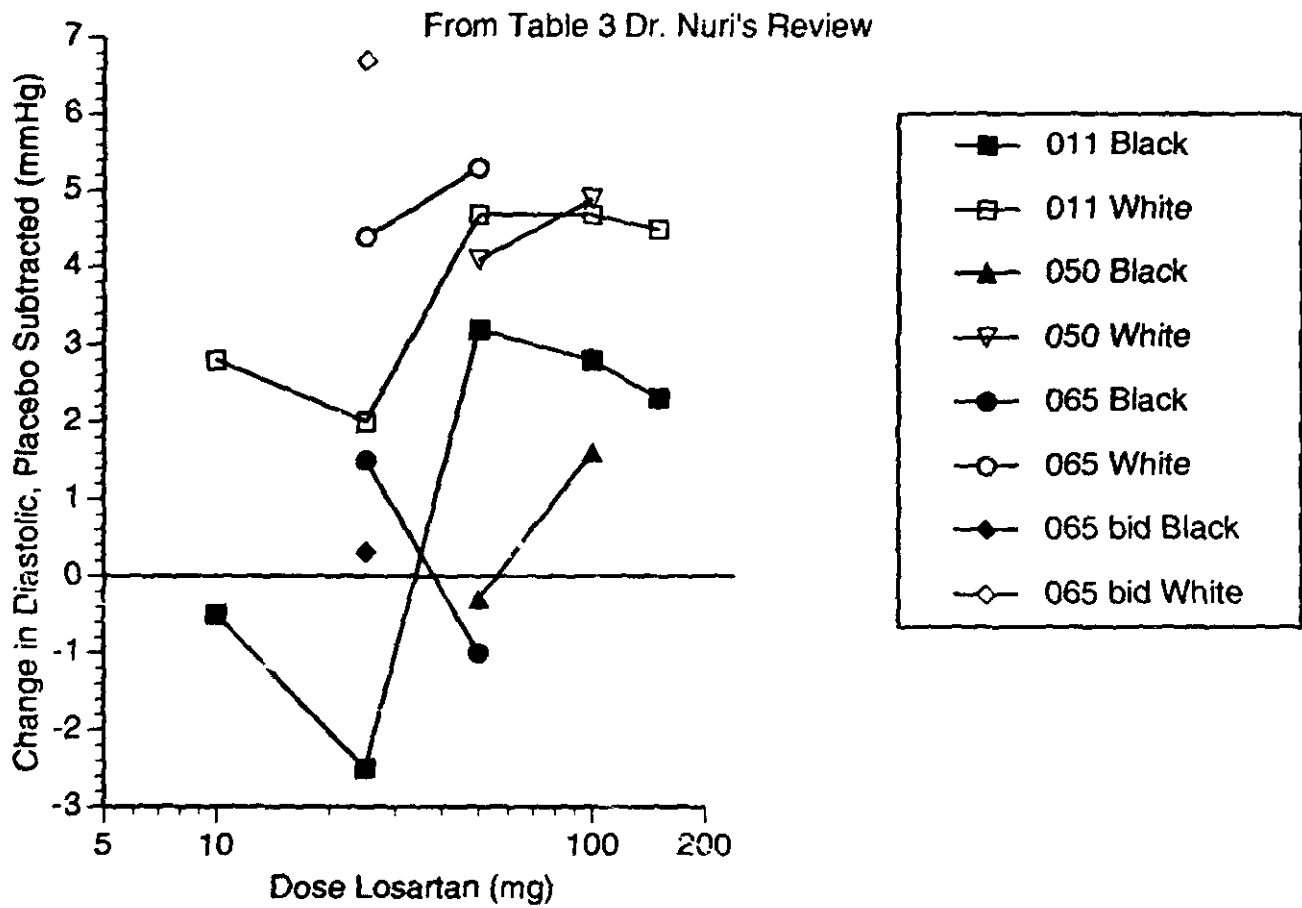


FIGURE 3. Losartan, trough, diastolic blood pressure, all placebo controlled trials. Comparison of race (black and non-black patient's response).

From Table 12.4, Page 138, Dr. Ganley's Review

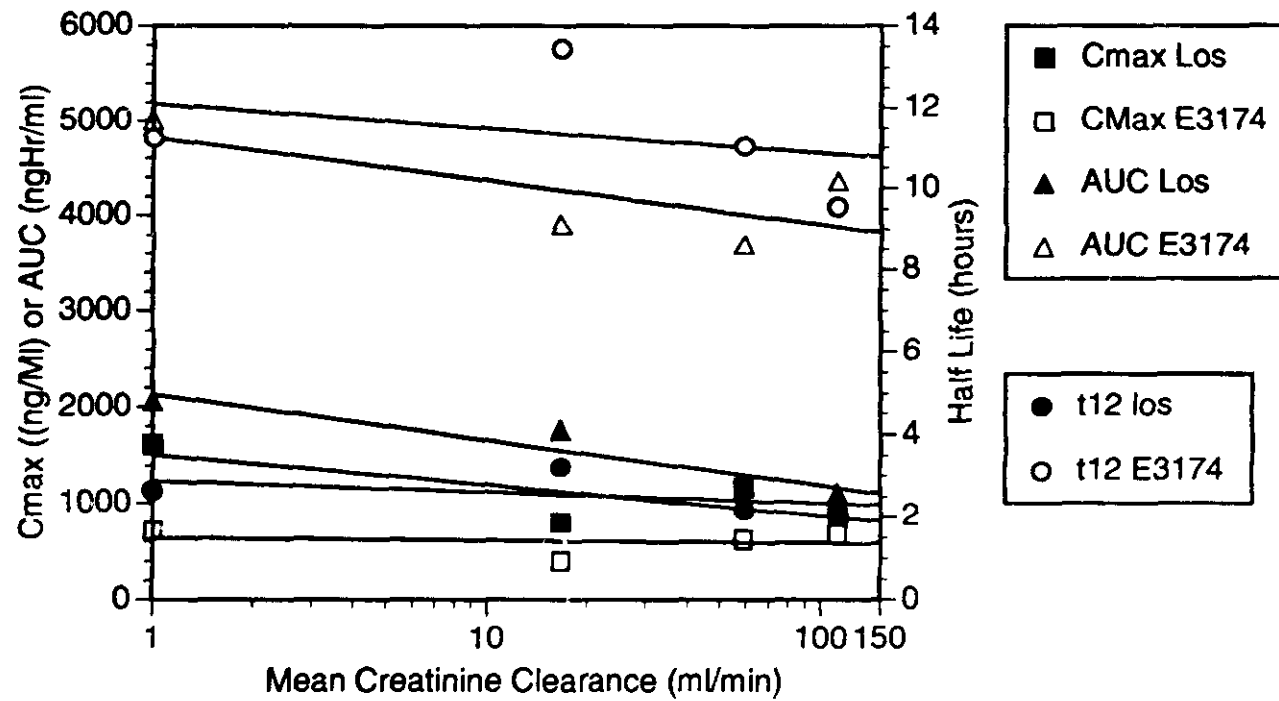


FIGURE 4. Summary of the effects of renal disease on the pharmacokinetic parameters of losartan (los) and its major, active, metabolite (E-3174). t1/2 = the plasma half-life.

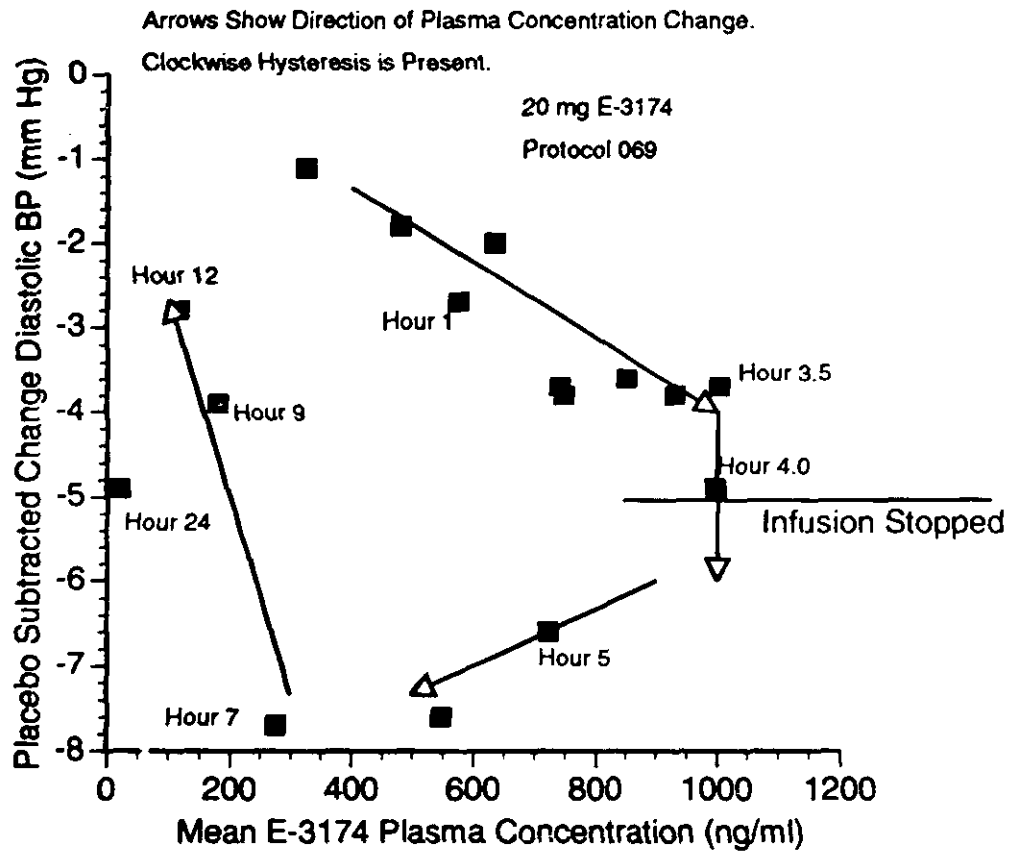


FIGURE 5. E-3174, plasma concentration-effect description.

MOR

Bangladesh

APR 12 1995

MEDICAL OFFICER REVIEW

NDA #: 20-386/
NDA Volume:
DRUG NAME: losartan
SPONSOR: Merck
TYPE OF DOCUMENT: Response to FDA approval letter
DATE RECEIVED:
DATE REVIEW COMPLETED: 3/30/95
MEDICAL OFFICER: Charles J. Ganley, M.D.

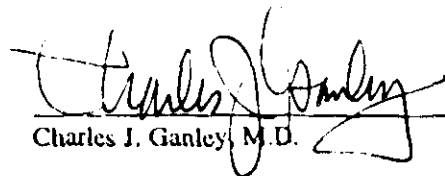
Merck's response to proposed labeling is included in this submission along with explanations of changes. There are only three issues that require comment.

1) Changes in labeling will be finalized by Dr. Temple and will not be included in this review. Documentation of changes are included in the division and cso file.

2) The losartan-warfarin issue is not resolved. Chronic Prothrombin Times (PT) for patients on warfarin/losartan from study 68 are included. It is difficult to make any comment from this data since the PT increase in some, decreases in others and remains unchanged in others. The major question is can losartan cause displacement of warfarin from protein binding sites leading to an increased PT and increased risk of bleeding. The sponsor has not adequately ruled out this possibility. [NOTE: Merck performed a norfloxacin-warfarin interaction study similar in design to the losartan-warfarin interaction study performed in the NDA. The norfloxacin-warfarin interaction study claimed there was no pharmacokinetic and pharmacodynamic interaction. There are reports, however, that link norfloxacin to an increase in PT in patients on warfarin. The American Hospital Formulary states that this interaction may be due to warfarin displacement from protein caused by norfloxacin. Could this happen with losartan?]

3) The sponsor does not feel that losartan will cause a syndrome of renal dysfunction, flank pain and hematuria as described with suprofen and ticrynafen. They base this opinion on the following:

- a) losartan does not adversely affect, GFR, renal blood flow or prostaglandin synthesis;
- b) it is not clear that uricosuria is a contributing factor;
- c) losartan is not structurally similar to suprofen or ticrynafen; and
- d) the syndrome was not reported in the losartan database (which is quite extensive).


Charles J. Ganley, M.D.

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HFD-110 / CSO / C. GANLEY / S.CHEN

Larry P. Bell, M.D.
Director
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March 14, 1995

Raymond J. Lipicky, M.D., Director
Division of Cardio-Renal Drug Products
HFD-110, Room 16B-45
Office of Drug Evaluation I (CDER)
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

Dear Dr. Lipicky:

NDA 20-386: Tablets COZAAR (Losartan Potassium)

Reference is made to the above New Drug Application submitted on December 3, 1993, an approvable letter dated March 2, 1995 from the FDA, which contained the Agency's comments on the submitted draft labeling, additional requested information on the Environmental Assessment portion of the above application, and a request to change the dissolution specifications for COZAAR prior to approval of the application. Specific reference is made to telephone conversations between Ms. K. Bongiovanni and Dr. L. Bell on March 6, 1995, Dr. E. Fadiran and Dr. L. Bell on March 8, 1995, Mr. M. Jones and Dr. L. Bell on March 8, 1995, and Dr. R. Wolters and Dr. L. Bell on March 8, 1995. Specific reference is also made to an approvable letter for HYZAAR (NDA 20-387), received from the FDA on March 10, 1995.

A response to the Agency's request to modify the dissolution specification will be provided in a subsequent submission.

By copy of this letter we are submitting a revised draft package circular. Attached are two separate documents to facilitate review. Attachment I is formatted as a two column document: The left hand column provides the draft labeling text as revised by the Agency in the March 2, 1995 approvable letter. Deletions to this draft are shown by strike-through and additions are shown in double-underline. The right hand column provides Merck Research Laboratories (MRL) comments along with supporting annotation. In addition, supporting documentation is included within this Attachment. Attachment II provides the entire text of the draft package circular, incorporating all proposed revisions.

MRL is also providing the entire text of the draft package circular, incorporating all proposed revisions in electronic format as individual disks. This information is formatted as a Macintosh Word Perfect 3.1 document.

Medical Officer Review

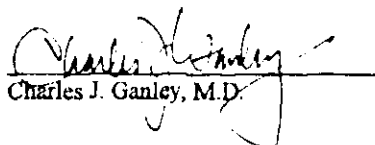
NDA #: 20-386/BM
Volume: 18.1
Drug Name: Losartan
Sponsor: MSDRL
Date of Receipt: 3/2/94
Review Start Date: 3/8/95
Medical Reviewer: Charles J. Ganley, M.D.

Re: Prothrombin Times of Patient #1031 from study 47

Patient #1031 had gingival bleeding and an elevated prothrombin time (PT) while receiving losartan 2.5 mg. Pre-study prothrombin time was 11.1 seconds on 4/24/92. The patient started losartan therapy on 5/18/92. The prothrombin time on 5/19/92 was 16.3 seconds. The prothrombin time on day 10 was 11.9 seconds. The prothrombin time on day 33 was 29.4 seconds. The dose of warfarin was the same for all of these dates. Subsequent prothrombin times on the same dose of warfarin and losartan 10 and 25 mg did not appear elevated.

Conclusion:

The increase in PT on day 33 can not be explained although the role of losartan appears questionable. The data suggests that a pharmacokinetic interaction is not likely although information regarding other therapies is not provided. The information does not rule out an interaction during the first days of losartan (e.g. related to displacement from albumin) therapy.


Charles J. Ganley, M.D.

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MAR 7 1995

MEDICAL OFFICER REVIEW

IND #: 20-386/BM
IND Volume: 16.1
DRUG NAME: losartan
SPONSOR: Merck
TYPE OF DOCUMENT: Response to request for information
DATE RECEIVED: 2/15/95
DATE REVIEW COMPLETED: 3/6/95
MEDICAL OFFICER: Charles J. Ganley, M.D.

This submission provides answers to questions concerning various studies in the NDA. All questions have been answered in a satisfactory manner. Additional information has been provided for patient #12 in study 075. This patient had barely detectable L-158,641 (E-3174) after losartan 50 mg. A metabolic profile was performed under study 060 for cytochrome P-450 activity. CYP1A2, CYP2D6 and CYP3A4 were evaluated by the administration of caffeine, dextromethorphan and dapsone.

In vitro studies with isoform-specific inhibitors of CYP450 indicated that CYP3A4 and at least one isoform of the CYP2C family can catalyze the conversion of losartan to L-158,641. CYP3A4 specific inhibitors, gestodene and ketoconazol, and a CYP2C9-10 inhibitor, sulphaphenazole, decreased the formation of L-158,641 and 2 hydroxylated metabolites. The CYP2D6 inhibitor, quinidine, did not inhibit formation of L-158,641.

Table 1. lists the results of the metabolic ratios after single doses of caffeine, dextromethorphan and dapsone.

Table 1. Metabolic Ratios for Patient 12 (#07 in study 60).

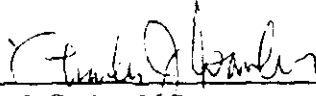
Probe Drug	Metabolic Ratio (MR)	Result	Conclusion
Caffeine	$MR = \ln\{\ln[(AFMU + 1U + 1X)/1,7X]\}$	.018	Slow Metabolism
Dextromethorphan	$MR = [DM]/[DT]$	.7841	Poor metabolism
Dapsone	$MR = [NHD]/(dapsone + [NHD])$	.796	Normal Activity

NHD = N-hydroxydapsone dapsone; DM = dextromethorphan; DT = dextrophan; 1U = 1-methyluric acid
AFMU = 5-acetyl-amino-6-formylamino-3-methyluracil; 1X = 1-methylxanthine; 1,7X = paraxanthine

Patient 12 received losartan 30 mg i.v., losartan 100 mg p.o. and L-158,641 20 mg i.v. After losartan dosing, L-158,641 was barely detectable. After L-158,641 dosing, the elimination half-life of L-158,641 was approximately 8 hours.

Conclusions:

Decreased activity of CYP3A4 was not apparent in this patient as one might expect from the in vitro CYP data. CYP2C9 activity was not evaluated in this patient.


Charles J. Ganley, M.D.

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HFD-110 / R. Temple

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Medical Officer Review

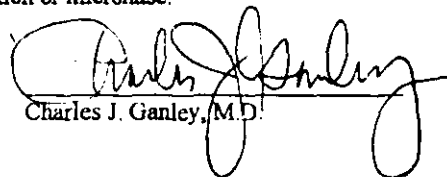
NDA #: 20-386/BM
Volume: 15.1 - 15.4
Drug Name: Losartan
Sponsor: MSDRI
Type of Document: Request to FDA request for information
Date of Receipt: 2/13/95
Review Start Date: 3/2/95
Medical Reviewer: Charles J. Ganley, M.D.

MAR 1 1995

This submission contains requested case report forms. There is little additional information to be derived from the CSRs. As with the CSRs included in the NDA, the CSRs are computerized recreations of the original data. They have been signed by the investigators.

Summary/Conclusions

- 1) Twelve of the thirteen patients with either eyelid edema, orbit edema or face edema can be ruled out as having angioedema. Patient #2365 (losartan 50 mg) in study 050 cannot. This patient had edema of the face and eyes and a photosensitivity rash while working in the yard on 4/24/92. Reportedly a photo is available (this has been requested from Dr. Bell, MSDRL). A similar reaction apparently occurred on 3/12/85 while the patient was receiving chlorthalidone. Thus, there are two patients (the other being patient # 488 in study 011) on losartan therapy who had face or eyelid edema. Angioedema cannot be ruled out from the information provided.
- 2) Ataxia was used as a code for adverse events such as "physically clumsy" and "slight imbalance in the head". The patients did not have ataxia.
- 3) Patient #4551 (losartan 100 mg/HCTZ 25 mg) in study 64 had elevations in ALT and AST and hepatomegaly. Other than fatigue, starting 14 days prior to detection of LFT abnormalities, there were no other symptoms suggesting hepatitis. The patient also had hyperglycemia possibly related to the discontinuation of micronase.



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Medical Officer Review

MAR 1 1995

NDA #: 20-386/BM
 Volume: 174-173
 Drug Name: Losartan
 Sponsor: MSDRL
 Type of Document: Request to FDA request for information
 Date of Receipt: 2/15/95
 Review Start Date: 3/1/95
 Medical Reviewer: Charles J. Ganley, M.D.

Due to malfunctioning of the CANADA, queries of the database could not be performed in a timely manner. Queries of liver function tests, electrolytes, urine blood and renal function tests were requested from the sponsor. This submission includes the results of the queries except for those involving urine blood.

Liver Function Test Abnormalities

Liver function test abnormalities were queried by several criteria: AST and ALT > 2 times the upper limit of normal, AST and ALT > 80 U/L, AST or ALT increased, alkaline phosphatase, or total bilirubin or GGT increased and hyperbilirubinemia. For the most part, abnormalities followed several patterns. Many patient had elevations of AST and ALT on one or several labs only to have them return to normal with continued losartan therapy. Some had mild abnormalities at baseline that increased after the initiation of treatment. Others had increases in ALT and AST that returned toward normal after discontinuation of therapy. Several patients had elevation in ALT or AST on the final reported lab with no additional follow-up. Three patients in the CHF trial (study 47) had abnormal tests. It was not clear whether this was due to underlying disease or losartan. Two losartan treated patients withdrew from studies due to LFT abnormalities. Patient #548 in study 011 had hepatitis A. Patient #2230 in study 050 had mild baseline abnormalities that worsened with therapy. Table 1 lists liver function test results for several patients where losartan therapy could not be ruled out as a factor in increases in LFTs. Patient #1008 had increasing edema on day 127 (?worsening heart failure). Additional information is needed to document that LFT abnormalities were due to worsening heart failure. In conclusion, asymptomatic abnormal liver function tests occurred occasionally. Their clinical significance is unknown. Clinical hepatitis (symptomatic) does not appear to be a problem.

Table 1. Liver Function Test Results for Selected Patients

	Day	ALT (U/L)	AST (U/L)	Alk. Phos. (U/L)	Total Bilirubin (U/L)
Patient #4561, Study 064					
	-4	41	24	72	
Losartan 100 mg	29	49	30	70	
Losartan 100 mg/HCTZ 25 mg	43				
Losartan 100 mg/HCTZ 25 mg/Felodipine 10mg	88	38	26	68	
Losartan 100 mg/HCTZ 25 mg/Felodipine 10mg	97				
Losartan 100 mg/HCTZ 25 mg/Felodipine 5 mg	201	63	43	82	
Losartan 100 mg/HCTZ 25 mg/Felodipine 5 mg	271	113	86	81	
Patient #8685, Study 054					
	-15	29	24	73	
Losartan 50 mg/HCTZ 6.25 mg	21	52	35	84	
Losartan 50 mg/HCTZ 6.25 mg	85	45	28	79	
Losartan 50 mg/HCTZ 6.25 mg	201	89	72	77	
Losartan 50 mg/HCTZ 12.5 mg	378	168	94	91	
off-drug	532	105	83	103	
Patient #5689, Study 059					
	1	18	19	170	
Losartan 100 mg	29	32	28	86	
Losartan 100 mg/HCTZ 12.5 mg	44	49	33	89	
Losartan 100 mg/HCTZ 25 mg	58	92	47	94	
Losartan 100 mg/HCTZ 25 mg/Atenolol 100 mg	86	87	35	118	
Losartan 100 mg/HCTZ 25 mg/Atenolol 100 mg	148	221	93	89	
Losartan 100 mg/HCTZ 25 mg/Atenolol 100 mg	268	91	39	68	
Patient #7102, Study 049					
	-43	32	21	83	
	-1	21	23	77	
Losartan 50 mg/HCTZ 25 mg	10	101	81	137	
off-drug	18	76	21	116	

Table 1. (Cont)

	Day	ALT (U/L)	AST (U/L)	Alk. Phos. (U/L)	Total Bilirubin (U/L)
Patient #4551, Study 064					
	-6	57	51	90	
Losartan 100 mg	8	65	39	100	
Losartan 100 mg/HCTZ 25 mg	15				
Los. 100 mg/HCTZ 25 mg/Diltiazem 240mg	29				
Los. 100 mg/HCTZ 25 mg/Diltiazem 300 mg	92	170	101	150	
off-drug	102	163	99	134	
off-drug	131	97	58	115	
Patient #6007, Study 048					
	-11	18	12	40	.8
Losartan 50 mg	29	18	14	42	.7
Losartan 50 mg/HCTZ 6.25 mg	53	14	14	62	1.0
Losartan 50 mg/HCTZ 6.25 mg	113	37	33	9.1	
Losartan 50 mg/HCTZ 12.5 mg	184	33	86	1.8	.9
Losartan 50 mg/HCTZ 12.5 mg	344	37	22	2.1	3.7
Patient #1008, Study 47					
	-8	42	36	93	.8
Losartan 2.5 mg	10	40	28	86	.9
Losartan 2.5 mg	32	56	42	85	1.2
Losartan 2.5 mg	66		56	113	1
Losartan 2.5 mg	95	80	58	116	1.1
Losartan 2.5 mg	109	92	59	143	1.5
Losartan 10 mg	115	86	69	137	1.5
Losartan 10 mg	125	91	76	163	1.7
Losartan 10 mg	130	216	220	266	4.4
off-drug	137	119	68	313	8.5
off-drug	144	43	40	238	6.1
off-drug	151	26	36	169	4.6
off-drug	157	22	29	143	3.5
off-drug	172				3.1
off-drug	194				4.0
Patient #1185, Study 47					
	-7	16	29		
	-1	18	21	65	
Losartan 10 mg	9	16	33	63	
Losartan 10 mg	30	29	57	56	
Losartan 10 mg	63				
Losartan 10 mg	75	16	17	48	
Losartan 10 mg	103	197	189	75	
Patient #1070, Study 047					
	-24	13	19	61	
	-1	18	23	71	
Losartan 25 mg	1				
Losartan 25 mg	10	57	30	86	
Losartan 25 mg	17	99	101	80	
off-drug	32	21	25	89	

Table 1. (cont)

	Day	ALT (U/L)	AST (U/L)	Alk. Phos. (U/L)	Total Bilirubin (U/L)
Patient #834, Study 011					
	-15	24	29	92	.5
Losartan 10 mg	14	18	26	87	.7
Losartan 10 mg	31	20	30	98	.1
Losartan 10 mg	56	19	27	83	.8
Losartan 100 mg/HCTZ 12.5 mg	108	15	22	96	.6
Losartan 150 mg/HCTZ 12.5 mg	129	17	23	82	.6
Losartan 150 mg/HCTZ 12.5 mg	157	24	35	87	.7
Losartan 150 mg/HCTZ 12.5 mg	179	25	31	88	.8
Losartan 150 mg/HCTZ 12.5 mg	235	20	27	82	.9
Losartan 150 mg/HCTZ 25 mg	270	24	27	95	.4
Losartan 150 mg/HCTZ 25 mg	340	28	27	87	.7
Losartan 150 mg/HCTZ 25 mg	405	25	30	79	.6
Losartan 150 mg/HCTZ 25 mg	461	28	38	93	.1
Losartan 150 mg/HCTZ 25 mg	524	29	39	72	.8
Losartan 150 mg/HCTZ 25 mg	580	25	31	68	.7
Losartan 150 mg/HCTZ 25 mg	649	21	31	81	.6
Losartan 150 mg/HCTZ 25 mg	691	22	28	99	.5
Losartan 150 mg/HCTZ 25 mg	748	243	186	98	.9
Losartan 150 mg/HCTZ 25 mg	776	244	167	128	.9

Elevations in total bilirubin alone occurred but the majority of patients had baseline elevations. In a few patients with normal baseline total bilirubin, increases were observed without increases other liver function tests. In most of these cases, the total bilirubin did not exceed 3.0 mg/dl. There are several cases where minor increases in total bilirubin were associated with minor increases in other tests of liver function. None of these cases appear to be associated with symptoms. Thus, their clinical relevance is questioned. None of the cases of isolated total bilirubin increase was associated with decreasing hemoglobin (R/O hemolytic anemia).

Hepatitis

Patient 0548 in study 011 had hepatitis A. Patient 7411 in study 049 did not have abnormal liver function tests so it is unclear why this patient was listed with hepatitis as an adverse event.

Hyperkalemia

Thirty-two patients had hyperkalemia (no limit defined) as an adverse event. Twenty-five of these patients received losartan. Four patients received losartan/HCTZ. The majority (22) of the losartan patients with hyperkalemia were from study 58 (renal insufficiency patients).

One-hundred and twenty-seven patients had serum potassium ≥ 5.5 mEq/L on at least one occasion. For the majority of patients, the increased potassium was an isolated event.

Hypernatremia

Five patients had hypernatremia as an adverse event. For the most part, if patients had increases in sodium while on losartan, the sodium returned to normal with continued therapy.

Hypokalemia

One hundred and eight patients had hypokalemia. The lowest potassium for all except two patients were between 3.0 and 3.4 mEq/L. The majority of patients with hypokalemia were receiving losartan/HCTZ. Two patients had potassiums less than 3.0 mEq/L. Both were enrolled in study 47 (CHF) and were receiving losartan and presumably a diuretic.

Creatinine and BUN Increased

Forty-eight patients had "creatinine increased" as an adverse event. Seven cases appeared to have clinically relevant changes in creatinine. Four of these received losartan/HCTZ. Creatinine improved in two of these patients when HCTZ was discontinued. Of the remaining three patients, one had CHF. Overall, the effect of losartan on renal function probably does not differ much from ACEI.

Partial Thromboplastin (PTT) or Prothrombin Time (PT) Increased

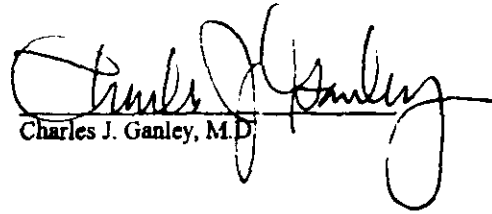
Four patients had increased PT or PTT. Lab results are not provided.

Study 58 Baseline and Last Value Creatinine and Potassium

The mean baseline and last values for creatinine and potassium does not include 12 patients and eliminates much of the data. This is the data the FDA requested and in retrospect, it is probably insufficient to make conclusion about creatinine and potassium in this population (renal insufficiency).

Conclusions:

- 1) Although losartan cannot be ruled out entirely as the cause of elevation of transaminases, the incidence of events is low and clinical hepatitis does not appear to be a problem.
- 2) Hypokalemia can still occur in patients on losartan/HCTZ.
- 3) There is nothing new to add to previous comments in the NDA review regarding increases in creatinine. Isolated instances of increased creatinine (reversible) occurred.
- 4) Creatinine and potassium data from study 58 is insufficient to make conclusions regarding changes in these parameters with losartan therapy.
- 5) No data is provided for patients with increased PT or PTT.


Charles J. Ganley, M.D.

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Medical Officer Review - Addendum to NDA Review

Safety Summary of Losartan and Renal Cell Carcinoma

NDA #: 20-386
 Drug Name: Losartan (DuP 753, MK-954)
 Sponsor: MSDRL
 Date Completed:
 Medical Reviewer: Charles J. Ganley, M.D.

The purpose of this addendum to the Medical Review of the NDA is to summarize the issue of losartan and renal cell cancer. It was not included in the primary Medical Officer review of the NDA because the original NDA database does not contain all of the clinical and pre-clinical data pertinent to the discussion. Over the course of 1994, pre-clinical trial data and information pertaining to renal cell cancer in losartan treated patients has been submitted to the NDA. These have been summarized in a separate review by Dr. Proakis (Review Date 1/18/95) and consultation by Dr. Burkhart (Division of Epidemiology Consultation Dated 11/14/94).

Background

In July of 1992, Merck submitted to the IND the results of an animal study from independent Italian investigators lead by Andrea Remuzzi. Forty-eight male Sprague-Dawley rats were treated with one of three treatments: 1) control, no treatments; 2) single dose of streptozotocin [STZ] (60 mg/kg i.v.), insulin as needed for blood sugar control; 3) single dose of streptozotocin (60 mg/kg i.v.), insulin as needed for blood sugar control, and losartan 30 - 35 mg/kg in drinking water. Table 1 outlines the treatments of this study.

Table 1.

SHORT- AND LONG-TERM EFFECT OF ANGIOTENSIN II RECEPTOR BLOCKADE IN RATS WITH EXPERIMENTAL DIABETES

Treatment Groups	Dose mg/kg	Males/Group
Untreated Control	0/0	16
STZ*⊗	60/0	16
STZ*⊗/Losartan†	60/30	16

- * Intravenous streptozotocin administered on Day 1
- ⊗ Insulin administration to STZ-treated animals from Day 3
- † Losartan administration from Day 3

The purpose of the study was evaluate glomerular injury in diabetic rats (streptozotocin induced) treated with losartan. Eight rats of each treatment group would be sacrificed at 1 month and at one year to evaluate glomerular histology. When necropsy was performed after one year, the investigators observed gross tumors in losartan treated rats but not in control animals. Table 2 outlines the results. Five of eight losartan treated rats had gross tumors identified as cancers (3 renal cell, 1 sarcoma, 1 unidentified).

Table 2.

SHORT- AND LONG-TERM EFFECT OF ANGIOTENSIN II RECEPTOR BLOCKADE IN RATS WITH EXPERIMENTAL DIABETES

TREATMENT GROUPS MG/KG	REPORTED INCIDENCE	GROSS FINDINGS	HISTOLOGICAL DIAGNOSIS
Untreated Control 0/0	0/8	—	—
STZ 60/0	0/8	—	—
STZ/Losartan 60/30	5/8	4/5, 0.3 to 0.9 cm, round, nodular, pale-yellow, soft, well-delineated, anterior polar (3) or multifocal (1), left kidney 1/5, 6.0 cm, multinodular, multicystic, pale yellow to dark red-brown, soft, with significant renal parenchymal destruction, right kidney	3/4*, renal epithelial tumors (reported as renal cell carcinoma) renal mesenchymal tumor (reported as sarcomatous carcinoma)

*One tumor not evaluated histologically

The observation from the Remuzzi study raised a concern within the Cardio-Renal Division (DCRDP) that losartan may be acting as a promoter of renal tumors. This possibility was apparently also raised by Dr. Remuzzi who speculated that tumor promotion may be linked to increased levels of angiotensin II caused by losartan. In July/August 1992, Merck was encouraged by DCRDP to repeat the Remuzzi protocol to determine if this is a reproducible finding. Merck initiated two studies after discussions with DCRDP.

In February of 1994, Merck submitted information on six cases of renal cell cancer in patients enrolled in clinical trials. Five of the patients received losartan or losartan/HCTZ and one patient received placebo. The number of renal cancers in the NDA appeared to be high compared to anecdotal experience of past NDA submissions for hypertensive drugs. Since the patient exposure in the losartan and losartan/HCTZ NDAs is large relative to previous experience, it was important to determine whether the renal cancer incidence rate deviated from the expected rate. The Division of Epidemiology was consulted to address this issue.

Table 3 lists submissions to the NDA after February 1994 by Merck pertaining to renal cell cancer in animals or humans.

Table 3. NDA Submissions Pertaining to Renal Cell Carcinoma

Date Received	Submission (Volume)	Information Included in Submission
4/15/94	20-386/BM (4.1 - 4.2)	1) Case Report Forms for six patients diagnosed with renal cell carcinoma 2) Report on Pro-Renin as a marker for renal cell carcinoma 3) Reference/Report outlining increased risk for renal cell carcinoma in hypertensive patients. 4) MedWatch report of a possible seventh case of renal cell cancer in the losartan database.
7/22/94	20-386/BM (6.1)	1) Preliminary report on the results of the Merck STZ trials. 2) Report of 28 days genotoxicity/cytotoxicity study in STZ rats. 3) Summaries of eight patients with renal cell cancer. 4) Renal cell cancer epidemiology report. 5) Reports of expert consultants.
7/28/94	20-386/NC (7.1)	1) References from the medical literature pertaining to the risk factors associated with renal cancer.
8/19/94	20-386/BM (7.1)	1) Methodology used in the calculation of person years in the losartan and enalapril/lisinopril data.
8/30/94	20-386/BM (7.1)	1) References pertaining to the incidence of renal tumors in STZ treated animals. 2) Incidence of renal tumors in 2 year rat carcinogenicity studies (Merck Database Control Animals)
9/13/94	20-386/NC (7.1)	1) Incidence of Renal Cell Cancer in the SOLVD Study.
10/7/94	20-386/AP (9.1 - 9.3)	1) Merck study report of their STZ trials.
10/25/94	20-386/BM (10.1)	1) Report on Incidence of All Cancers in Losartan, Enalapril and Lisinopril database.

Summary of Pre-Clinical Data Exclusive of the Remuzzi Study

There are three relevant sources of pre-clinical data that address the observations presented by the Remuzzi study. These include: 1) Losartan 2-year carcinogenicity study in Sprague-Dawley rat; 2) a Merck sponsored 28 day in vivo genotoxicity study in Sprague-Dawley rats; and 3) Merck sponsored replication of the Remuzzi protocol

In the 105 week carcinogenicity study in Sprague-Dawley rats, 150 rats (75 males, 75 females) per treatment group received losartan in daily oral doses of 15 mg/kg, 45 mg/kg or 135/270 mg/kg. There was one control group of 260 rats (130 males, 130 females). There were no malignant renal tumors observed in any group. Benign tumors were observed in one (.4%) control animal, in two (1.3%) 15 mg/kg animals, in two (1.3%) 45 mg/kg animals and in three (2.0%) 135/270 mg/kg animals. The following conclusions could be inferred from this study. Losartan did not significantly increase the incidence of benign tumors with increasing doses of losartan. Conclusions about malignant renal tumors requires more caution. The expected underlying incidence of any malignant renal tumors in Sprague-Dawley rats on no therapy is .5%. [Reviewer's Note: This is based on information provided by Merck in the 8/30/94 submission. The incidence of transitional cell or tubular adenocarcinoma is about .1%.] Thus, in a study of 150 animals with a drug that is not a carcinogen, one malignant renal tumor might be expected to be seen. The likelihood of observing a tubular or transitional cell carcinoma is less. Since no malignant renal tumors were observed, it suggests that losartan is not a tumor promoter. On the other hand, it might also suggest that the size of the study is insufficient to detect promoter activity because of the low incidence of renal malignancy in control populations. But by definition, tumor promoters should increase the incidence of benign, not just malignant tumors, and that is not seen in this study.

Merck performed an in vivo 28 day genotoxicity study (in vivo alkaline elution assay on kidney tissue) in rats treated with STZ with or without losartan. This study has been summarized by Dr. Proakis. Losartan showed no effect on the STZ damage in the kidney. Losartan alone showed no evidence of a genotoxic effect in rat kidney.

The two animal studies conducted by Merck which attempted to reproduce the results of the Remuzzi study were summarized in detail by Dr. Proakis (date review 1/18/95). The protocol followed by Merck was similar to Remuzzi with the following exceptions: 1) Merck treated 50 rats per treatment group as opposed to 8 in the Remuzzi study, 2) the purpose of the Merck study was to identify gross and microscopic tumors whereas the Remuzzi study attempted to identify glomerular changes; 3) Merck studied multiple doses of losartan (5, 30, 90 mg/kg) whereas the Remuzzi study included one dose (30 mg/kg), and 4) one of the Merck treatment groups included the combination of losartan and lisinopril in STZ treated animals whereas Remuzzi did not (The purpose of the combination was to prevent the elevations of angiotensin II seen with losartan alone.). The Merck studies produced the following results:

- 1) There were no tumors in the placebo control group (gross or histologically diagnosed).
- 2) The percentage of animals with gross tumors (benign or malignant) in STZ +/- losartan treated animals ranged from 37% - 42%. There was no significant difference between treatments groups
- 3) The treatment group, STZ plus losartan plus lisinopril, had a significant increase in the number of rats with gross tumors (benign or malignant). Seventy percent of the animals had gross tumors. However, the percentage of animals with histologically detected malignant renal tumors was 18% compared to 14% in the STZ control group
- 4) The percentage of animals with malignant tumors (histologically detected) was not significantly different between treatment groups.

Conclusion from Pre-Clinical Data

- 1) The Merck studies that followed the Remuzzi protocol did not reproduce the results observed in the Remuzzi trial. The incidence of gross renal tumors was approximately 40% in STZ control and STZ/losartan treated animals. There was no difference in malignant tumors between losartan and control animals. The incidence of tumors in STZ treated animals in the Merck trials is consistent with the published reports.
- 2) Based on the literature references provided (8/30/94 submission), the absence of tumors in the STZ control group of the Remuzzi study appears to be the aberration. The appearance of tumors in the STZ/losartan animals would be expected.
- 3) Losartan is not genotoxic to renal tissue.
- 4) The rat carcinogenicity studies do not suggest that losartan is a promoter of renal tumors.

Summary of Clinical Information

As of August 1994, Merck submitted information on eight cases of renal cancer diagnosed in the losartan database. Six of the patients received losartan or losartan/HCTZ therapy, one received placebo and one received captopril/HCTZ. The duration of treatment prior to diagnosis ranged from 158 to 929 days in the losartan +/- HCTZ patients, 42 days in the placebo patient and 51 days in the captopril/HCTZ patient (NOTE: this patient had symptoms, flank pain, referable to tumor starting on day 1 of therapy). A table listing pertinent information on these eight patients and narrative summaries for these patients are provided in the appendix. As of February 1995, there have been no additional cases of renal cancer diagnosed (personal communication with Dr. Bell, MSDRL).

A formal consultation was made to the FDA Division of Epidemiology to determine whether the rate of renal cell tumors in the losartan NDA was elevated. In order to sort out the incidence rate of renal cell cancer in the losartan database, comparative information was obtained from several sources. This information included the following:

- 1) information on patient exposure and renal cell carcinoma in the enalapril and lisinopril NDA databases (Merck),
- 2) the DCRDP requested that several pharmaceutical companies provide information on all cancers and patient exposure in NDAs from other anti-hypertensive agents;
- 3) the incidence of renal cell cancer in the SOLVD Trial [Reviewer's Note: This database in CHF patients could be compared to enalapril hypertensive database.]
- 4) the FDA Division of Epidemiology obtained cancer incidence rates from the SHEP trial,
- 5) the National Institute of Health's Surveillance, Epidemiology and End Results (SEER) project data which provided renal cell cancer rates based on age and gender for the general population;
- 6) a review of the medical literature for the relative risk of developing renal cell cancer in hypertensives.

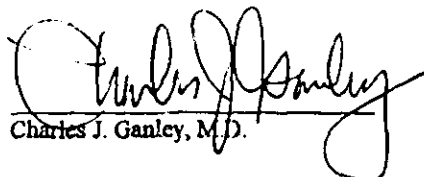
Dr. Burkhart has summarized the pertinent information in his consultation. Please refer to Dr. Burkhart's consultation for details. There was no difference in the renal cell cancer incidence rates between the losartan database and enalapril/lisinopril database. Compared to the SEER data, patients in both the losartan and enalapril/lisinopril database had increased relative risk ratios for renal cancer. There are at least two possible explanations for this observation. Either losartan and the ACE inhibitors increased the risk for renal cancer or hypertension is a risk factor for renal cell cancer. The latter explanation appears to be the more plausible based on the following reasoning. In the SOLVD Trial, enalapril did not increase the incidence of renal cancer compared to placebo. If a pharmacologic class of drugs increases the risk of developing a tumor, this should occur in all patients regardless of underlying diagnosis. Thus, failing to increase tumors in all patients supports the conclusion that the underlying disease may be the risk factor. This is supported by the cohort studies in the literature (see submission dated 7/28/94) which suggest that hypertension is a risk factor for renal cell cancer. Since enalapril is not perceived to be a promoter of renal tumors, the increased risk in the losartan and enalapril/lisinopril hypertension database could be attributed to underlying disease.

The cancer incidence rates and patient exposure databases obtained from other sponsors were not helpful for two reasons. First, most of the databases contained a limited amount of patient exposure greater than one year. Second, there was doubt that the surveillance mechanisms in these databases were as rigorous as those utilized by Merck since the expected overall cancer incidences reported was less than expected from the SEER data.

Overall Summary

When the pre-clinical data is viewed in its entirety, there is no convincing evidence that leads one to believe that losartan acts as a promoter of kidney tumors. The Remuzzi study observations are not supported by studies performed by Merck or by data from the medical literature.

Although the number of renal cancers reported in the losartan database seems high, the incidence is comparable to that observed in the enalapril/lisinopril database. The pre-clinical and clinical database do not suggest that losartan is a promoter of renal tumors.



Charles J. Ganley, M.D.

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HF'D-730/greg burkhart

Plus 11 appendix pages

The appendix contains narrative summaries for the patients diagnosed with renal cell cancer in the NDA. There are some corrections. For patient #8111, there is no data to support a 20 year history of hematuria. For Patient #575, Dr. Sealey did not contact the investigator prior to randomization and inform him of the patient's high pro-renin level. All of the urine tests collected in the double-blind and open label period showed no urine blood or at most 1-3 RBC/HPF until gross hematuria developed. Patient 7411 is a lawyer and it is unlikely that a renal cystic mass diagnosed in 1984 was thought to be cancerous. Although not stated, there must have been a change in the scans performed 12/92 compared to previous.

Table

**EIGHT CASES OF RENAL CELL CARCINOMA
REPORTED TO DATE IN LOSARTAN CLINICAL TRIALS**

WAES #	Protocol/ Study #	AN	Age/ Sex	Treatment (mg Daily Dose)	Treatment Duration* (Days)	Date of Diagnosis	History/Pre-Study Evaluations	Symptoms/ Rel Day of SX Onset***	Diagnoses/Pathology	Drug Relationship
93110403	011/028	0575	75/M	Losartan 50	929	10/25/93	Essential hypertension Elevated pre-study prorenin (163 ng A ₁ /ml/hr)	Gross hematuria/ Day 689	7x7x3.7 cm right renal cell carcinoma, clear cell type Tumor positive for prorenin Post nephrectomy plasma prorenin activity 33 ng A ₁ /ml/hr	Not Drug Related
92080592	047/008	1071	74/F	Losartan 50	158	8/15/92	Essential hypertension NYHA Class II heart failure Microscopic hematuria (20-29 ; 30-39 RBC/HPF)	Asymptomatic - Discovered during follow-up of renal insufficiency	6x5x3.5 cm right renal cell carcinoma, tubulopapillary pattern	Not Drug Related
92121500	049/023	7411	62/M	Losartan 50/ HCTZ 12.5	292	12/9/92	Essential hypertension Tobacco use 8 cm left renal mass - 1984 Microscopic hematuria (3-5 RBC/HPF)	Asymptomatic - Discovered during follow-up of pre- existing left renal mass	7x7x8 cm left renal cell carcinoma, multifocal papillary renal cell carcinoma	Not Drug Related
93120159	054/011	8255	43/M	Losartan 50/ HCTZ 6.25	484	10/7/93	Essential hypertension Tobacco use Chronic low back pain - 1991	Gross hematuria, Dysuria, Right flank pain/Day 348	10x10x10 cm right renal cell carcinoma, predominantly clear cell type	Not Drug Related
93101058	054/019	8876	63/F	Losartan 50/ HCTZ 12.5/ Felodipine 5	452	10/4/93	Essential hypertension	Gross hematuria Left flank pain Urinary retention with clots/Day 448	8.2x8.2x8.0 cm left renal cell carcinoma, predominantly clear cell type	Not Drug Related
**93110771	076/001	102	59/M	Placebo	42	11/11/93	Essential Hypertension	Urinary frequency Nocturia	7 cm left renal cell carcinoma	Not Drug Related
4040801	084/008	0081	67/F	Captopril 50/ HCTZ 25	51	4/11/94	Hypertension	Lumbar pain/ Day 3	8x5x5 cm left renal cell carcinoma, nuclear grade II	Not Drug Related
4040165	054/005	8111	56/M	Losartan 50/ HCTZ 6.25	651	3/14/94	Essential Hypertension Unexplained mild microscopic hematuria - past 20 years	Gross hematuria/ Day 633	5x 5x4.3 cm left renal cell carcinoma, clear cell type.	Not Drug Related

* Treatment duration is based on calendar days post initiation of losartan therapy up to and including date of diagnosis

** This patient was found to have a renal cell carcinoma at the time of his participation in the felodipine/enalapril interaction study subsequent to his participation in the RAAS II study during which he received placebo therapy.

*** Day symptoms were first noted (approximately) relative to the start date of losartan or comparative agent therapy.

Study #011-028 AN 0575
WAES # 93110403

Patient AN 0575 is a 75 year-old Caucasian male with a past medical history of essential hypertension. The patient was enrolled into the placebo baseline phase of A Double-Blind, Randomized, Parallel, Placebo-Controlled Study to Investigate the Antihypertensive Efficacy and Safety of Different Doses of DuP 753 (MK-954) on 2/10/91. The patient was randomized to double-blind treatment with losartan 50 mg once-daily on 3/10/91. The patient completed the 8 week double-blind treatment phase of the study and began open-label maintenance therapy with losartan 50 mg once-daily on 5/13/91. At the time of the diagnosis of renal cell carcinoma, the patient had been receiving losartan 50 mg therapy for 929 days.

The patient's clinical and laboratory safety profiles during the double-blind phase of the study were unremarkable with the exception of microscopic hematuria (10-15 RBC/HPF) noted in a routine urinalysis performed on 3/23/91. During open-label maintenance, the patient developed intermittent gross hematuria, the episodes of hematuria becoming more frequent. The hematuria was first noted in a clinic visit on September 3, 1993. When questioned about the first occurrence of the hematuria, the patient stated that it had been intermittently occurring since February, 1993, but had not been reported by the patient to the study physician. Periodic urinalyses performed as a part of study procedures during this time period were totally devoid of blood.

During follow-up of the gross hematuria on 10/1/93, an IVP was performed, which indicated the presence of a right renal mass. Subsequent CT scan located the solid mass coming off the lower pole of the right kidney. Cystoscopic examination did not reveal any abnormalities to account for the hematuria. Based on these findings, right renal exploratory surgery was performed on 10/26/93 which resulted in a right radical nephrectomy. The kidney with attached perirenal adipose tissue was subjected to pathological examination. The mass was diagnosed as a 7x7x3.7 cm renal cell carcinoma, clear cell type, extending through the renal capsule into perirenal fat. Metastasis was not noted. The patient recovered and was discharged from the hospital. The patient was discontinued from the study due to the development of the renal cell carcinoma. The investigator felt the development of renal carcinoma was not related to study drug therapy.

Plasma renin (PRA) and plasma prorenin activity were measured prior to the start of double-blind treatment and periodically thereafter during the course of double-blind and open-label therapy for all patients participating in the clinical trial. These measurements were performed by Dr. Jean Sealey at Cornell University. Prior to the patient's randomization to losartan therapy in 1991, Dr. Sealey contacted the study investigator to alert him to this patient's high prorenin activity (163 ng A1/ml/hr on 3/9/91), displayed in Table below. It was Dr. Sealey's opinion that the elevated pre-study prorenin value could have been indicative of the presence of a renal tumor. A plasma sample obtained from the patient post-nephrectomy revealed that the prorenin activity normalized to 33 ng A1/ml/hr (normal range : 28-44 ng A1/ml/hr). Analysis of

the tumor revealed staining for prorenin. The surrounding normal tissue stained positive for renin.

Table

Plasma Renin and Prorenin Activity Levels
Patient AN #0575

Study Phase	Sample Date	Plasma Renin Activity ng A ₁ /ml/hr	Prorenin Activity * ng A ₁ /ml/hr
Pre-Study	3/9/91	4.4	163
Double-Blind	5/4/91	19.0	111
	5/5/91	5.5	123
	5/12/91	3.2	163
Post-Nephrectomy	1/15/94	1.6	33

*Normal Levels Prorenin Activity = 28-40 ng A₁/ml/hr

Study #047-008 AN 1071
WAES # 92080592

Patient AN #1071 is a 73 year-old black female with a past medical history of hypertension, atrial fibrillation, coronary artery disease, NYHA Class II heart failure, hyperthyroidism and hematuria. This patient was enrolled into the Multicenter, Double-Blind, Randomized, Parallel, Multiple-Dose, Placebo-Controlled Study of the Hemodynamic and Clinical Effects of Losartan in Patients with Heart Failure on 2/24/92. Baseline urinalysis performed prior to the initiation of double-blind therapy indicated the presence of microscopic hematuria (20-29 RBC/HPF on 2/24/92, 30-39 RBC/HPF on 3/9/92). The patient began double-blind therapy with losartan 2.5 mg once-daily on 3/10/92. She entered open label maintenance on 6/10/92 with losartan 2.5 mg once-daily and was gradually titrated to a final maximal dose of losartan 50 mg once-daily on 7/16/92 which was maintained for the duration of her open-label participation. At the time of diagnosis of the renal cell carcinoma, the patient had been receiving losartan therapy for 158 days. Concomitant medication included quinidine gluconate, quinine sulfate, sodium warfarin, furosemide, digoxin, potassium chloride, and acetaminophen-codeine.

On 8/15/92, the patient was admitted to the hospital complaining of nausea, vomiting and general malaise. Laboratory tests performed on 8/14/92 indicated elevated BUN, serum creatinine and digoxin levels. Losartan therapy was discontinued on 8/14/92; therapy with all other previous concomitant therapies was discontinued on 8/15/92. An initial diagnosis of renal insufficiency was made. The patient was discontinued from the study due to the development of renal insufficiency; early termination procedures required by the study protocol were completed on 8/28/92. Further work-up of the patient's renal insufficiency included a sonogram followed by a CAT scan of her abdomen and pelvis, which revealed a large right renal mass believed to be a neoplasm. A left renal calculus was also observed. A CAT scan of her chest and a bone scan revealed no other evidence of disease. On 9/9/92, the patient underwent a right nephrectomy. Pathological examination of the tumor revealed a single nodular mass measuring 6x5x3.5 cm. The microscopic diagnosis was renal cell carcinoma, predominantly tubulopapillary pattern, Stage I. The patient was discharged from the hospital on 9/19/92 and subsequently recovered. The investigator felt the renal insufficiency and renal carcinoma were not related to study drug therapy.

Study #049-023 AN 7411
WAES #92121300

Patient AN 7411 is a 62 year-old Caucasian male patient with a medical history of hypertension and tobacco use. The patient also had a documented history of an asymptomatic 8 cm left upper pole renal cyst first discovered in a CT scan of the abdomen performed in 1984. The impression of the consulting physician at the time of the initial discovery of the mass was that the calcifications and general appearance of the mass suggested the possibility of a renal cell carcinoma. The physician suggested further evaluation of the mass by skinny needle biopsy and/or arteriography. These tests were not performed. Status of the mass was evaluated periodically over the course of the next 8 years, prior to the patient's entry into the losartan clinical trial. The last prior examination of the cyst had occurred in 1988, via IVP analysis. The impression from this examination was that the asymptomatic left renal cyst was unchanged in appearance and therefore was believed to be benign. The patient was enrolled into A Randomized, Double-Blind, Parallel Study of the Safety and Antihypertensive Efficacy of Hydrochlorothiazide in Combination with Losartan on 1/30/92. On 2/13/92, the patient began single blind therapy with 25 mg hydrochlorothiazide once daily. On 3/5/92, the patient was randomized to double-blind therapy with 100 mg losartan once-daily in addition to the 25 mg hydrochlorothiazide. At the time of diagnosis of the renal cell carcinoma, the patient had been receiving losartan therapy for 292 days.

Clinical and laboratory safety data from this period were unremarkable with the exception of mild microscopic hematuria (3-5 RBC/HPF) noted on a routine urinalysis performed on 3/4/92, prior to initiation of the losartan therapy. The patient completed the double-blind phase of the study and entered the open-label study extension on 5/28/92. Therapy was initiated with 50 mg losartan once-daily. Hydrochlorothiazide 6.25 mg therapy was added after 2 weeks and eventually titrated to 25 mg once-daily. Combination therapy with losartan 50 mg/hydrochlorothiazide 25 mg once-daily was maintained until 12/15/92. During the patient's participation in the study extension, the patient initiated further follow-up of the renal mass at the Baylor VA hospital. The evaluation consisted of a renal ultrasound and CT scan. A bone scan for metastatic workup was also performed. The metastatic workup was negative. The ultrasound and CT scan revealed two calcified cystic densities in the left kidney. There was also a questionable calcification on the right kidney. The patient was admitted to the hospital on 12/9/92 for a radical nephrectomy of the left kidney. Pathological examination of the kidney revealed a large 7x7x8 cm necrotic tumor in the upper pole extending through the capsule into adjacent fat. An additional multifocal papillary renal cell carcinoma in the lower pole and remainder of the kidney parenchyma was discovered. The patient recovered from the surgery and was discharged on 1/8/93. Follow-up of this patient was planned to evaluate the lesion seen on the patient's right kidney. The patient was discontinued from the clinical trial on 12/22/92 due to the left renal carcinoma. The investigator did not feel this adverse experience was study drug related.

Study #054-011 AN 8255

WAES # 93120150

Patient AN 8255 is a 43 year-old Caucasian male patient with a medical history of essential hypertension, chronic low back pain (from 1991) and tobacco use. The patient entered A Randomized, Placebo-Controlled, Double-Blind Parallel Study of the Safety and Antihypertensive Efficacy of Losartan Monotherapy as Compared to HCTZ Monotherapy and to the Combination of Losartan and HCTZ in Patients with Mild to Moderate Hypertension on 5/13/92. He was randomized to double-blind therapy with losartan 50mg once-daily on 6/11/92. The patient's clinical and laboratory safety profiles during the double-blind phase of the study were unremarkable. The patient entered open-label maintenance therapy with losartan 50mg/ HCTZ 6.25mg once-daily on 9/3/92. At the time of diagnosis of the renal cell carcinoma, the patient had been receiving losartan therapy for 484 days.

On 5/21/93, the patient experienced dysuria, gross hematuria and right flank pain. He was treated for a urinary tract infection with antibiotics; the condition resolved. Follow-up of the gross hematuria was performed. An IVP revealed a distorted right renal collecting system. Subsequent renal ultrasound identified a right renal mass. The patient was admitted to the hospital on 10/4/93 for additional work-up of the mass by computerized tomography and magnetic resonance imaging. A chest X-ray performed upon admission showed no evidence of metastatic disease. Based on the tomography and MRI results, exploratory surgery of the renal mass was performed on 10/7/93, which led to a right radical nephrectomy. The patient recovered from the surgery and was discharged from the hospital on 10/15/93. The patient continued with study medication during hospitalization and post-nephrectomy.

Pathological examination of the kidney revealed a 10x10x10 cm mass expanding the renal capsule without identified gross penetration. Gross renal vein involvement was apparent. Microscopic analysis identified the mass as a renal cell carcinoma, predominantly clear cell type but with some granular cells. The patient is continuing with the clinical trial. The investigator felt the renal carcinoma was not related to study drug therapy.

Study # 054-019 AN 8876

WAES # 93101058

Patient AN 8876 is a 63 year-old Caucasian female patient with a medical history of essential hypertension. The patient entered A Randomized, Placebo-Controlled, Double-Blind, Parallel Study of the Safety and Antihypertensive Efficacy of Losartan Monotherapy as Compared to HCTZ Monotherapy and to the Combination of Losartan and HCTZ in Patients with Mild to Moderate Hypertension on 6/10/92. She was randomized to double-blind therapy with losartan 50mg once-daily on 7/9/92. The patient's clinical and laboratory safety profiles during the double-blind phase of the study were unremarkable. The patient entered open-label maintenance therapy with losartan 50mg/ HCTZ 6.25mg once-daily on 10/1/92. Her treatment was eventually titrated to losartan 50mg/ HCTZ 12.5mg/ felodipine 5mg once-daily on 9/29/93, and was maintained as such for the duration of her participation in the study. At the time of diagnosis of the renal cell carcinoma, the patient had been receiving losartan therapy for 452 days.

On 9/30/93, the patient experienced an episode of gross hematuria and was placed on antibiotics for treatment of a suspected urinary tract infection. The hematuria reoccurred on 10/1/93 and was accompanied by left flank pain and urinary retention with clots. An IVP revealed a large left renal mass. A CT scan indicated that the mass had an appearance fairly typical for that of renal cell carcinoma. No signs of metastases were observed on the CT scan. Subsequent chest X-ray and bone scan also failed to show any evidence of metastases. The patient was admitted to the hospital on 10/4/93. A left radical nephrectomy, extended lymphadenectomy and unilateral salpingo-oophorectomy were performed. Pathological examination of tissue samples indicated that the lesion was confined to the kidney. Gross examination of the kidney revealed a mass encompassing the entire lower pole which measured 8.2x8.2x8.0 cm. No tumor encroached into the renal pelvis, calyces or renal vein. Microscopic examination confirmed the diagnosis of stage I renal cell carcinoma, predominantly clear cell type, with focal sarcomatoid features. Metastases to hilar lymph nodes were not found. The patient recovered from the surgery and was discharged on 10/15/93. Her study medication was continued during hospitalization. The patient was discontinued from the clinical trial upon discharge from the hospital. The study investigator felt the renal cell carcinoma was not related to study drug therapy.

Study # 076-001 (017-001) AN 102 (0003)*
WAES #93110771

Patient AN 102 is a 59 year-old Caucasian male patient with a medical history of essential hypertension. The patient entered an Open, Randomized, Three-Period Crossover Study to Investigate the Pharmacokinetic Interaction Between Felodipine ER and Enalapril in Hypertensive Patients on 9/9/93. On 9/28/93 he was randomized to enalapril maleate 5 mg once-daily. On 10/12/93 he was placed on therapy with felodipine ER 5 mg/enalapril maleate 5 mg once-daily. On 10/18/93 felodipine ER 5 mg/enalapril maleate 5 mg was discontinued as per protocol and on 10/26/93 he resumed therapy with felodipine ER 5 mg once-daily through 11/1/93. The patient's clinical and laboratory safety profiles during the double-blind phase of the study were unremarkable. Prior to entry into this study, the patient had been a participant in the RAAS II study during which he received placebo therapy (the patient had never received losartan therapy).

In 1993 (exact date unknown), the patient experienced urinary frequency, nocturia, and slowing of his stream. Ultrasound revealed a 7 cm solid mass in the upper pole of the left kidney. A CT scan revealed a solid tumor without evidence of perirenal lymphadenopathy or renal vein involvement. On 11/15/93 the patient was hospitalized for a left radical nephrectomy. On 11/21/93 the patient was voiding well, his wound was clean and he was discharged; however, the patient was considered not recovered.

Pathological examination of the kidney revealed renal cell carcinoma. The vascular margins, renal capsular margins, and ureteral margins were free of tumor. In addition, there were no positive lymph nodes. The investigator felt the renal cell carcinoma was not related to study drug therapy.

*This patient was found to have a renal cell carcinoma at the time of his participation in the felodipine/enalapril interaction study subsequent to his participation in the RAAS II study during which he received placebo therapy only.

Study # 084-008 AN 0081
WAES # 93110771

Patient AN 0081 is a 67 year-old Latin American female with a past medical history of hypertension. The patient entered the double-blind treatment phase of A Randomized, Double-Blind, Multicenter Study of the Safety and Antihypertensive Efficacy of the Losartan 50 mg/Hydrochlorothiazide (HCTZ) 12.5 mg Combination Compared to the Captopril 50 mg/HCTZ 25 mg Combination in Elderly and Younger Patients With Mild to Moderate Essential Hypertension on 2/20/94 and was randomized to Captopril 50 mg/HCTZ 25 mg once-daily. At the time of diagnosis of the renal cell carcinoma, the patient had been receiving Captopril/HCTZ therapy for 51 days and had never received losartan therapy.

On 2/23/94, the patient began to experience lumbar pain. On 4/4/94, an abdominal examination revealed mild pain in the left kidney. A sonogram performed on 4/11/94 revealed a renal mass. The presence of the mass was confirmed by a CT scan performed on 4/13/94. Surgery to explore the mass was performed on 4/18/94.

The final pathological report on specimens obtained during the exploratory surgery confirmed that the 8x5x5 cm tumor found in the upper lobe of the left kidney was a renal cell adenocarcinoma (hypernephroma), nuclear grade II, with microscopic involvement of the perirenal fat. There was no evidence of metastases. The patient recovered from the surgery and continued to participate in the study. The investigator felt the renal cell carcinoma was not related to study drug therapy.

Study # 054-005 AN 8111

WAES # 94040165

Patient AN 8111 is a 56 year-old Caucasian male patient who had been treated with "cholesterol medication" with a medical history of essential hypertension and unspecified orthopedic surgery. He had unexplained mild microscopic hematuria present for the past twenty years, which could not be attributed to any type of chronic infection, as well as borderline/mildly increased BUN and serum creatinine levels. The patient entered A Randomized, Placebo-Controlled, Double-Blind Parallel Study of the Safety and Antihypertensive Efficacy of Losartan Monotherapy as Compared to HCTZ in Patients with Mild to Moderate Hypertension on 5/22/92. He was randomized to double-blind therapy with losartan 50 mg/HCTZ 6.25 mg once-daily on 6/19/92. The patient's clinical safety profile during the double-blind phase of the study was unremarkable. The patient's baseline laboratory revealed microscopic hematuria (RBC 8-18/HPF) which remained relatively constant throughout the study until the patient developed gross hematuria. The patient started open-label maintenance therapy with losartan 50 mg/HCTZ 6.25 mg once-daily on 9/11/92. At the time of diagnosis of the renal cell carcinoma, the patient had been receiving Losartan therapy for 633 days.

On 3/14/94, the patient developed gross painless hematuria. A subsequent MRI revealed a left kidney mass. An intravenous urogram was abnormal and a CT scan showed a large mass in the left kidney. Cytoscopic examination revealed a clear bladder and some "mild" prostatitis. Based on the MRI, urogram and CT scan results, the patient was hospitalized for a left radical nephrectomy performed on 4/1/94. There was no evidence of metastases discovered during the surgery. The patient recovered from the operation and continued with study drug therapy.

Histopathological examination of the mass and surrounding tissue was conducted post-nephrectomy. The report indicated that the left kidney weighed 260 gm and measured 11x6.5x6 cm. The adrenal gland was not seen and no hilar lymph nodes were noted. A "canary yellow, fairly circumscribed neoplasm" measuring 5x5x4.3 cm was noted extending from the mid portion of the kidney near the hilum. The tumor extended into the capsule and bulged above the surrounding parenchyma to a height of 2.5 cm with areas of central scarring and focal cyst formation. The nephric capsule was not penetrated. The renal vein contained an approximately 1.8 cm tumor from the renal vein line of surgical resection. The renal vein margin was free of tumor and the capsule was intact. In addition, no adenopathy was noted during surgery. A diagnosis of a renal cell carcinoma, clear cell variant with invasion of the renal vein was made. It was considered to be a T3bNXMX lesion under the American Joint Committee on cancer staging. The patient is continuing with the clinical trial. The investigator felt the renal cell carcinoma was not related to study drug therapy.

Medical Officer Review

FEB 27 1995

NDA #: 20-386/BM
Drug Name: Losartan
Sponsor: MSDRL
Date of Receipt: 2/10/94
Review Start Date: 2/27/95
Medical Reviewer: Charles J. Ganley, M.D.

Merck has proposed losartan labeling that states there is no drug interaction of clinical significance between losartan and warfarin. The support for this statement is based on the results of study 70. In study 70, ten healthy male subjects received a 30 mg dose of warfarin on the seventh day of a 12 day course of losartan and placebo. The pharmacokinetic parameters did not differ for warfarin enantiomers. The AUC for the prothrombin time was not different between treatments. In addition, the sponsor notes that 25% of the patients in study 47 (CHF study) received warfarin and an increased prothrombin time was only noted in patient 1031 (associated with bleeding gums). This submission contains the prothrombin times from patients in study 68 (CHF study).

Study 70 appears to show that there is not a pharmacokinetic and pharmacodynamic interaction between losartan and warfarin. However, similar trial designs performed in the past have not predicted an interaction when one may be present. The most compelling example is the interaction between norfloxacin and warfarin. Bjornsson et al. (the primary investigator in study 70) published a trial (J Clin Pharmacol 1990;30: 728-732) in which subjects received warfarin 30 mg on the fourth day of a nine day treatment period of norfloxacin and placebo. Unlike study 70, total warfarin concentration was measured as opposed to the individual enantiomers. The study suggested that warfarin pharmacokinetics did not change with norfloxacin. Pharmacodynamics as measured by AUC for prothrombin time did not change. Thus, the conclusion by the investigator was that a clinically important interaction of norfloxacin and warfarin is unlikely to occur. Why then does the Physicians Desk Reference and the American Hospital Formulary Service (AHFS) Drug Information book suggest otherwise? The PDR labeling (1994 edition) for norfloxacin states, "Quinolones, including norfloxacin, may enhance the effects of the oral anticoagulant warfarin or its derivatives". The AHFS (1993) states the following:

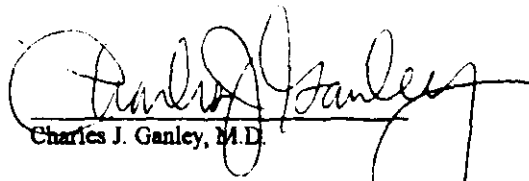
Initiation of oral norfloxacin therapy in patients stabilized on warfarin has resulted in prolongation of the prothrombin time in several patients and, in at least one patient, concomitant use of the drugs resulted in an increased prothrombin time and fatal pontine hemorrhage. Concomitant use of some other quinolones (e.g., ciprofloxacin, nalidixic acid) in patients receiving coumarin anticoagulants has also resulted in increased prothrombin times. The mechanism of this interaction has not been determined to date, but norfloxacin, like nalidixic acid, may displace the anticoagulants from serum albumin binding sites. Norfloxacin should be administered with caution in patients receiving a coumarin anticoagulant and prothrombin time or another appropriate coagulation test should be closely monitored.

Conclusion:

Prothrombin times included in this submission are not helpful in providing proof that there is no interaction. Additional information for patient #1031 from study 47 has not been provided

Losartan is a > 99% bound to plasma protein, primarily albumin. If losartan displaces warfarin from albumin binding sites, the acute increase in free warfarin concentration may be sufficient to be clinically significant. Although study 70 suggests that there is not a pharmacokinetic interaction, it does not rule out a clinically significant pharmacodynamic interaction acutely.

It would be worthwhile to have FDA Division of Biopharm comment on the discrepancy between the results of the norfloxacin study and the labeling for norfloxacin and what should be done with the labeling for losartan. The proposed labeling should not be permitted.


Charles J. Ganley, M.D.

cc: orig
HFD-110
HFD-110/cso/ganley/chen/lipicky
HFD-426/e.fadiran; HFD-100/robert temple

Medical Officer Review

JAN 31 1995

NDA #: 20-386
Drug Name: Losartan
Sponsor: MSDRL
Date of Receipt: 10/7/94
Review Start Date: 1/26/95
Medical Reviewer: Charles J. Ganley, M.D.

This submission contains responses to following request for information:

1) Further clarification of the circumstances surrounding the withdrawal of patients from clinical trials for the reasons —> Patient Withdrew or Lost to follow-up. In the long term extension studies, 16 patients withdrew due to Lost to Follow-up and 27 for Patient Withdrew. In the acute double blind period, 30 patients were lost to follow-up and 48 are listed as Patient Withdrew.

For patients lost to follow-up, I am interested in knowing what attempts were made by the investigator to contact the patients and if there are other circumstances that may have contributed to the patients not returning for additional visits (i.e. adverse events or lack of therapeutic benefit).

For patients listed as Patient Withdrew, this is really not an acceptable explanation for withdrawing a patient. Lists of patients Lost to Follow-up and Patient Withdrew are attached.

2) I am interested in looking at all of the coagulation profile (i.e. PT, INR) information on all patients who received an anticoagulant while on losartan therapy. I have attached a list of patients in the CANDAs who have been on anticoagulants and losartan. Most are from studies 016 and 047 although 4 patients are not. These labs are not in the CANDAs. Where can I find them in the paper copy? If the data for patients in 016 and 047 is not together, can a spreadsheet be generated from your database that makes this information available on a floppy disk for Excel on the Canda?

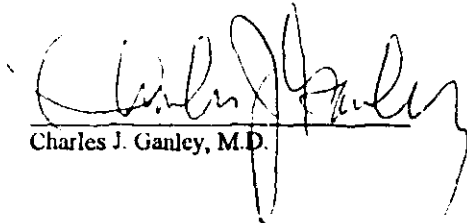
In the extension studies, WMA database:

3) In the CANDAs, patients #648 and #2248, are listed as withdrawing due to clinical AE in the extension periods. They are not included in the summary table 87a of the sponsor's CSR. Please explain?

4) In table 87a, the ae responsible for discontinuation of patient 0322 is decreased libido. Is this correct?

If additional clarification for any of these requests is needed, please contact me?

The responses to these questions have been incorporated into the NDA review


Charles J. Ganley, M.D.

cc: orig
HFD-110
HFD-110/cso/ganley/chen

JUL 19 1994

Medical Officer Review

NOA

IND # 20-386/BM
Drug Name: Losartan
Sponsor: MSDRL
Date of Receipt: 7/15/94
Date of Completion: 7/19/94
Medical Reviewer: Charles J. Ganley, M.D.

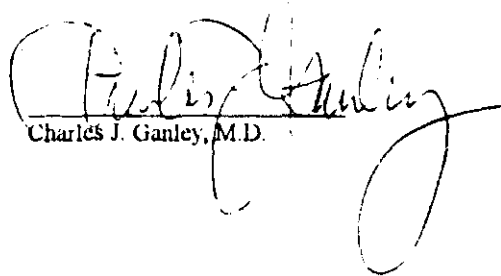
In a 4/15/94 submission describing cases of renal cell cancer in patients on losartan, a MedWatch report describing a case of a patient with a newly diagnosed renal mass (see attachment). This submission provides the pathology report of the kidney post resection.

This is a 56 year old male who entered an open label study of losartan on 7/16/92. The patient received losartan 50 mg/HCTZ 6.25 mg. Apparently, he had a 20 year history of unexplained mild hematuria as well as borderline increased BUN and creatinine (values not provided). In March of 1994, the patient developed painless, gross hematuria. A left kidney mass was diagnosed by MRI scan. The patient had a nephrectomy performed on 4/1/94. The pathology report indicates the mass is a renal cell (clear cell) carcinoma.

This is the sixth case of renal cell cancer in a patient receiving losartan.

Regulatory Action:

The sponsor needs to provide a complete case report form (copies of the original --not computerized copy of information), including lab reports, for this patient. The sponsor should also obtain from the investigator any information on this patient pertaining to past work-ups for the 20 year history of painless hematuria prior to entering this trial.



Charles J. Ganley, M.D.

cc: orig
HFD-110
HFD-110/cso/ganley/chen
greg burkhart (Room 655 in Woodmont II Bldg.)

AD

MERCK HUMAN HEALTH DIVISION

Merck Form 100 of FDA Form 3500A

For use by user-facilities,
distributors and manufacturers for
MANDATORY reporting

Approved by FDA (10/21/1988)

MedWatch

FDA MEDICAL PRODUCTS REPORTING PROGRAM

Page 1

MR report #	WAES 94040165
LF/DR report #	
FDA Use Only	

A. Patient information			
1. Patient identifier	2. Age at time of event or 56 YRS	3. Sex ☐ female ☒ male	4. Weight 155 LBS
Date of both: _____			

B. Adverse event or product problem			
1. ☒ Adverse event and/or ☐ Product problem (e.g., defect/malfunction)			
2. Outcome attributed to adverse event (check all that apply)			
☐ death	☐ disability	☐ congenital anomaly	
☐ life-threatening	☐ required intervention to prevent permanent impairment/damage		
☒ hospitalization - initial or prolonged	☐ other: _____		
3. Date of event (month/day/yr) 03/14/94	4. Date of this report (month/day/yr)		

6. Describe event or problem

A 56-year-old male entered a study comparing the safety and antihypertensive efficacy of losartan monotherapy, hydrochlorothiazide monotherapy and the combination of losartan and hydrochlorothiazide in patients with mild to moderate essential hypertension. He had unexplained "mild" microscopic hematuria present for the past twenty years, which could not be attributed to any type of chronic infection, as well as "borderline/mildly" increased BUN and serum creatinine levels. The patient entered the open-label extension phase of the study and was placed on therapy with losartan 50 mg daily and hydrochlorothiazide 6.25 mg daily on 16JUL92 for the treatment of hypertension. On 14MAR94, the patient

(CONTINUED ON ATTACHED PAGE)

8. Relevant test/laboratory data, including dates	
DIAGNOSTIC TEST	DATE
MRI	
COMMENT: LEFT KIDNEY TUMOR	

7. Other relevant history, including preexisting medical conditions (e.g., allergy, renal, hepatic, cardiac and central nervous system dysfunction, etc.)

CONCURRENT CONDITIONS: Hematuria, microscopic; Bun increased; Serum creatinine increased

C. Suspect medication(s)			
1. Name (give labeled strength & manufacturer, if known)			
*1 Tab Losartan 50 mg			
*2 Tab HydroDIURIL® 6.25 mg			
2. Dose, frequency & route used		3. Therapy dates (month/yr) of occurrence, give duration	
*1 50 mg/DAILY/PO		*1 07/16/92-CONT	
*2 6.25 mg/DAILY/PO		*2 07/16/92-CONT	
4. Diagnosis for use (indication)			
*1 Hypertension			
*2 Hypertension			
5. Lot # (if known)		7. Exp. date (if known)	
#1		#1	
#2		#2	
8. Event started after use stopped or dose reduced			
#1	yes	no	N/A
#2	☐	☐	☒
9. Event worsened after reinitiation			
#1	yes	no	N/A
#2	☐	☐	☒
10. Concomitant medical products and therapy dates (include treatment of event)			
UNKNOWN			

G. All manufacturers	
1. Contact office - name/address	2. Phone number
Merck Human Health Division Merck & Co., Inc. P.O. Box 4 West Point, PA 19488-0004	(215)997-2416
3. Report source (check all that apply)	
☐ foreign	
☒ user	
☐ distributor	
☐ other: _____	
4. Date received by manufacturer (month/day/yr) 04/01/94	5. NANDA #
	NO # 33.383
6. FDA IND, protocol # GENSTUDY 054005	PLA #
7. Type of report	pre-1988 ☐ yes
☐ 5-day	OTC product ☐ yes
☐ 10-day	
☐ 15-day	
☐ periodic	
☒ initial	
☐ follow-up	
8. MR report number WAES 94040165	

9. Adverse event term(s) MASS, KIDNEY

E. Initial reporter			
1. Name, address & phone #			
UNKNOWN PHONE #			
2. Health professional?	3. Occupation	4. Initial reporter sent report to FDA	
☒ yes ☐ no	H.D.	☐ yes ☐ no ☒ N/A	

FDA

Submission of a report does not constitute an admission that medical personnel, user facility distributor, manufacturer or product caused or contributed to the event.

FDA HUMAN HEALTH DIVISION

Page 2

MFR REPORT #: WAES 94040165 (CONT.)

4. ADVERSE EVENT OR PRODUCT PROBLEM**5. DESCRIBE EVENT OR PROBLEM**

developed gross hematuria. A subsequent MRI revealed a left kidney mass. The patient was hospitalized for a left radical nephrectomy on 01APR94. A biopsy was not performed prior to surgery but histopathological examination of the mass and surrounding tissue was to be done post-nephrectomy. At the time of the report, the patient had not recovered. Study drug continued and the investigator felt that the patient's experience was not related to study drug therapy.

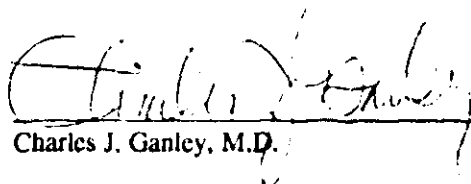
Bongiovanni

MEDICAL OFFICER REVIEW

SEP 23 1994

IND #: 20/386/BM
IND Volume: 7.1
DRUG NAME: losartan
SPONSOR: Merck
TYPE OF DOCUMENT: information amendment
DATE RECEIVED: 9/20/94
DATE REVIEW COMPLETED: 9/23/94
MEDICAL OFFICER: Charles J. Ganley, M.D.

This submission contains information on the incidence of renal cell ca in the felodipine database.


Charles J. Ganley, M.D.

cc: orig.
HFD-110
HFD-110 / CSO / C. GANLEY ~~7-11-94~~

Medical Officer Review

FEB 21 1995

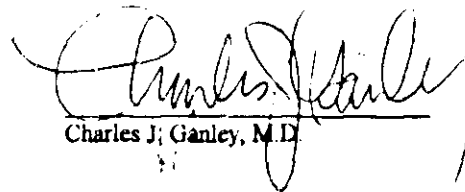
NDA #: 20-386/SU
Volume: 11.1
Drug Name: Losartan (DuP 753, MK-954)
Sponsor: MSDRL
Date Received: 2/1/95
Review Completed: 2/21/95
Medical Reviewer: Charles J. Ganley, M.D.

This Safety Update includes case report forms submitted to Merck by the cut-off date of 6/30/94 or 7/14/94, depending on the study. Additional information was provided for 1,114 patients previously exposed to losartan and 695 patients newly exposed.

Seventy-seven patients discontinued losartan +/- HCTZ therapy due to adverse experiences. A complete listing of patients withdrawn due to adverse events is provided in the appendix.

Adverse events incidence rates (clinical or laboratory) for losartan alone therapy appeared to be similar to previous safety updates. There is a distinction between laboratory adverse events in the losartan/HCTZ patients and losartan alone patients. Increases in creatinine and BUN and decreases in potassium occurred more frequently in the losartan/HCTZ patients. In the losartan alone patients, neither of these adverse lab experiences occurred with greater than 1% frequency. In the losartan/HCTZ group, creatinine increased in approximately 1.2%, BUN increased in approximately 2.0 - 2.7% and potassium decreased in approximately 2.7 - 3.2%. The decreases in potassium are not unexpected with HCTZ. However, the changes in creatinine and BUN are suggestive of renal insufficiency. This could possibly be explained by a diuretic induced volume depleted state combined with a drug that inhibits the RAAS system. In this regard, it would not be much different than an ACEI.

There were three deaths in hypertensive patients. Two were related to cardiac disease and one from Hodgkin's Disease. Four patients with renal insufficiency died (one aortic aneurysm, one hepatitis unrelated to losartan therapy, one myocardial infarction, one DIC). Seven patients in CHF trials died (five cardiac, one trauma, one sudden death of unknown cause). One patient died in a non-Merck Research Labs trial due to complications of pneumonia.



Charles J. Ganley, M.D.

cc: orig.
HFD-110 file
HFD-110/c.ganley/r.lipicky/cso

7 appendix pages attached

N 20386
COZAR

2 OF 10

Losartan and Losartan/HCTZ
 Clinical Documentation
 Safety Update Report 2
 I. Summary

Table 10 Discontinuations Due to Adverse Experiences in Losartan-Treated Hypertensive Patients in Open-Label Trials (Based upon case report form information received Oct. 5, 1993 to July 14, 1994)

Protocol No./ Study No.	AN	Sex/Age	Treatment	Daily Dose (mg)	Relative Day of Onset	Adverse Experience	Serious	Drug Relationship	Outcome
011/005	0088	M/88	Los/HCTZ	100/12.5	1046	Dizziness	No	Possibly	Recovered
011/005	0094	M/57	Los	50	862	Cramp, Muscle	No	Possibly	Present
				100	894	Headache	No	Possibly	Recovered
				100	894	Flushing	No	Possibly	Recovered
				100	895	Atrial Fibrillation	No	Possibly	Recovered
011/009	0177	F/60	Los/HCTZ	100/12.5	1127	Rt. Bundle Branch Block	No	Probably Not	Not Reported
011/019	0381	M/50	Los	50	607	Myocardial Infarction	Yes	Definitely Not	Recovered
011/037	0763	F/42	Los/HCTZ	150/25	769	Urticaria	No	Possibly	Recovered
011/038	0781	F/56	Los/HCTZ	100/25	823	Nephrotic Syndrome	No	Probably Not	Present
011/038	0783	M/61	Los/HCTZ	100/12.5	282	Neoplasm, Anal/Rectal, Malignant	Yes	Probably Not	Recovered
044/008	3143	M/49	Los/HCTZ	50/12.50	225	Headache	No	Probably Not	Present
044/011	3180	M/56	Los/HCTZ	50/6.25	352	Myocardial Infarction	Yes	Definitely Not	Present
045/003	4101	M/52	Los	50	120	Proteinuria	No	Probably	Not Reported
			Off-Drug	--	211	Creatinine Clearance Decreased	No	Probably	Not Reported
			Off-Drug		211	Renal Insufficiency	No	Probably	Recovered
045/009	4132	F/71	Los	50	104	Pain, Abdominal	No	Possibly	Present
045/012	4138	M/56	Los	50	281	Headache	No	Possibly	Present
045/012	4203	M/58	Off-Drug+	--	182	Myocardial Infarction	Yes	Possibly	Recovered

+On Los 50 mg through Study Day 181.

Losartan and Losartan/HCTZ
 Clinical Documentation
 Safety Update Report 2
 I. Summary

Table 10 (Cont.) Discontinuations Due to Adverse Experiences in Losartan-Treated Hypertensive Patients in Open-Label Trials (Based upon case report form information received Oct. 5, 1993 to July 14, 1994)

Protocol No./ Study No.	AN	Sex/Age	Treatment	Daily Dose (mg)	Relative Day of Onset	Adverse Experience	Serious	Drug Relationship	Outcome
048/004	6381	M/58	Los/HCTZ/ Felodipine	50/12.5/5	155	Headache	No	Probably	Recovered
048/006	6019	F/42	Los/HCTZ Los/HCTZ	50/12.5 50/12.5	208 208	Glycosuria Hyperglycemia	No No	Probably Not Probably Not	Not Reported Not Reported
048/029	6209	M/54	Los	50	183	Urticaria	No	Definitely	Recovered
048/029	6223	M/43	Los/HCTZ/ Diltiazem	50/12.5/240	573	Hyperglycemia	No	Probably	Not Reported
049/005	7114	F/59	Off-Drug*	-	156	Edema/Swelling	No	Probably	Present
049/013	7214	F/47	Los/HCTZ	50/6.25	354	Myocardial Infarction	Yes	Definitely Not	Recovered
050/001	2006	M/57	Los/HCTZ Los/HCTZ Lo /HCTZ	50/6.25 50/6.25 50/6.25	674 674 674	Headache Tinnitus Asthenia/Fatigue	No No No	Possibly Possibly Possibly	Present Present Present
050/002	2032	M/73	Los	50	105	Weight Gain	No	Definitely Not	Recovered
050/008	2131	F/66	Los	50	584	Pain, Chest	No	Definitely Not	Present
050/013	2225	F/49	Los	50	715	Myocardial Infarction	Yes	Definitely Not	Present
050/013	2421	F/63	Los	50	726	Myeloma, Multiple	Yes	Probably Not	Present
054/001	8009	M/67	Los/HCTZ/ Felodipine	50/12.5/5	428	Heart Disorder, Ischemic	Yes	Probably Not	Present
054/004	8085	M/51	HCTZ** HCTZ**	6.25 6.25	497 497	AST Increased ALT Increased	No No	Possibly Possibly	Not Reported Not Reported

*On Los/HCTZ/50/12.5 prior to discontinuation.
 **Last dose of Los/HCTZ (50/6.25) was 13 days prior to discontinuation.

Appendix 2

Losartan and Losartan/HCTZ
 Clinical Documentation
 Safety Update Report 2
 I. Summary

Table 10 (Cont.) Discontinuations Due to Adverse Experiences in Losartan-Treated Hypertensive Patients in Open-Label Trials (Based upon case report form information received Oct. 5, 1993 to July 14, 1994)

Protocol No./ Study No.	AN	Sex/Age	Treatment	Daily Dose (mg)	Relative Day of Onset	Adverse Experience	Serious	Drug Relationship	Outcome
054/004	8090	M/50	Los/Felodipine	50/10	462	Dizziness	No	Possibly	Recovered
054/004	8095	M/48	Los/HCTZ	50/12.5	392	Libido Decreased	No	Possibly	Present
054/025	8522	M/74	Los/HCTZ	50/12.5	208	Edema/Swelling	No	Probably Not	Present
054/025	8529	M/59	Los/HCTZ/ Felodipine	50/12.5/10	373	Edema/Swelling	No	Definitely	Present
054/034	8716	M/44	Los/HCTZ	50/12.5	193	Headache	No	Probably Not	Recovered
054/036	8749	F/64	Los/HCTZ	50/12.5	341	Dizziness	No	Possibly	Present
054/037	8774	M/55	Los/HCTZ	50/6.25	100	Headache	No	Possibly	Present
054/038	8800	F/41	Los/HCTZ	50/12.5	141	Serum Creatinine Increased	No	Probably Not	Not Reported
			Los/HCTZ	50/12.5	141	Hyperuricemia	No	Probably Not	Not Reported
054/039	8818	F/73	Los/HCTZ/ Felodipine	50/12.5/5	602	Atrial Fibrillation	No	Probably Not	Recovered
			Los/HCTZ/ Felodipine	50/12.5/5	602	Sinus Tachycardia	No	Probably Not	Recovered
054/040	8176	M/31	Los/HCTZ	50/12.5	113	Urinary Frequency	No	Probably	Present
055/010	5171	F/66	Los	50	122	CVA	Yes	Probably No	Recovered
056/001	3506	M/67	Los	100	352	Neoplasm, Prostate, Malignant	Yes	Definitely Not	Present
056/002	3509	F/54	Los	50	75	Heart Failure	No	Probably Not	Present
056/004	3521	F/42	Los	50	231	Swelling, Joint	No	Definitely Not	Present
			Los	50	231	Pain, Ankle	No	Definitely Not	Present
056/008	3543	F/39	Los	50	53	Cough	No	Definitely	Recovered
056/008	3547	M/51	Los	50	65	Cough	No	Probably	Recovered
056/009	3561	F/53	Los	50	97	Cough	No	Possibly	Present

Appendix 3

Losartan and Losartan/HCTZ
 Clinical Documentation
 Safety Update Report 2
 I. Summary

Table 10 (Cont.) Discontinuations Due to Adverse Experiences in Losartan-Treated Hypertensive Patients in Open-Label Trials (Based upon case report form information received Oct. 5, 1993 to July 14, 1994)

Protocol No./ Study No.	AN	Sex/Age	Treatment	Daily Dose (mg)	Relative Day of Onset	Adverse Experience	Serious	Drug Relationship	Outcome
056/009	3564	M/50	Los	50	98	Cough	No	Possibly	Recovered
			Los	50	98	Diarrhea	No	Possibly	Present
			Los	50	98	Asthenia/Fatigue	No	Possibly	Present
			Los	50	98	Headache	No	Possibly	Present
			Los	50	98	Impotence	No	Possibly	Recovered
056/015	3683	M/63	Los/Felodipine	100/10	284	Angina Pectoris	Yes	Probably Not	Present
059/005	5550	M/47	Los/HCTZ/ Felodipine	100/25/10	67	Headache	No	Possibly	Present
			Los/HCTZ/ Felodipine	100/25/10	68	Edema/Swelling	No	Possibly	Present
			Los/HCTZ/ Felodipine	100/25/10	102	Pain, Back	No	Definitely Not	Present
			Los/HCTZ/ Felodipine	100/25/10	119	Nausea	No	Possibly	Present
			Los/HCTZ/ Felodipine	100/25/10	119	Vomiting	No	Possibly	Present
			Los/HCTZ/ Felodipine	100/25/10	126	Tremor	No	Possibly	Present
			Los/HCTZ/ Felodipine	100/25/10					

Appendix 4

Losartan and Losartan/HCTZ
 Clinical Documentation
 Safety Update Report 2
 I. Summary

Table 10 (Cont.)

Discontinuations Due to Adverse Experiences in Losartan-Treated Hypertensive Patients in Open-Label Trials (Based upon case report form information received Oct. 5, 1993 to July 14, 1994)

Protocol No./ Study No.	AN	Sex/Age	Treatment	Daily Dose (mg)	Relative Day of Onset	Adverse Experience	Serious	Drug Relationship	Outcome
059/012	5614	F/45	Los/HCTZ/ Amlodipine	100/25/5	108	Hemoglobin Decreased	No	Possibly	Recovered
			Los/HCTZ/ Amlodipine	100/25/5	108	Hematocrit Decreased	No	Possibly	Recovered
055/015	5648	F/45	Los	100	38	Pain, Back	No	Probably Not	Present
064/019	4546	M/60	Los/HCTZ/ Atenolol/ Felodipine	100/50/100/10	448	Angina Pectoris	No	Possibly	Recovered
065/001	1434	F/66	Los	50	321	CVA	Yes	Probably Not	Recovered
065/007	1761	M/43	Los	50	98	Hypokalemia	No	Possibly	Not Reported
065/010	1240	M/37	Los	100	187	Impotence	No	Possibly	Present
065/012	1459	M/45	Los	100	180	Pain, Chest	No	Probably Not	Present
065/014	1473	M/39	Los/Atenolol	100/50	334	Atrial Fibrillation	Yes	Possibly	Recovered
065/014	1480	M/52	Los/HCTZ/ Felodipine	100/25/10	335	Myocardial Infarction, Non Q wave	Yes	Possibly	Present
065/014	1483	M/62	Los/Felodipine	100/10	336	Impotence	No	Possibly	Present
065/015	1269	F/35	Los	50	527	Asthenia/Fatigue	No	Possibly	Present

Losartan and Losartan/HCTZ
 Clinical Documentation
 Safety Update Report 2
 I. Summary

Table 10 (Cont.) Discontinuations Due to Adverse Experiences in Losartan-Treated Hypertensive Patients in Open-Label Trials (Based upon case report form information received Oct. 5, 1993 to July 14, 1994)

Protocol No./ Study No.	AN	Sex/Age	Treatment	Daily Dose (mg)	Relative Day of Onset	Adverse Experience	Serious	Drug Relationship	Outcome
065/017	1336	M/60	Los/Atenolol	100/50	196	Pain, Chest	Yes	Probably Not	Present
065/017	1338	M/66	Off-Drug++	-	108	Pain, Chest	Yes	Probably Not	Recovered
065/019	1506	F/51	Los	50	172	Pain, Chest	No	Possibly	Present
065/029	1183	M/58	Los/Felodipine	100/10	513	Irritability	No	Probably Not	Recovered
			Los/Felodipine	100/10	513	Pain, Chest	No	Probably Not	Recovered
			Los/Felodipine	100/10	526	Spasm	No	Possibly	Recovered
065/034	1304	F/55	Los	50	345	Dizziness	No	Possibly	Recovered
			Los	50	345	Nausea	No	Possibly	Recovered
			Los	50	345	Vomiting	No	Possibly	Recovered
			Los	50	345	Pain, Abdominal	No	Possibly	Recovered
065/037	1645	M/63	Los/Felodipine	100/5	258	Polymyositis	No	Probably Not	Present
065/037	1646	M/67	Los	50	90	Pain, Abdominal	No	Probably	Recovered
065/037	1649	M/55	Los	50	104	Libido Decreased	No	Possibly	Recovered
065/038	1151	M/61	Los/Atenolol	100/50	351	Angina Pectoris	No	Definitely Not	Present
065/041	1440	M/39	Off-Drug++	-	146	ALT Increased	No	Possibly	Not Reported
065/041	1443	M/65	Los	100	210	Angina Pectoris	No	Definitely Not	Recovered
065/041	1446	F/36	Los	50	116	Dizziness	No	Probably	Recovered
			Los	50	116	Hypesthesia	No	Probably	Recovered
065/042	1678	M/45	Los	50	100	Tachycardia	No	Probably Not	Present
			Los	50	100	Atrial Fibrillation	No	Probably Not	Not Reported
			Los	50	100	Ventricular Arrhythmia	No	Probably Not	Not Reported
085/005	3047	M/51	Los/HCTZ	100/25	75	Serum Creatinine Increased	No	Possibly	Not Reported

++On los 50 prior to discontinuation.

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Losartan and Losartan/HCTZ
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 I. Summary

Table 10 (Cont.) Discontinuations Due to Adverse Experiences in Losartan-Treated Hypertensive Patients in Open-Label Trials (Based upon case report form information received Oct. 5, 1993 to July 14, 1994)

Protocol No./ Study No.	AN	Sex/Age	Treatment	Daily Dose (mg)	Relative Day of Onset	Adverse Experience	Serious	Drug Relationship	Outcome
085/007	3065	M/51	Los/HCTZ	50/12.5	3	Dizziness	No	Possibly	Present
			Los/HCTZ	50/12.5	3	Pain, Chest	No	Possibly	Present
			Los/HCTZ	50/12.5	3	Palpitation	No	Possibly	Present
			Los/HCTZ	50/12.5	3	Tremor	No	Possibly	Present
			Los/HCTZ	50/12.5	6	Diarrhea	No	Possibly	Present
			Los/HCTZ	50/12.5	6	Pain, Elbow	No	Possibly	Present
			Los/HCTZ	50/12.5	6	Pain, Wrist	No	Possibly	Present
			Los/HCTZ	100/25	12	Asthenia/Fatigue	No	Possibly	Recovered
			Los/HCTZ	100/25	12	Somnolence	No	Possibly	Recovered
			Los/HCTZ/ Felodipine	100/25/10	35	Nausea	No	Possibly	Recovered
			Los/HCTZ/ Felodipine	100/25/10	35	Depression	No	Possibly	Recovered
085/008	3077	M/62	Los/HCTZ	50/12.5	2	Pain, Chest	Yes	Possibly	Recovered
085/011	3103	M/66	Los/HCTZ	50/12.5	2	Nervousness	No	Possibly	Recovered
			Los/HCTZ	50/12.5	6	Hypersomnia	No	Possibly	Recovered
085/014	3137	M/69	Los/HCTZ	100/25	57	Atrial Fibrillation	No	Probably Not	Recovered
085/014	3139	M/34	Los/HCTZ/ Felodipine	100/25/5	29	Nausea	No	Possibly	Present
			Los/HCTZ/ Felodipine	100/25/5	29	Headache	No	Possibly	Present
095/001	0012	M/67	Los/HCTZ	50/12.5	4	Hypotension, Orthostatic	Yes	Probably	Recovered
			Los/HCTZ	50/12.5	5	Syncope	Yes	Probably	Recovered

Los=Losartan
 HCTZ=Hydrochlorothiazide

FEB 13 1995

NDA #: 20-386/SU
 Drug Name: Losartan (DuP 753, MK-954)
 Sponsor: MSDRL
 Date Received: 4/5/94
 Review Start Date: 2/3/95
 Review Completed: 2/10/95
 Medical Reviewer: Charles J. Ganley, M.D.

The CANADA cannot be easily reviewed for safety data due to limitations in the Query function. Thus, the tables in the Safety Update cannot be validated. The safety update does not include a complete report for study 58 (Reviewer's Note: This study was not complete in the NDA). Within the Safety Update summary, the sponsor has reported the adverse events for several populations. The populations are all hypertensive patients in open label studies (most double-blind data was included in the WMA submission), as hypertensive patients with ≥ 1 year of losartan exposure, as hypertensive patients with ≥ 1 year of losartan/HCTZ exposure, as hypertensive patients with renal impairment and as patients with heart failure.

Table SU.1 lists the patient exposure to losartan in the WMA (original NDA) database and in the SUR (safety update) database. Of the 1712 patients included in the SUR database, 1282 had information included in the WMA database and 430 were newly exposed patients. The cut-off of case report forms for the safety update was 10/4/93. Serious adverse events were reported up until 12/31/93 (WAES Data).

Table SU.1. Number of Patients Exposed to Losartan as a Treatment Regimen

Indication For Losartan Therapy	Time Frame	Treatment Regimen		Total* (Losartan With or Without Other Antihypertensives)
		Losartan Alone	Losartan/HCTZ Alone	
Uncomplicated	WMA	2551	1386	3008
Essential Hypertension	SUR	791	989	1593
	CUM [†]	2823	1872	3384
Renally-Impaired Hypertensives	WMA	115	— [†]	115
	SUR	33	—	33
	CUM	148	—	148
Heart Failure	WMA	180	—	180
	SUR	84	—	84
	CUM	199	—	199
Clinical Pharmacology	WMA	263	63	325
	SUR	2	0	2
	CUM	265	63	327
All Indications	WMA	3109	1449	3628
	SUR	910	289	1712
	CUM	3435	1935	4058

* Patients who received losartan alone and later received losartan/HCTZ are counted in both treatment groups. However, the Total column only counts a given patient once and therefore does not reflect the addition of the Losartan Alone column plus the Losartan/HCTZ Alone column.

† The CUM column is not simply the addition of the WMA and SUR columns because a patient who was treated in the WMA time frame and continued to be treated in the SUR time frame is counted in both time frames. However, this patient is only counted once in the CUM time frame.

† No data. (These studies were not designed to evaluate the safety profile of losartan/HCTZ alone.)

The patients whose data were received during the SUR time frame were in the vast majority, those who participated in the open-label extension phases of 13 trials (protocols 011, 021, 044, 045, 048, 049, 050, 054, 055, 056, 059, 064, 065). Incidence tables for the open-label trials show cumulative values (i.e., adverse events on case report forms received as of October 4, 1993).

As of October 4, 1993, 2056 patients were treated with losartan alone or as part of a treatment regimen in open-label hypertension trials. The duration of treatment with losartan ranged from 2 days to approximately 2.2 years and the mean duration of drug exposure was approximately 8.2 months. Tables SU.2 - SU.2b. show the length of exposure to losartan therapy in hypertensive patients in open-label trials, hypertensives with renal insufficiency and heart failure.

Table SU.2. Number of Hypertensive Patients Treated With Respect to Duration of Therapy—Cumulative Time Frame (Based on Case Report Forms Received Through October 4, 1993)

Duration of Therapy (Days)	Losartan Alone	Losartan/HCTZ Alone	Losartan/HCTZ Plus Other Agents	Losartan Plus Other Agents Excluding HCTZ	Total (Losartan With or Without Other Agents)
1-30	533	279	87	40	87
31-91	429	318	125	42	284
92-183	149	263	106	18	411
184-365	255	438	220	16	1005
366-548	43	49	9	0	101
549-730	59	64	0	0	150
731-913	4	1	0	0	18
>913	0	0	0	0	0
Total Number of Patients	1472	1412	547	116	2056
Total Patient Days on Drug	184913	234953	79458	8632	507956
Range of Duration on Drug	1 to 789	1 to 768	1 to 485	1 to 277	2 to 804
Mean Duration on Drug	125.6	166.4	145.3	74.4	247.1

Table SU.2a. Number of Hypertensive Patients with Renal Impairment Treated By Duration of Therapy and Total Daily Dose

Days of Therapy	Losartan 50 mg		Losartan 100 mg		Losartan 150 mg	
	WMA	CUM	WMA	CUM	WMA	CUM
1 - 7	12	16	28	29	1	1
8 - 30	48	64	12	13	0	0
31 - 91	26	36	53	71	0	0
92 - 183	5	7	2	2	0	0
> 183	0	0	0	0	0	0
Total Number of Patients	115		148			
Total Patient Days on Drug	6982		9547			
Range of Duration on Drug (days)	2 to 124		2 to 124			
Mean Duration on Drug (days)	60.7		64.5			

Table SU.2b. Duration of Chronic Therapy by Total Daily Dose in Patients with Heart Failure

Days of Therapy	Losartan Dose*							
	2.5 mg	5 mg	10 mg	25 mg	50 mg	75 mg	150 mg	>150 mg
1-7	33	2	34	24	1	0	1	0
8-30	22	1	14	7	0	0	0	0
31-91	9	0	7	11	7	0	0	0
92-183	11	1	13	14	6	0	0	0
184-274	0	0	4	5	29	0	0	0
275-365	2	0	1	2	9	0	0	0
>365	0	0	0	1	0	0	0	0
* Three patients are not included in this table as they received doses not specified by the protocols.								
Total Number of Patients	78							
Total Patient Days on Drug	22899							
Range of Duration on Drug (Days)	89 to 718							
Mean Duration on Drug (Days)	293.6							

The distribution of the open-label hypertensive study population with respect to gender, age, race, and duration of disease is displayed in Table SU.3. The majority of patients who participated in the open-label trials were male (60%), Caucasian (78%) with a mean age of 53 years and a mean duration of hypertension of 10 years.

Table SU.3. Demographics of Hypertensive Patients in Open-Label Trials - Cumulative Time Frame (Based on Case Report Forms Received Through October 4, 1993)

		Losartan Alone		Losartan/HCTZ Alone		Total (Losartan With or Without Other Agents)	
Total Patients		1472		1412		2056	
Gender	Male	891	(61%)	853	(60%)	1230	(60%)
	Female	581	(39%)	559	(40%)	826	(40%)
Age (yrs)	<36	82	(6%)	92	(7%)	125	(6%)
	36-45	277	(19%)	278	(20%)	391	(19%)
	46-55	475	(32%)	450	(32%)	652	(32%)
	56-64	387	(26%)	372	(26%)	533	(26%)
	65-74	229	(16%)	206	(15%)	329	(16%)
	≥75	27	(1%)	14	(1%)	26	(1%)
	Mean	53.4		52.8		53.3	
Range	23.0-88.0		21.0-88.0		21.0-88.0		
Race	Caucasian	1157	(78%)	1095	(78%)	1606	(78%)
	Black	179	(12%)	191	(14%)	251	(12%)
	Hispanic	96	(7%)	77	(5%)	120	(6%)
	Other*	46	(3%)	49	(4%)	79	(4%)
Duration Of Disease (yrs)	<1	68	(5%)	57	(4%)	97	(5%)
	1.00-5.00	470	(32%)	448	(32%)	668	(32%)
	5.01-10.00	340	(23%)	336	(24%)	475	(23%)
	>10	559	(38%)	545	(39%)	777	(38%)
	Unknown	35	(2%)	26	(2%)	39	(2%)
	Mean	9.97		10.26		10.05	
Range	0.00-52.00		0.08-56.00		0.00-56.00		

* Other includes: Oriental, Latin American, Asian, Hawaiian, Indian, Spanish, Mestizo, Mulatto, Vietnamese, Cape Verdean, Maori

Deaths

One hypertensive patient died while receiving losartan or within 14 days after discontinuation of therapy during the reporting period July 1, 1993 through December 31, 1993. Data for this patient are summarized in Table SU.4. A narrative providing more detail is presented following the table.

Table SU.4. Serious Fatal Adverse Experiences From All Sources -- Hypertensive Patients, Report Time Frame: July 1, 1993 through December 31, 1993

Protocol/ Study #	Patient #	Age Sex	Treatment	Daily Dose (mg)	Day of Onset	Adverse Experience
065-042	1684	61/M	Losartan	100	340 340 340	Myocardial Infarction Cardiac Arrest Death

Patient #1684 was 61-year-old hypertensive male with a history of arthritis started therapy with losartan 50 mg on January 12, 1993, and his dose was increased to 100 mg on September 7, 1993. He was transported to a hospital on November 11, 1993, in full cardiac arrest. He subsequently died after unsuccessful resuscitation. The cause of death was reported as probable myocardial infarction and cardiopulmonary arrest. At the time of the event, the patient had been receiving losartan 100 mg a day and allopurinol 150 mg.

In patients with CHF, death has been reported for a total of 8 patients from July 1, 1993 through December 31, 1993. All deaths resulted from cardiovascular events with the exception of Study 047-017, # 1207, who had metastatic cancer leading to cardiopulmonary failure. All serious adverse experiences, reported from July 1, 1993 through December 31, 1993, in patients who died while receiving losartan or within 14 days after discontinuation of therapy are tabulated in Table SU.5. The adverse experiences are categorized by body system.

Table SU.5. Serious Clinical Adverse Experiences From All Sources in Losartan-Treated Patients with Heart Failure Who Died-Report Time Frame: July 1, 1993 through December 31, 1993

Study #/ Protocol #	Patient #	Age/Sex	Treatment	Daily Dose (mg)	Study Day of Onset	Adverse Experience
047-017 047-21	1207	60/Male	Losartan	20 20 20 20	285 396 Unknown 515	Metastatic Neoplasm Worsening Heart Failure Intestinal Obstruction Respiratory Failure, Malignant Neoplasm, Death
047-001 047-20	1002	52/Male	Losartan	50	590	Myocardial Infarction, Death
047-001 047-20	1010	71/Male	Losartan	25 25	440 466	Myocardial Infarction Cardiac Arrest, Death
047-015 047-21	1167	55/Male	Losartan	50 50	Unknown 512	Coronary Artery Disease, Chronic Obstructive Pulmonary Disease Death
047-021 047-21	1135	75/Male	Losartan	50 50	637 641	Myocardial Infarction Cardiac Arrest Death
071-001 071-10	135	60/Male	Losartan	25	285	Sudden Death
071-003 071-10	106	69/Male	Losartan	50	189	Sudden Death
071-019 071-10	80	72/Male	Losartan	50 50 50	166 167 202	Anemia Ventricular Tachycardia Worsening Heart Failure, Sudden Death

This 60-year-old male (# 1207 - Protocol #047-21, Study #047-017) with heart failure, multiple bony metastases and a history of herpes zoster, diverticulitis, cancer of the larynx and partial laryngectomy received a single daily dose of losartan 2.5 mg for 12 weeks. Concomitant medication included isosorbide dinitrate, furosemide, acetylsalicylic acid, diclofenac, lorazepam dextropropoxyphene HCl, augmentin, morphine sulfate, fluoxetine, paraffin and lactitolium monohydratum. He entered open-label extension on a single daily dose of losartan 5 mg and was titrated to 20 mg. On Day 285 the patient was hospitalized with sciatic pain and a diagnosis of lytic pelvic lesion was made. He was released from the hospital and treated with radiotherapy. On Day 396 he experienced worsening heart failure and was hospitalized. The patient was hospitalized again on Day 512 due to stenosis of the colon. On Day 515 the patient died of cardiopulmonary failure and terminal stage of cancer.

This 52-year-old male (# 1002 - Protocol #047-20, Study #047-001) with heart failure and a history of silent myocardial infarctions and mitral and tricuspid valve replacements received placebo for 12 weeks. Concomitant medication included furosemide and potassium chloride. He entered open-label extension on a single daily dose of losartan 2.5 mg and was titrated to 50 mg. On Day 590 (day 500 of losartan therapy) the patient was at home working on his roof when he collapsed. He was found dead by his wife. An autopsy was performed which revealed myocardial infarction as the cause of death.

This 71-year-old male (# 1010 - Protocol #047-20, Study #047-001) with heart failure, hypertriglyceridemia, coronary artery disease and a history of myocardial infarction and PVCs received placebo for 12 weeks. Concomitant medication included furosemide, triamterene, digoxin, potassium chloride and cholestyramine. He entered open-label extension on a single daily dose of losartan 2.5 mg and was titrated to 25 mg. On Day 440 (day 348 of losartan therapy) the patient developed chest pain and was hospitalized with a diagnosis of myocardial infarction. The patient recovered and was released from the hospital. On Day 466 (day 374 of losartan therapy) he suffered cardiac arrest while golfing. He was hospitalized, treated with dopamine and subsequently died.

This 55-year-old male (# 1167 - Protocol #047-21, Study #047-015) with heart failure, gout, angina pectoris, chronic obstructive pulmonary disease, coronary artery disease, and a history of myocardial infarction received placebo for 12 weeks. Concomitant medication included furosemide, potassium chloride, allopurinol, salbutamol and beclomethasone. He entered open-label extension on a single daily dose of losartan 2.5 mg and was titrated to 50 mg. On Day 512 (Day 427 of losartan therapy) the patient experienced myocardial infarction, ventricular fibrillation and died later that day. Probable causes of death were identified as acute myocardial infarction, ventricular fibrillation, coronary artery disease, congestive heart failure and chronic obstructive airways disease.

This 75-year-old male (# 1135 - Protocol #047-21, Study #047-021) with heart failure, atrial fibrillation, angina pectoris, ventricular tachyarrhythmia and a history of myocardial infarction, renal cancer and nephrectomy received placebo for

12 weeks. Concomitant medication included furosemide, amiodarone, digitoxin, allopurinol, thyroxine, warfarin, trichlormethiazide and spironolactone. He entered open-label extension on a single daily dose of losartan 2.5 mg and was titrated to 50 mg. On Day 637 (Day 486 of losartan therapy) the patient was admitted to the hospital due to a myocardial infarction and cardiac arrest. The patient was resuscitated after 25 minutes but never regained consciousness. On Day 641 (Day 490 of losartan therapy) he died at the hospital.

This 60-year-old male (# 135 - Protocol #071-10, Study #071-001) with heart failure and a history of diabetes, hypercholesterolemia, myocardial infarction and transient ischemic attack was titrated from a single daily dose of losartan 12.5 to 50 mg for 8 weeks. Concomitant medication included warfarin, furosemide, and lovastatin. The patient entered open-label extension and received a single daily dose of losartan 25 mg. On Day 285, the patient died suddenly. No autopsy results are available.

This 69-year-old male (# 106 - Protocol #071-10, Study #071-003) with heart failure and a history of myocardial infarction, hernia surgery, mitral regurgitation, and nephrolithiasis was titrated from a single daily dose of losartan 12.5 to 50 mg for 8 weeks. Concomitant medication included isosorbide mononitrate, digoxin, furosemide, warfarin and amiodarone. The patient entered open-label extension and received a single daily dose of losartan 50 mg. On Day 189, the patient died suddenly. No autopsy results are available.

This 72-year-old male (# 80 - Protocol #071-10, Study #071-019) with heart failure and a history of myocardial infarction, stroke, abdominal aortic aneurysm, pacemaker, angina pectoris, hyperuricemia, hypokalemia, and ulcer was titrated from a single daily dose of losartan 12.5 to 50 mg for 8 weeks. Concomitant medication included digitoxin, furosemide, isosorbide dinitrate, allopurinol, ranitidine, and potassium. The patient entered open-label extension and received a single daily dose of losartan 50 mg. On Day 166 the patient was hospitalized due to anemia. Ventricular tachycardia was observed the next day. Metoprolol therapy was initiated to treat the ventricular arrhythmias. Iron sulphate therapy was initiated approximately 1 month later to treat the anemia. On Day 202 the patient died suddenly. Autopsy revealed signs of heart failure.

Adverse Events - Clinical

The reporting of adverse event incidence rates is made difficult by the fact that many patients received multiple therapies during the open label period. In the tables that follow, if an adverse event occurred while the patient received losartan alone and again while on combination therapy, it was counted as occurring with each therapy. If a adverse event started while a patient was on one therapy and continued after they added an additional therapy, it was counted only for the therapy that the patient was receiving at the start of the adverse event. Adverse events which occurred in the double-blind period are not included in these counts.

Table SU.6 presents the most frequently reported clinical adverse experiences that occurred in uncomplicated essential hypertensive patients. Specifically, Table SU.4 shows adverse events that occurred in $\geq 1\%$ and 2 or more patients exposed to a given losartan treatment group. The most frequently reported adverse experiences in the cumulative losartan monotherapy group were headache (11.8%), upper respiratory infection (9.6%), dizziness (3.8%), asthenia/fatigue (3.3%), and cough (3.1%). The most frequently reported adverse experiences in the cumulative losartan/HCTZ group were upper respiratory infection (10.3%), headache (3.1%), dizziness (4.7%) and back pain (4.0%). With few exceptions, the safety profile of losartan/HCTZ plus other antihypertensives was similar to losartan/HCTZ alone in the cumulative time frame. The exceptions included higher incidence values for edema/swelling (1.9% and 7.7%), joint swelling (0.2% and 1.3%) and flushing (0.3% and 3.1%) in the losartan/HCTZ plus other antihypertensives category, which is most likely due to the adverse experience profile of the antihypertensives that were administered in addition to the losartan/HCTZ (e.g., calcium channel blockers).

Table SU.6 Percentage of Clinical Adverse Experiences That Occurred in $\geq 1\%$ of Losartan-Treated Hypertensive Patients*: Open-Label Trials

	Losartan Monotherapy		Losartan/HCTZ		Losartan/HCTZ Plus Other Antihypertensives		Losartan Plus Other Antihypertensives Without HCTZ	
	WMA n=831	CUM n=1472	WMA n=601	CUM n=1412	WMA n=212	CUM n=347	WMA n=12	CUM n=116
Body as Whole								
Asthma/fatigue	3.4	3.3	2.8	3.0	1.9	2.2	16.7	3.4
Edema/swelling	1.9	2.3	1.3	1.9	6.6	7.7	0.0	5.2
Fever	0.6	0.5	0.5	1.1	0.5	0.7	0.0	0.9
Flu-like illness	0.4	0.6	1.3	1.0	0.5	0.5	0.0	0.0
Pain, abdominal	2.3	2.4	2.3	2.1	0.5	1.5	0.0	1.7
Pain, chest	2.0	1.6	3.0	2.5	0.9	2.6	0.0	0.0
Syncope	0.1	0.2	0.2	0.3	0.5	0.5	8.3	1.7
Cardiovascular System								
Palpitation	0.6	0.7	0.3	0.8	0.5	0.7	8.3	2.6
Digestive System								
Diarrhea	3.1	2.3	2.0	2.8	1.4	2.4	0.0	2.6
Dyspepsia	1.1	1.0	1.3	1.6	1.4	0.9	0.0	0.9
Nausea	1.9	1.8	1.3	1.3	0.5	1.6	0.0	0.0
Pain, dental	0.6	0.5	0.5	1.1	0.0	0.9	0.0	0.9
Vomiting	0.2	0.3	0.3	1.0	0.0	0.4	0.0	0.9
Musculoskeletal System								
Cramp, muscle	0.4	0.7	1.3	1.3	1.4	0.5	0.0	0.0
Myalgia	1.2	1.0	0.5	0.9	0.5	1.3	0.0	0.0
Pain, knee	0.7	1.0	0.8	0.8	0.9	0.5	0.0	0.9
Pain, back	2.2	2.7	2.7	4.0	1.4	2.0	0.0	0.9
Pain, leg	1.0	0.9	0.3	0.5	0.0	0.2	0.0	0.0
Pain, neck	0.4	0.5	0.7	1.0	0.0	0.2	0.0	0.0
Pain, shoulder	0.6	0.5	1.5	1.5	0.5	0.4	0.0	0.0
Swelling, joint	0.6	0.4	0.0	0.2	0.0	1.3	0.0	0.0
Nervous System and Psychiatric								
Anxiety	0.8	1.0	0.8	1.3	1.9	2.0	0.0	0.9
Depression	1.2	0.7	0.2	0.7	0.5	1.3	0.0	0.0
Dizziness	3.7	3.8	5.8	4.7	4.2	6.6	8.3	4.3
Headache	12.5	11.8	8.5	9.1	7.5	10.8	0.0	12.1
Insomnia	1.3	1.2	1.0	1.1	0.0	0.7	0.0	0.9
Libido decreased	0.4	0.3	0.2	0.3	0.0	0.0	0.0	1.7
Paresthesia	0.7	0.7	1.3	1.6	0.0	0.5	8.3	1.7
Somnolence	0.4	0.4	0.2	0.9	0.5	1.1	0.0	2.6
Respiratory System								
Bronchitis	0.7	1.6	1.5	3.1	0.5	1.5	0.0	0.9
Congestion, Nasal	1.1	1.2	2.0	1.3	0.9	0.5	0.0	0.0
Cough	2.5	3.1	2.7	3.3	1.9	2.4	0.0	4.3
Dyspnea	0.7	0.4	0.8	0.6	0.5	0.2	0.0	1.7
URI	9.1	9.6	6.7	10.3	6.6	9.3	16.7	10.3
Influenza	0.5	1.5	1.0	2.0	0.9	2.6	0.0	1.7
Pharyngitis	2.5	2.2	2.0	2.3	1.4	3.1	0.0	2.6
Sinus disorder	1.3	1.4	0.8	1.2	0.5	0.5	0.0	3.4
Sinusitis	1.8	1.8	0.7	2.1	0.5	1.6	8.3	2.6
Skin and Skin Appendage								
Flushing	0.2	0.2	0.5	0.3	2.8	3.1	0.0	1.7
Rash	2.0	1.8	1.5	1.8	0.9	1.3	8.3	0.9
Special Senses								
Fullness in ears	0.2	0.1	0.3	0.2	0.0	0.0	0.0	1.7
Urogenital System								
Impotence	0.6	0.5	1.2	1.1	1.4	1.6	0.0	0.9
Infection, Urinary Tract	1.7	1.5	1.5	1.2	0.9	1.3	0.0	0.9

* Occurring in $\geq 1\%$ and 2 or more hypertensive patients in at least one of the losartan treatment groups.

Table SU.6a list the incidence of adverse events occurring in hypertensives with renal impairment. Headache, dizziness, URI, edema, chest pain, and nausea were the most commonly reported adverse events.

Table SU.6a. Percentage of Clinical Adverse Experiences that Occurred in More Than One Losartan-Treated Hypertensive Patient with Renal Impairment

Body System	WMA Losartan (n = 115)	Cumulative Losartan (n=148)	Body System	WMA Losartan (n = 115)	Cumulative Losartan (n=148)
Body as a Whole			Nervous System and Psychiatric		
Asthenia/Fatigue	3.5	4.1	Dizziness	9.6	9.5
Distention, Abdominal	0.9	1.4	Headache	16.5	18.9
Edema/Swelling	5.2	5.4	Hypesthesia	1.7	1.4
Fever	1.7	2.0	Insomnia	1.7	2.0
Orthostatic Effects	1.7	2.0	Neuropathy, Peripheral	1.7	1.4
Pain, Abdominal	4.3	4.1	Sleep Disorder	1.7	1.4
Pain, Chest	4.3	6.1	Somnolence	1.7	1.4
Pain, Flank	1.7	2.0	Tremor	0.9	1.4
Syncope	0.9	2.0	Vertigo	0.9	1.4
Cardiovascular System			Respiratory System		
Blood Pressure Increased	0	1.4	Congestion, Nasal	1.7	1.4
Hypotension	3.5	4.1	Cough	2.6	3.4
Occlusion, Vascular Graft	0.9	1.4	Dyspnea	4.3	4.1
Tachycardia	1.7	2.0	Epistaxis	2.6	2.0
Digestive System			Infection, Respiratory, Upper	12.2	13.5
Constipation	1.7	1.4	Influenza	2.6	2.0
Diarrhea	1.7	2.0	Pharyngitis	2.6	2.0
Flatulence	2.6	2.0	Pneumonia	0.9	1.4
Nausea	7.0	6.8	Skin and Skin Appendage		
Vomiting	6.1	5.4	Infection, Skin	0	2.0
Metabolic/Nutritional System/Immune			Pruritus	0	1.4
Allergy	0.9	1.4	Rash	1.7	1.4
Fluid Overload	1.7	1.4	Special Senses		
Gout	1.7	1.4	Blurred Vision	2.6	2.0
Weight Gain	0	1.4	Urogenital System		
Musculoskeletal System			Dysuria	0.9	1.4
Cramp, Muscle	2.6	2.7	Impotence	2.6	2.0
Osteoarthritis	1.7	1.4			
Pain, Arm	0.9	1.4			
Pain, Back	4.3	4.7			
Pain, Hip	0.9	1.4			
Pain, Leg	1.7	1.4			
Pain, Neck	1.7	1.4			
Pain, Shoulder	1.7	2.0			
Stiffness	1.7	1.4			
Weakness, Muscle	0.9	1.4			

Table SU.6b list adverse event incidences for CHF patients. The profile is similar to the patient populations just described except that dyspnea is a more common complaint.

Table SU.6b. Number of Clinical Adverse Experiences in >1 Patient with Heart Failure Receiving Chronic Therapy With Losartan

Body System	Losartan (n=78) # Pts. (%)	Body System	Losartan (n=78) # Pts. (%)
Any Adverse Experience	59 (75.6)	Nervous System and Psychiatric	23 (29.5)
Body as a Whole	33 (42.3)	Headache	10 (12.8)
Asthemia/Fatigue	14 (17.9)	Dizziness	9 (11.5)
Edema/Swelling	6 (7.7)	Respiratory System	31 (39.7)
Chest Pain	5 (6.4)	Dyspnea	15 (19.2)
Fever	5 (6.4)	Cough	7 (9.0)
Death [†]	4 (5.1)	URI	5 (6.4)
Sudden Death [†]	3 (3.8)	Pneumonia	3 (3.8)
Syncope	3 (3.8)	Exertional Dyspnea	2 (2.6)
Orthostatic Effects	2 (2.6)	Nasal Congestion	2 (2.6)
Unknown Cause of Death ^{††}	2 (2.6)	Pulmonary Congestion	2 (2.6)
Cardiovascular System	21 (26.9)	Rhinorrhea	2 (2.6)
Heart Failure (worsening)	14 (17.9)	Sinus Disorder	2 (2.6)
Palpitation	3 (3.8)	Skin and Skin Appendage	11 (14.1)
Angina Pectoris	2 (2.6)	Rash	4 (5.1)
Hypertension Increased	2 (2.6)	Laceration	2 (2.6)
Myocardial Infarction	2 (2.6)	Skin Infection	2 (2.6)
Orthostatic Hypotension	2 (2.6)	Special Senses	6 (7.7)
Digestive System	17 (21.8)	Blurred Vision	2 (2.6)
Nausea	7 (9.0)	Cataract	2 (2.6)
Diarrhea	5 (6.4)		
Constipation	4 (5.1)		
Endocrine System	2 (2.6)		
Diabetes Mellitus	2 (2.6)		
Metabolic/Nutritional/Immune	3 (3.8)		
Weight Gain	3 (3.8)		
Musculoskeletal System	16 (20.5)		
Shoulder Pain	4 (5.1)		
Back Pain	3 (3.8)		
Arm Pain	2 (2.6)		
Jaw Pain	2 (2.6)		
Leg Pain	2 (2.6)		
Muscle Cramp	2 (2.6)		

[†] WAES report information on deaths of these 7 patients were presented in the losartan WMA.

^{††} Unknown cause of death was reported for 2 of the 7 patients.

Adverse Events - Laboratory

Laboratory adverse events were treated the same as was described for clinical adverse events. The major difference between the clinical data and laboratory data is that not all patients had labs obtained by 10/4/93. As a consequence, it is difficult to interpret the percentages of patients with losartan adverse events. The safety update is deficient in that actual laboratory values for these patients are not provided.

Table SU.7 summarizes the most frequently reported (i.e., in $\geq 1\%$ and in a parameter tested in at least 100 patients) laboratory adverse experiences. The incidences of laboratory adverse experiences in the cumulative time frame are similar to those presented in the WMA. In the losartan monotherapy group for the cumulative time frame, the most frequently reported laboratory adverse events were urine blood increased (3.8%), urine hemoglobin increased (3.6%), ALT increased (3.0%), urine RBCs increased (2.5%), and urine WBC increased (2.5%). In the losartan/HCTZ alone group, the most common adverse events were urine blood increased (3.5%), ALT increased (3.3%), serum potassium decreased (2.5%), fasting serum glucose increased (2.5%), and AST increased (2.4%).

Table SU.7. Laboratory Adverse Experiences Occurring in $\geq 1\%$ of Hypertensive Patients Treated With Losartan*--Open-Label Trials [Reviewer's Note: The denominator for each lab is the number of patients who had that lab obtained.]

Laboratory Parameter	Losartan Monotherapy				Losartan/HCTZ				Losartan/HCTZ Plus Other Antihypertensives				Losartan Plus Other Antihypertensives Without HCTZ			
	WMA (n=831)		CUM (n=1472)		WMA (n=601)		CUM (n=1412)		WMA (n=212)		CUM (n=547)		WMA (n=12)		CUM (n=116)	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Hematology																
Hemoglobin decreased	5/504	1.0	7/825	0.8	4/479	0.8	7/1066	0.7	2/197	1.0	4/487	0.8	1/8	12.5	1/79	1.3
WBC Count increased	2/504	0.4	2/825	0.2	5/479	1.0	7/1065	0.7	1/197	0.5	1/487	0.2	0/8	0.0	0/79	0.0
WBC Count decreased	0/504	0.0	0/825	0.0	1/479	0.2	4/1065	0.4	2/197	1.0	3/487	0.6	0/8	0.0	0/79	0.0
Eosinophils increased	1/503	0.2	3/824	0.4	0/479	0.0	3/1065	0.3	2/198	1.0	5/487	1.0	0/8	0.0	0/79	0.0
Blood Chemistry																
Blood Urea increased	1/64	1.6	1/162	0.6	1/47	2.1	2/185	1.1	1/24	4.2	1/102	1.0	0/1	0.0	0/4	0.0
Serum Creatinine increased	2/508	0.4	3/842	0.4	6/489	1.2	8/1086	0.7	1/198	0.5	5/489	1.0	0/8	0.0	1/79	1.3
Total Serum Bilirubin increased	1/508	0.2	3/817	0.4	5/489	1.0	7/1046	0.7	1/198	0.5	5/473	1.1	0/8	0.0	0/80	0.0
AST increased	5/509	1.0	8/839	1.0	14/489	2.9	26/1078	2.4	2/198	1.0	8/488	1.6	0/8	0.0	0/81	0.0
ALT increased	14/507	2.8	25/839	3.0	19/486	3.9	36/1081	3.3	5/198	2.5	15/487	3.1	0/8	0.0	3/81	3.7
Serum Alkaline Phosphatase increased	5/507	1.0	6/836	0.7	6/489	1.2	10/1083	0.9	0/198	0.0	1/488	0.2	0/8	0.0	0/80	0.0
Serum Glucose increased	3/327	0.9	8/628	1.3	12/344	3.5	19/921	2.1	4/117	3.4	11/401	2.7	0/5	0.0	1/73	1.4
Fasting Serum Glucose increased	1/181	0.6	1/211	0.5	3/146	2.1	4/163	2.5	3/80	3.8	4/91	4.4	0/3	0.0	0/6	0.0
Triglycerides increased	0/91	0.0	2/252	0.8	1/110	0.9	5/489	1.0	0/20	0.0	0/160	0.0	0/6	0.0	0/53	0.0
Serum Uric Acid increased	3/496	0.6	5/826	0.6	8/478	1.7	15/1072	1.4	3/198	1.5	7/489	1.4	0/8	0.0	0/79	0.0
Serum Potassium decreased	3/508	0.6	4/843	0.5	18/490	3.7	27/1088	2.5	4/198	2.0	10/489	2.0	0/8	0.0	0/79	0.0
Serum Phosphorus decreased	1/496	0.2	1/826	0.1	2/488	0.4	2/1075	0.2	5/197	2.5	4/488	0.8	0/8	0.0	0/79	0.0
Urinalysis																
Urine Protein increased	4/498	0.8	5/819	0.6	7/477	1.5	8/1055	0.8	0/193	0.0	3/480	0.6	0/7	0.0	0/77	0.0
Urine WBCs increased	7/359	1.9	11/436	2.5	8/337	2.4	9/780	1.2	4/114	3.5	5/275	1.8	0/4	0.0	0/10	0.0
Urine RBCs increased	7/359	1.9	11/436	2.5	9/337	2.7	12/780	1.5	4/114	3.5	7/275	2.5	0/4	0.0	0/10	0.0
Bacteria	1/359	0.3	2/436	0.5	1/337	0.3	1/780	0.1	2/114	1.8	2/275	0.7	0/4	0.0	0/10	0.0
Urine Blood increased	4/126	3.2	7/185	3.8	3/110	2.7	5/141	3.5	2/59	3.4	1/89	1.1	0/3	0.0	0/18	0.0
Urine Hemoglobin increased	-----	-----	5/140	3.6	-----	-----	0/6	0.0	-----	-----	1/40	2.5	-----	-----	2/49	4.1
Any Laboratory Adverse Experience	59/539	11	106/894	12	88/494	18	143/1095	13	33/198	17	70/490	14	1/8	12.5	8/82	9.8

†The dashes denote that no tests were performed on this parameter

Table SU.7a lists the number of hypertensive patients with renal impairment who experienced laboratory adverse events. Compared to hypertensives without renal impairment (table SU.7.), more patients with renal impairment had increases in potassium and creatinine. These cases will require additional data from the sponsor. It is not clear that this increase is due to losartan or underlying disease.

Table SU.7a. Laboratory Adverse Experiences Occurring in More Than One Losartan-Treated Hypertensive Patient with Renal Impairment

	Losartan No. (%) WMA	Losartan No. (%) CUM
Any Laboratory Adverse Experiences	21/114 (18.4)	36/145 (24.8)
Hematology		
Increased Eosinophils	3/113 (2.7)	3/143 (2.1)
Blood Chemistry		
Increased BUN	0/101 (0.0)	4/132 (3.0)
Increased Serum Creatinine	4/114 (3.5)	6/145 (4.1)
Increased AST	1/112 (0.9)	2/142 (1.4)
Increased ALT	3/112 (2.7)	4/142 (2.8)
Increased Serum Alkaline Phosphatase	2/114 (1.8)	3/145 (2.1)
Increased Serum Glucose	1/75 (1.3)	2/105 (1.9)
Increased Serum Potassium	7/114 (6.1)	16/145 (11.0)
Decreased Serum Calcium	3/112 (2.7)	3/142 (2.1)
Urinalysis		
Increased Urine WBCs	1/93 (1.1)	2/118 (1.7)
Decreased Urine Chloride	0/59 (0.0)	2/82 (2.4)
Decreased Creatinine Clearance	1/89 (1.1)	2/112 (1.8)

Table SU.7b lists the incidence of lab adverse events.

Table SU.7b. Laboratory Adverse Experiences In >1 Patient with Heart Failure Receiving Chronic Therapy With Losartan

	Losartan No. + (%)
Any Laboratory Adverse Experience	15/77 (19.5)
Blood Chemistry	
Increased Serum Glucose	5/77 (6.5)
Increased Blood Urea Nitrogen	4/77 (5.2)
Increased Serum Creatinine	3/77 (3.9)
Decreased Serum Potassium	2/77 (2.6)
Hematology	
Decreased Hemoglobin	2/77 (2.6)
Urinalysis	
Increased Urine Glucose	3/76 (3.9)
Increased Urine White Blood Cells	3/76 (3.9) ⁺
⁺ One patient died prior to any laboratory evaluations; therefore, laboratory values are reported for only 77 patients.	

Adverse Event - Serious

All nonfatal serious adverse experiences that occurred in patients while receiving losartan or within 14 days after discontinuation of therapy during the reporting period July 1, 1993, through December 31, 1993, are presented in Table SU.8. Serious nonfatal adverse experiences have been reported for a total of 77 patients. At the time of the adverse event, 21 were on losartan monotherapy, 31 on losartan/HCTZ, 21 on losartan/HCTZ plus other antihypertensives and 4 on losartan plus other antihypertensives. Nonfatal serious adverse experiences attributed to the cardiovascular system were observed in 20 of the patients and 17 patients had serious adverse experiences attributed to the urogenital system. One patient with renal impairment experienced a serious adverse event (table SU.8b.)

Table SU. 8. Serious Nonfatal Adverse Experiences From All Sources – Hypertensive Patients; Report Time Frame: July 1, 1993 through December 31, 1993

Protocol/ Study #	Patient #	Age/Sex	Treatment	Daily Dose (mg)	Study Day of Onset	Adverse Experience	Outcome
011-028	0583	80/M	Los	50	871	Pain, Chest	Recovered
055-015	5318	88/M	Los	100	237#	Hernia	NR
065-010	1432	50/F	Los/HCTZ/Aten	100/12.5/100	482	Pain, Chest	Recovered
085-008	3077	62/M	Los/HCTZ	50/12.5	9	Pain, Chest**	Still Present
011-003	0025	65/M	Los	100	NR	Obstruction, Cr. otid Artery	Recovered
011-040	0830	40/F	Los	150	488	Myalgia**	Recovered
			Los	150	500	Angina Pectoris	Recovered
			Los	150	500	Occlusion, Coronary Artery	Still Present
011-040	0836	55/F	Los/HCTZ	100/12.5	647#	Occlusion, Arterial	Recovered
044-006	3101	65/M	Los	50	173	Palpitation	Recovered
044-011	3180	57/M	Los/HCTZ	50/6.25	382#	Myocardial Infarction**	Recovered
045-001	4024	68/M	Los	50	206#	Claudication, Intermittent	Recovered
048-007	0590	42/F	Los	50	10	Supraventricular Tachycardia**	Recovered
054-001	8009	69/M	Los/HCTZ	50/12.5	426	Atherosclerosis, Coronary**	Still Present
			Los/HCTZ	50/12.5	419	Fibrosis, Pulmonary	Still Present
054-005	8105	62/F	Los/HCTZ	50/12.5	411#	Atherosclerosis, Coronary	Still Present
054-008	8184	72/M	Los/HCTZ	50/6.25	389#	Heart Failure**	Still Present
			Los/HCTZ	50/6.25	389#	Pneumonia	Still Present
054-021	8454	71/M	Los/HCTZ	50/6.25	337	Premature Ventricular Contrac.	Still Present
054-016	8348	69/M	Los/HCTZ/Fel	50/25/5	159#	Atherosclerosis, Coronary	Recovered
054-019	8879	64/M	Los/HCTZ/Fel	50/12.5/10	190#	Aneurysm, Aortic	Recovered
054-027	8558	67/M	Los/HCTZ	50/12.5	377#	Pain, Chest	Recovered
			Los/HCTZ	50/12.5	377#	Atherosclerosis, Coronary	Recovered
054-029	8608	59/F	Los/HCTZ/Fel	50/12.5/5	306#	Angina, Unstable**	Recovered
056-015	3683	64/M	Los	100	207#	Angina Pectoris**	NR
059-011	5604	34/M	Los/HCTZ/Aten/Nif	100/25/100/40	142	Hypertension	Recovered
065-011	1584	70/M	Los/HCTZ/Aten	100/25/100	230#	Angina Pectoris	Recovered
065-014	1473	39/M	Los/Aten	100/50	333	Atrial Fibrillation**	Recovered
065-028	1387	51/F	Los	50	159	Syncope**	Recovered
			Los	50	159	Dizziness	Recovered
			Los	50	159	Blurred Vision	Recovered
			Los	50	159	Headache	Recovered
			Los	50	159	Pain, Abdominal	Recovered
			Los	50	159	Cholelithiasis	Still Present
011-013	0255	--/M	Los	NR	NR	Inflammatory Bowel Disease	Recovered
045-003	4095	57/M	Los	50	67#	Ulcer, Duodenal w/ Hemorrhage	Recovered
			Los	50	67#	Melena	Recovered
048-016	6295	43/F	Off-drug	--	213	Pancreatitis**	Recovered
054-004	8092	40/M	Los/HCTZ/Fel	50/12.5/10	281#	Cholelithiasis	Recovered
054-011	8247	63/M	Los/HCTZ	50/6.25	337#	Cholelithiasis	Recovered
054-015	8334	44/F	Los/HCTZ	50/6.25	415#	Cholecystitis	Still Present
054-026	8557	69/F	Los/HCTZ/Fel	50/6.25/5	489#	Vomiting	Recovered
			Los/HCTZ/Fel	50/6.25/5	489#	Diarrhea	Recovered
			Los/HCTZ/Fel	50/6.25/5	489#	Dehydration	Recovered
059-007	5557	67/M	Los	100	319	Neoplasm, Intestinal, Malignant**	Still Present
065-019	1505	54/M	Los/Aten/HCTZ	100/100/25	283#	Ileus	Still Present
065-038	1159	43/F	Los/Fel/HCTZ	100/10/25	416	Cholecystitis	Still Present
065-042	1683	58/M	Los/Fel/HCTZ	100/5/12.5	379	Cholecystitis	Recovered
054-009	8206	56/F	Los/HCTZ/Fel	50/12.5/5	381#	Neoplasm, Thyroid, Malignant	Still Present
055-010	5166	76/F	Los/Fel	100/15	369	Hypoglycemia	Recovered
			Los/Fel	100/15	369	Confusion	Recovered
055-010	5166	76/F	Los/Fel	100/15	379	Hypoglycemia	Recovered
			Los/Fel	100/15	379	Confusion	Recovered
044-009	3005	35/M	Los/HCTZ	50/6.25	290	Pain, Back	Recovered
050-018	2318	52/M	Los/HCTZ/Fel	50/12.5/10	385#	Pain, Neck	Recovered
054-003	8047	45/M	Off drug	--	295	Fracture, Leg, Multiple	Recovered

Table SU. 8. Serious Nonfatal Adverse Experiences From All Sources – Hypertensive Patients; Report Time Frame: July 1, 1993 through December 31, 1993 (con't)

Protocol/ Study #	Patient #	Age/Sex	Treatment	Daily Dose (mg)	Study Day of Onset	Adverse Experience	Outcome
059-010	5593	51/M	Los/HCTZ Los/HCTZ	100/12.5 100/12.5	229# 229#	Fracture, Femur Fracture, Foot	Still Present Still Present
059-021	5728	56/F	Los/HCTZ/Aten	100/25/100	296	Fracture, Ankle	Still Present
065-038	1150	65/M	Los/Fel Off-drug	50/5 --	225 232	Pain, Knee Hematoma	Still Present Recovered
011-040	2528	65/M	Los	100	607	Dizziness	Recovered
045-010	175	69/M	Los/HCTZ Los/HCTZ Los/HCTZ	50/12.5 50/12.5 50/12.5	217 217 240	Stiffness Akinesia/Bradykinesia Confusion	Recovered Recovered Recovered
045-015	4250	45/F	Off-drug	--	162	Sclerosis, Multiple**	Still Present
050-023	2403	53/M	Los Los	50 50	506# 506#	Hyposthesia Pain, Chest	Still Present NR
011-002	0027	60/M	Los/HCTZ	100/25	230#	Neoplasm, Lung, Metastatic	Still Present
011-030	0611	66/F	Los/HCTZ	100/50	824#	Neoplasm, Lung, Malignant	Recovered
044-005	3082	69/M	Los	50	177	Neoplasm, Lung, Malignant**	Still Present
045-001	4019	67/M	Los/HCTZ Los/HCTZ	50/6.25 50/6.25	365# 341#	Neoplasm, Lung, Malignant Dyspnea	Still Present Still Present
054-011	8257	63/M	Los/HCTZ/Fel	50/12.5/5	308#	COPD	Still Present
055-010	5169	82/M	Los	100	128	Neoplasm, Pharyngeal, Malignant**	Still Present
048-007	6014	43/M	Los/HCTZ/Nif	50/12.5/40	169	Neoplasm, Skin, Malignant	Recovered
050-008	2133	70/F	Los	50	119	Neoplasm, Skin, Malignant	Recovered
050-015	2254	46/F	Los/HCTZ	50/50	518	Neoplasm, Skin Malignant	Recovered
054-019	8409	61/M	Los/HCTZ	50/12.5	505#	Neoplasm, Skin, Malignant	Still Present
064-014	4597	68/M	Los/HCTZ	100/25	312#	Neoplasm, Skin, Malignant	Recovered
054-026	8549	66/M	Los/HCTZ Los/HCTZ	50/6.25 50/6.25	331 356	Visual Loss** Glaucoma	Still Present Still Present
011-028	0575	75/M	Los	50	929	Neoplasm, Kidney, Malignant**	Still Present
011-034	0697	79/F	Los/HCTZ	100/25	810#	Septicemia (Urosepsis)	Recovered
011-038	0781	58/F	Los/HCTZ	100/25	727	Nephrotic Syndrome	Still Present
011-038	0784	54/F	Los/HCTZ	100/12.5	704	Implant, Breast, Complication	Recovered
044-006	3101	66/M	Los	50	354#	Neoplasm, Prostate, Malignant	Recovered
044-011	3170	58/M	Los	50	105	Neoplasm, Prostate, Malignant**	Recovered
045-001	4022	43/M	Los	50	327#	Benign Prostatic Hypertrophy	Recovered
048-004	6109	44/M	Los/HCTZ	50/12.5	15#	Obstruction, Urinary Tract	Recovered
050-013	2423	51/F	Los/HCTZ/Fel	50/12.5/10	491#	Neoplasm, Breast, Malignant	Still Present
054-005	8132	55/M	Los/HCTZ Los/HCTZ Los/HCTZ	50/12.5 50/12.5 50/12.5	329# 346# 377#	Neoplasm, Prostate, Malignant Diverticulitis, Intestinal Neoplasm, Urethral, Malignant	Still Present Still Present Still Present
054-011	8244	71/M	Los/HCTZ/Fel	50/12.5/5	4#	Neoplasm, Prostate, Malignant	Still Present
054-011	8255	43/M	Los/HCTZ	50/6.25	484#	Neoplasm, Kidney, Malignant	Recovered
054-016	8342	34/F	Los/HCTZ Los/HCTZ	50/12.5 50/12.5	391# 392#	Pyelonephritis Anemia	Recovered Recovered
054-019	8876	63/F	Los/HCTZ/Fel	50/12.5/5	452	Neoplasm, Kidney, Malignant	Still Present
056-001	3558	--/M	Los/HCTZ/Fel	100/12.5/10	230#	Neoplasm, Bladder, Malignant	Still Present
056-009	3550	48/F	Los/HCTZ	100/6.25	274#	Neoplasm, Uterine, Malignant	Still Present
085-016	3152	70/M	Los/HCTZ	100/25	31	Neoplasm, Prostate, Malignant	Still Present

*Case Report Form data in-house during the SUR time frame take precedence over the WAES report.** = DISCONTINUED

#Study day of onset calculated from start of open-label extension; Aten=Atenolol; Fel= Felodipine; HCTZ=Hydrochlorothiazide; Los=Losartan, Nif=Nifedipine

Table SU.8a. Serious Clinical Adverse Experiences During the Safety Update Report Time Frame in Hypertensive Patients With Renal Impairment Who Did Not Die

Protocol-Study	Patient #	Age/ Sex	Treatment	Dose (mg)	Day of Onset	Adverse Experience	Outcome
058-003	131	61 M	Losartan	100	58	Pain, chest	Recovered

Serious nonfatal adverse experiences have been reported for a total of 30 CHF patients who are listed in table SU.8b.

Table SU.8b. Nonfatal Serious Clinical Adverse Experiences From All Sources in Losartan-Treated Patients with Heart Failure—Report Time Frame: July 1, 1993 through December 31, 1993 [All patients received losartan]

Study #/ Protocol #	Patient #	Age/Sex	Losartan Daily Dose (mg)	Day of Onset	Adverse Experience	Discontinued	Outcome
047-006 047-20	1051	70/Male	10	480	Syncope	No	Recovered
047-007 047-20	1061	68/Male	25	490	Dizziness	No	Recovered
047-008 047-20	1077	62/Male	50	448	Syncope	No	Still Present
047-011 047-20	1103	57/Male	10 12.5	420 476	Syncope Worsening Heart Failure	No Yes	Recovered Recovered
047-015 047-20	1180	53/Male	50	373	Abdominal Pain	No	Recovered
068-014 068-00	169	54/Male	25	428	Syncope	No	Recovered
071-006 071-10	185++	68/Male	12.5	63	Abdominal Pain	No	Recovered
071-014 071-00	176	53/Male	50	20	Trauma	No	Recovered
047-003 047-20	1025	63/Male	50 50 12.5	514 548 567	Ventricular Tachycardia Worsening Heart Failure, Acute Renal Failure, Coagulopathy, Hypotension Orthopnea, Exertional Dyspnea, Nausea, Vomiting	No No No No No No No	Recovered Recovered Recovered Recovered Recovered Recovered Recovered
047-004 047-20	1035	47/Male	50	541	Worsening Heart Failure	No	Unknown
047-012 047-20	1120 ⁺	53/Male	50	573	Worsening Heart Failure	No	Recovered
047-015 047-21	1177	66/Male	50	432	Cerebral Vascular Accident	No	Still Present
068-003 068-00	90	49/Male	50 50	145 147	Sweating, Dizziness, Chest Pain Atrial Fibrillation, Atrial Flutter	No No No No	Still Present Still Present Still Present Still Present
068-006 068-00	65	81/Male	12.5 12.5	247 251	Worsening Heart Failure Atrial Fibrillation	No No	Recovered Unknown
068-008 068-00	85	61/Male	50	362	Angina	No	Recovered
068-008 068-00	88	43/Male	50	235	Palpitations, Syncope	No No	Recovered Recovered
071-003 071-10	102	47/Male	50	142 168	Atrial Fibrillation Worsening Heart Failure	No No	Still Present Recovered
071-003 071-10	104	67/Male	50 50 50	194 196 207	Worsening Heart Failure Atrial Fibrillation Worsening Heart Failure, Ventricular Fibrillation	No No No No	Still Present Recovered Still Present Recovered
071-004 071-10	146	72/Male	50	214	Worsening Heart Failure	No	Recovered
071-007 071-10	246	74/Male	50	131	Worsening Heart Failure	Yes	Recovered
071-009 071-10	223	57/Female	50	174	Worsening Heart Failure	Yes	Still Present
071-018 071-00	67	55/Male	25	29	Pulmonary Edema, Worsening Heart Failure	No No	Recovered Unknown
047-012 047-20	1115	66/Male	50	661	Gastrointestinal Bleed	No	Recovered
068-010 068-00	110	38/Male	50	163	Cholelithiasis	No	Recovered

Table SU.8b. Nonfatal Serious Clinical Adverse Experiences From All Sources in Losartan-Treated Patients with Heart Failure—Report Time Frame: July 1, 1993 through December 31, 1993 [All patients received losartan] (cont.)

Study # Protocol #	Patient #	Age/Sex	Losartan Daily Dose (mg)	Day of Onset	Adverse Experience	Discontinued	Outcome
071-006 071-10	185++	68/Male	50	243	Duodenal Ulcer	No	Recovered
047-012 047-20	1120*	53/Male	50	329	Vertebral Fracture	No	Unknown
047-015 047-21	1162	61/Male	50	558	Musculoskeletal Pain	No	Recovered
047-015 047-21	1169	44/Male	50	639	Dizziness	No	Unknown
071-012 071-00	12	60/ Unknown	12.5	12	Orthopnea, Dyspnea	Yes Yes	Recovered Unknown
071-020 071-00	128	71/Male	25	51	Pulmonary Edema, Hypotension	No No	Recovered Recovered
071-014 071-10	179	64/Male	50	204	Psoriasis	No	Recovered
047-015 047-21	1147	76/Male	50	515	Prostate Disorder	No	Still Present

Discontinuations Due to Adverse Events

Case report forms were received in-house for 27 double-blind patients during the SUR time frame. Of these, 1 patient (AN 0590, Study 048-007) had an adverse experience that resulted in discontinuation. This patient was a 45-year-old male who was treated with losartan 50 mg and developed severely increased blood pressure accompanied by dizziness, headache, and palpitations on the fourth day of double-blind therapy.

Fifty-four of patients in open label hypertension trials had adverse experiences that resulted in discontinuation. Three patients (not included in the WMA) were discontinued due to laboratory adverse experiences during the SUR time frame. A table listing the patients discontinued for adverse events and the reason for discontinuation has been requested.

Four patients with renal impairment discontinued due to adverse events during the SUR time frame. Table SU.9 lists the patients and the reason for withdrawal.

Table SU.9. Hypertensive Patients With Renal Impairment Discontinued Due to Clinical Adverse Experiences During the Safety Update Report Time Frame [Reviewer's Note: Study 58 is an open label study.]

Protocol- Study	Patient #	Age/ Sex	Treatment	Dose (mg)	Day of Onset	Day Stopped	Adverse Experience
058-003	134	59 M	Losartan	50	9	9	Allergy
058-008	316	58 M	Off drug	--	29	28	Hypotension
058-008	315	78 M	Losartan	100	45	72	Hyperkalemia
058-020	671	36 M	Losartan	100	83	85	AST Increased ALT Increased

Patient #316 received losartan 50 mg on day 28. The time of onset of hypotension is not provided in the CANDAs. It is unclear that drug can be excluded as responsible for this adverse event. Patient #315 had baseline potassium between 4.7 mEq/L and 5.6 mEq/L. During treatment with losartan, potassium were between 5.6 and 6.5 mEq/L. Serum creatinine and BUN increased slightly from baseline also. (baseline creatinine = 2.6 mg/dl, day 61 creatinine = 3.0 mg/dl; baseline BUN = 45 mg/dl; day 61 BUN = 76 mg/dl).

Ten patients with CHF withdrew from CHF trials due to adverse events. A table listing the patients discontinued for adverse events and the reason for discontinuation has been requested.

Cancers

The SUR database lists 27 patients with the diagnosis of a malignant neoplasm (Table SU.10.). Three patients had multiple cancers listed. Two of these patients had skin and intestinal cancer. The third had lung cancer with metastatic disease to liver and bone. There were ten skin cancers, five prostate cancers and six intestinal cancers.

Table SU. 10. Cancers in the Safety Update Database

Study	Patient #	AE Drug Dose	Age	Sex	Race	Neoplasm	Day
11	27	150mg losartan/25mg HCTZ	57	M	Caucasian	INTESTINAL	577
						SKIN, MALIGNANT	403
11	70	50mg losartan	53	M	Caucasian	INTESTINAL	484
11	71	50mg losartan	49	M	Caucasian	SKIN, MALIGNANT	237
11	508	150mg losartan/12.5mg HCTZ	66	M	Caucasian	INTESTINAL, MALIGNANT	645
						SKIN, MALIGNANT	498
11	577	50mg losartan	44	F	Caucasian	BREAST, MALIGNANT	459
11	656	150mg losartan	51	M	Caucasian	INTESTINAL	630
11	666	100mg losartan	58	F	Caucasian	SKIN, MALIGNANT	66
11	828	OFF-DRUG	65	M	Caucasian	SKIN, MALIGNANT	133
11	832	100mg losartan/12.5mg HCTZ	59	F	Caucasian	BLADDER, MALIGNANT	589
11	833	150mg losartan/25mg HCTZ	68	M	Caucasian	PROSTATE, MALIGNANT	769
44	3170	50mg losartan	58	M	Caucasian	PROSTATE, MALIGNANT	105
47	1071	50mg losartan	73	F	Negro	KIDNEY, MALIGNANT	158
48	6014	40mg NIFEDIPINE/12.5mg HCTZ/50mg losartan	43	M	Mulatto	SKIN, MALIGNANT	169
49	7145	50mg losartan	47	M	Caucasian	SKIN, MALIGNANT	366
49	7279	50mg losartan	52	M	Caucasian	TONGUE, MALIGNANT	267
49	7280	25mg losartan/25mg HCTZ	62	M	Black	LUNG, MALIGNANT	48
49	7411	50 mg losartan/25 mg HCTZ	61	M	Caucasian	KIDNEY, MALIGNANT	293
49	7418	100mg losartan/25mg HCTZ	64	M	Caucasian	INTESTINAL, MALIGNANT	42
49	7447	50mg losartan/12.5mg HCTZ	48	M	Caucasian	BONE, METASTATIC	310
						LIVER, METASTATIC	310
						LUNG, MALIGNANT	309
50	2022	50mg losartan/12.5mg HCTZ/5mg FELODIPINE	66	M	Caucasian	PROSTATE, MALIGNANT	336
50	2133	50mg losartan	70	F	Caucasian	SKIN, MALIGNANT	119
50	2254	50mg losartan/50mg HCTZ	46	F	Caucasian	SKIN, MALIGNANT	518
54	8254	50mg losartan/6.25mg HCTZ	71	M	Caucasian	PROSTATE, MALIGNANT	288
54	8433	OFF-DRUG	69	M	Black	PROSTATE, MALIGNANT	98
54	8871	50mg losartan/6.25mg HCTZ	70	F	Caucasian	SKIN, MALIGNANT	208
59	5567	100mg losartan	67	M	Black	INTESTINAL, MALIGNANT	319
65	1194	50mg losartan	64	M	Caucasian	MALIGNANT	15
65	1421	2 TABLETS PLACEBO	66	M	Caucasian	INTESTINAL, METASTATIC	43

Of special interest is the incidence of kidney cancer. During the development of losartan, an independent Italian investigator (Remuzzi) performed a study in diabetic (streptozocin induced) Sprague-Dawley rats. Diabetic rats (n = 8 per group) whose blood sugars were controlled by insulin, were treated with oral losartan or placebo for a period of one year for the purpose of evaluating glomerular morphology. A non-diabetic control group treated with nothing was also included. After one year, five of eight losartan treated rats had gross kidney tumors evident on necropsy. All were cancerous. Neither the diabetic or non-diabetic control groups had any gross tumors. A systematic histologic evaluation of the tissue was not performed to search for microscopic tumors. Two patients in the SUR data were diagnosed with kidney cancer. Four additional cases, three in patients treated with losartan and one placebo, are included in the Safety Update summary report. All of the cases of renal cancer as of February 28, 1994 are summarized in table SU.11.

Table SU.11. Renal Cancers

Protocol/ Study #	Patient #	Age/ Sex	Treatment (mg Daily Dose)	Treatment Duration* (Days)	Date of Diagnosis	History/Prestudy Evaluations	Symptoms	Diagnoses/Pathology
011/028	0575	75/M	Losartan 50	962	10/26/93	Essential hypertension Elevated prestudy prorenin (163 ng A ₁ /mL/hr)	Gross hematuria	7 x 7 x 3.7 cm right renal cell carcinoma, clear cell type Tumor positive for prorenin Post nephrectomy plasma prorenin activity 33 ng A ₁ /mL/hr
047/008	1071+	73/F	Losartan 50	159	8/15/92	Essential hypertension NYHA Class II heart failure Microscopic hematuria (20-29 ; 30-39 RBC/HPF)	Asymptomatic - Discovered during follow-up of renal insufficiency	6 x 5 x 3.5 cm right renal cell carcinoma, tubulopapillary pattern
049/023	7411+	62/M	Losartan 50/ HCTZ 25	280	12/9/92	Essential hypertension Tobacco use 8 cm left renal mass - 1984 Microscopic hematuria (3-5 RBC/HPF)	Asymptomatic - Discovered during follow-up of pre- existing left renal mass	7 x 7 x 8 cm left renal upper pole necrotic tumor, lower pole multifocal papillary renal cell carcinoma
054/011	8255	43/M	Losartan 50/ HCTZ 6.25	484	10/7/93	Essential hypertension Tobacco use Chronic low back pain - 1991	Gross hematuria Dysuria Right flank pain	10 x 10 x 10 cm right renal cell carcinoma, predominantly clear cell type
054/019	8876	63/F	Losartan 50/ HCTZ 12.5/ Felodipine 5	453	10/4/93	Essential hypertension	Gross hematuria Left flank pain Urinary retention with clots	8.2 x 8.2 x 8.0 cm left renal cell carcinoma, predominantly clear cell type
076/001	102	59/M	Placebo	42	11/11/93	Essential Hypertension	Urinary frequency Nocturia Slowing of urinary stream	7 cm left renal cell carcinoma

* Treatment duration is based on calendar days post initiation of losartan therapy up to and including date of diagnosis.

** This patient was found to have a renal cell carcinoma at the time of his participation in the felodipine/enalapril interaction study subsequent to his participation in the losartan RAAS II study during which he received placebo therapy.

+ Case presented in WMA

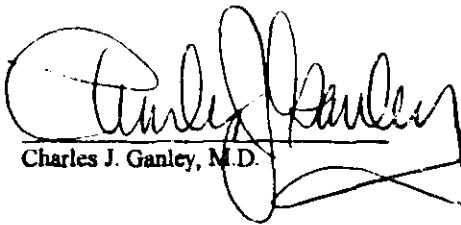
Summary.

There are no major differences in the incidence of clinical adverse events with losartan during the open label period compared to the WMA database. Laboratory adverse events incidence rates are difficult to interpret for the reasons stated in the review. CANDA failures limit the ability to review the laboratory data in the SUR database. For this reason, multiple requests for additional laboratory information has been made to the sponsor.

The data from the Remuzzi streptozocin study raised the issue of losartan being a promoter of kidney tumors. The concern was enhanced by the observation that renal cancer has been reported in five losartan or losartan/HCTZ patients as of February 28, 1994. Additional data, both clinical and pre-clinical, is summarized in separate reviews by Dr. Proakis and Dr. Burkhart. This information provides a compelling argument that there is insufficient evidence to conclude that losartan is a promoter of kidney tumors. A complete summary of the information is provided in a separate review document. However, before this issue can be laid to rest, the sponsor needs to supply additional information on patients with hematuria, reported either as an adverse event or as an abnormal laboratory value.

Requests for Information:

- 1) Provide a table listing the patients withdrawn and the reason for withdrawal (plus other pertinent information) during the SUR time period for clinical or laboratory adverse events from the CHF population and hypertensive population.
- 2) A complete report for study 58 (Open study of losartan in hypertensive patients with renal impairment) has not been submitted. Although this not a controlled study, it would be interesting to determine the mean changes in laboratory parameters with time.
- 3) Queries of the Safety Update database for liver function tests, creatinine/BUN, potassium abnormalities and urine blood have been sent to Merck.



Charles J. Ganley, M.D.

cc: orig.
HFD-110 file
HFD-110/c.ganley/r.lipicky/cso/k.knudson/a.proakis

FEB - 1 1995

Medical Officer Review

NDA #: 20-386
 Drug Name: Losartan (N-954)
 Sponsor: MST
 Date of Approval:
 Date of Receipt:
 Review Start:
 Review Completed: 2/1/95
 Medical Reviewer: Charles J. Ganley, M.D.

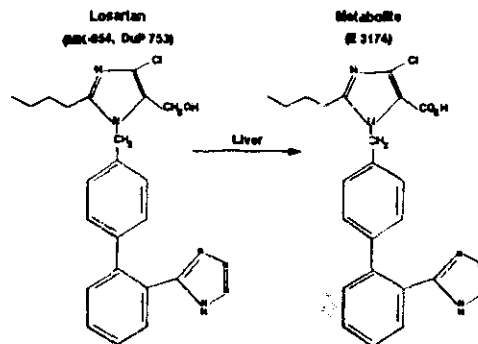
General Information

Name of Drug

Generic: losartan potassium

Trade: COZAAR

Chemical: 2-n-butyl-4-chloro-5-hydroxy-methyl-1- [2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methylimidazole potassium salt:



M.W. = 461.0

Pharmacologic Category: Angiotensin II Receptor AntagonistProposed Indication: Treatment of Essential HypertensionDosage Form: 25 mg, 50 mg and 100 mg film coated tabletsRoute of Administration: OralRelated Drugs: None ApprovedApproved for this Indication in: Not Approved in Other Countries; Applications Pending

Resume

Losartan is an angiotensin II receptor antagonist. It has an absolute bioavailability in humans of approximately 23% with an elimination half-life of approximately 2 hours. Losartan is metabolized by a cytochrome P450 enzyme to an active metabolite, E-3174. E-3174 has a elimination half-life of approximately 9 hours and may be responsible for the blood pressure lowering effect 24 hours post-dosing with losartan.

There are three randomized, double-blind, placebo controlled, parallel dose trials of 8 to 12 weeks duration. Losartan 50 and 100 mg once a day significantly lowered diastolic blood pressure. Black patients have minimal, if any response, to losartan and as such, losartan should not be recommended as monotherapy in black patients.

There are no significant safety issues apparent. Cough may occur less frequently than with ACEI. There are instances of reversible elevation of creatinine with losartan and losartan/HCTZ. Facial and eyelid edema has been reported with losartan.

Losartan is an effective anti-hypertensive agent with a reasonable safety profile. The NDA is approvable pending review of the safety update and the review of the Division of Epidemiology of the cancer rates. [Medical Reviewer's Note: It is not apparent from the data in the NDA but there is a concern about the risk of developing renal cell cancer with losartan therapy based on animal and human data. This subject will be addressed in separate reviews by Dr. Knudson, Dr. Greg Burkhardt, Dr. Froakis and Dr. Ganley.]

Introduction

Losartan is an angiotensin II receptor antagonist. It selectively binds to angiotensin II receptor subtype 1 (AT₁). The location of angiotensin II receptors, the effect of angiotensin on the receptor and the potential response to blockade of the receptor are shown in table 1. In the NDA, the effect of losartan on the urinary excretion of electrolytes, GFR and plasma neurohormones are explored in numerous clinical pharmacology trials. The clinical efficacy (ability to decrease DBP) is explored in several placebo controlled trials of 8 weeks or greater duration. Active control trials and open label trials provide additional information regarding the safety of losartan.

Table 1. Angiotensin II Receptors.

Location	Action	Effect	Blockade	
			Initial	Long-Term
Vessels				
Afferent	↑R*	↓RBF, ↓ΔP, ↑GFR		↑RBF, ↑ΔP, ↓GFR
Efferent	↑R	↓RBF, ↑ΔP, ↑GFR	↑GFR, ↑UNa	↑RBF, ↓ΔP, GFR (+/-NC)
Vasa Recta	↑R	↑Medullary Osmolality	↓GFR, ↑UNa ↓OSM (↓UOSM)	
Mesangium	Contraction	↓Kf, ↓GFR ↑Uprot	↑Kf, ↑GFR ↓Uprot	↓Uprot ↑GFR
Tubules				
Proximal	↑NA/H Exchange	↓UNa ↓UHCO3 ↓UpH, ↑NH3 ↑UNH4	↑UNa ↓UNH4 ↑UHCO3, ↑UpH ↑V, ↑UCl, ↑UPO4 ↑Uurate ↑U _{Li}	?
Distal	↑Aldo	↓UNa ↑K secretion	↑UNa ↓UK, ↑SK	
JG Cells	↓Renin	Negative Feedback	↑Reactive Renin ↑A II (Blunt Blockade)	

*R - Resistance

✓ The original NDA or Worldwide Marketing Application (as designated by Merck; abbreviated WMA) was submitted 12/6/93. The cut-off date for inclusion of data from case report forms in the WMA was data received by Merck on or prior to 3/31/93. The 4 month Safety Update Report (SUR) was submitted on 4/4/94. The sponsor states that the Safety Update Report (SUR) provides incidence calculations based upon case report form information received by Merck through October 4, 1993. As of 10/4/93, 4058 patients/subjects have been exposed to losartan as monotherapy or as part of a treatment regimen. This may seem straight forward but it is not. For example, patient 1002 in study 047 died in September of 1993. A MedWatch report for this event was submitted to the NDA by the sponsor on 9/23/93. Although this patient died prior to the cut-off date for the SUR and the information was in the sponsor's database, this patient's event is not included in the CANDA safety update database. The explanation for this is that the sponsor did not have a completed case report form as of 10/4/93. To confuse things further, even though the death is not included in the CANDA database, the death is included in the sponsor's integrated summary of the safety update. This patient is included in the integrated summary because the WAES data (serious adverse events) covers data up until 12/31/93. Thus, I cannot validate all of the information included in the Safety Update Summary report. Table 2 indicates what data is included in the databases.

Table 2. Final Dates for Data Included in the CANDA Databases

CANDA Database	Case Report Information at Merck	WAES Data
World Marketing Application	3/31/93	6/30/93
Safety Update	10/4/93	12/31/93

In the WMA, the safety profile was presented for 3628* losartan-treated patients. The Safety Update Report (SUR) contained additional safety data on 1282 losartan-treated patients who were first presented in the WMA and continued in the studies post-WMA as well as information on 430 patients/subjects who were newly exposed to losartan therapy and were not included in the original WMA. Most of these 430 patients were on control agents during the acute phases in WMA studies and then switched to losartan subsequent to the completion of the acute phase. Of the 4058 patients/subjects treated with losartan therapy to date, 3384 were treated in studies for uncomplicated essential hypertension, 148 were treated in studies for hypertension involving renal impairment, 199 were treated in studies for heart failure, and 327 were subjects in clinical pharmacology studies.

dates are wrong

This review document will only review the Monotherapy CANDA. Clinical trials that include HCTZ will be reviewed by Dr. Knudson. The Safety Update data will not be included in this review but will be summarized in a separate review document.

Safety data is included in the CANDA for all trials. Efficacy measurements and laboratory data are included for selected studies. Case report forms were not included in the CANDA at the request of the medical reviewer. Computer generated reproductions of case report forms are included in the paper submission. Copies of actual case report forms are not included in the NDA. Information regarding the number of subjects enrolled at the screening visit is not provided for any study.

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* = designated pivotal by the sponsor

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Efficacy Summary

Placebo Controlled Multi-Dose Trials

Trough Diastolic Blood Pressure

The monotherapy NDA included six randomized, double blind, placebo controlled trials ranging in duration of treatment from 5 days to 12 weeks. Losartan monotherapy was also included in study 54 which was reviewed in the losartan/HCTZ NDA. Data from study 54 was not included in this review. Table E.1 lists the study characteristics of the six multi-dose placebo controlled trials. Protocols 005, 021 and 043 did not permit the inclusion of black patients. Protocols 011, 050 and 065 limited the enrollment of black patients as a percentage of those randomized. All of the trials had a primary endpoint involving changes in DBP except for study 043. The primary endpoint in study 043 evaluated the change in plasma renin and angiotensin II levels with losartan treatment. Blood pressure change was a secondary endpoint in study 043.

Table E.1. Placebo Controlled Trials

Protocol #	Design	Primary Measure of Efficacy	Treatment Groups	N
005	- randomized, double-blind, placebo controlled and active control, multi-center - 5 day treatment period - non-black hypertensives	Trough suDBP	- placebo - losartan 50 mg - losartan 100 mg - losartan 150 mg - enalapril 10 mg	23 20 18 20 19
011	- randomized, double blind, placebo controlled, multi-center parallel dose - hypertensives (limit 25% black) - 8 week treatment period	Trough suDBP at week 8.	- placebo - losartan 10 mg od. - losartan 25 mg od. - losartan 50 mg od. - losartan 100 mg od. - losartan 150 mg od. - enalapril 20 mg od.	78 80 82 79 90 84 83
050	- randomized, double-blind, placebo controlled, parallel, multi-center, dose titration - 12 week treatment period - hypertensives (limited to ≤ 30% black) - open label extension optional	Trough suDBP at week 12	- placebo - losartan 50/100 mg - losartan 50/P	116 123 127
065	- randomized, double blind, placebo controlled - 12 week treatment period - hypertensive, no more than 30% black, 30% with moderate hypertension - open label extension optional	Trough suDBP at week 12	- placebo - losartan 25 mg daily - losartan 25 mg bid - losartan 50 mg daily	108 108 106 106
021	- randomized, double blind, placebo controlled, parallel - 6 week treatment period - non-black hypertensives - Ambulatory Blood Pressure Monitoring (ABPM) - open label extension	Change in ABPM blood pressure at 4 weeks	- placebo - losartan 50 mg - losartan 100 mg - losartan 50 mg bid	32 29 30 31
043	- randomized, double-blind, placebo controlled and active control - 6 week treatment period - non-black hypertensives	Plasma renin Plasma angiotensin II	- losartan 25 mg od - losartan 100 mg od - placebo - enalapril 20 mg od	11 14 12 14

N = Number of Patients Randomized per Treatment Group

Table E.2 summarizes the placebo subtracted mean change in DBP in the placebo controlled studies. Doses of losartan greater than or equal to 25 mg daily significantly lowered diastolic blood pressure (supine or sitting) compared to placebo. Twice a day dosing was studied in protocols 065 (losartan 25 mg bid) and protocol 021 (losartan 50 mg bid). In both cases, the decrease in diastolic blood pressure was numerically but not significantly greater than the comparable total daily dose provided as a single once a day dose. The maximum dose studied was losartan 150 mg once a day in study 005. Patients were treated for 5 days in this trial. The blood pressure response for 150 mg was similar to 50 mg and 100 mg. Losartan 100 mg was slightly better numerically than losartan 50 mg in studies 005, 050 (titration to 100 mg) and 021. In study 011, there was no difference between losartan 100 mg and 50 mg treatment effect.

Table E.2. Placebo Subtracted Mean Change in Diastolic Blood Pressure (mmHg) in Multi-Dose Placebo Controlled Trials (All Patients Treated Data)

Dose	Study 005* (day 5)	Study 011* (week 8)	Study 050** (week 12)	Study 065** (week 12)	Study 021 (week 4)
enalapril 10 mg od	-5.9				
enalapril 20 mg od		-5.6			
losartan 10 mg od		-2.3			
losartan 25 mg od		-1.2		-3.8	
losartan 25 mg bid				-6.0	
losartan 50 mg od	-6.7	-4.5	-3.6	-4.3	-4.8
losartan 50/100 mg ¹			-4.3		
losartan 50 mg bid					-8.2
losartan 100 mg od	-8.1	-4.3			-6.3
losartan 150 mg od	-7.0				

different from p 61

¹ = once a day dosing, dose titration permitted at four weeks; * change in sDBP; ** change in siDBP; bid = twice a day dosing

Diastolic Blood Pressure Response in Subgroups

Diastolic blood pressure response in several subgroups based on sex, race and age are listed in tables E.3 - E.5. The placebo subtracted change in diastolic blood pressure suggests that losartan lowered diastolic blood pressure regardless of sex or age < 65 and ≥ 65 years. The change in ΔBP in black patients was unimpressive.

Table E.3. Diastolic Blood Pressure by Sex (All Patients Treated Data)

Dose	Study 011* (week 8)				Study 050** (week 12)				Study 065** (week 12)			
	Male		Female		Male		Female		Male		Female	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
enalapril 20 mg od	55	-5.3	27	-6.5								
losartan 10 mg od	51	-3.6	29	-3								
losartan 25 mg od	55	-1.0	27	-3.0					65	-3.9	40	-3.6
losartan 25 mg bid									67	-6.6	34	-4.9
losartan 50 mg od	53	-4.4	25	-5.0	81	-3.5	44	-4.0	68	-4.6	33	-3.8
losartan 50/100 mg ¹					77	-6.1	41	-1.0				
losartan 50 mg bid												
losartan 100 mg od	58	-5.4	31	-2.4								
losartan 150 mg od	62	-4.8	22	-2.9								

¹ = once a day dosing, dose titration permitted at four weeks; * change in sDBP; ** change in siDBP; bid = twice a day dosing

Table E.4. Diastolic Blood Pressure by Racial Subgroup (All Patients Treated Data)

Dose	Study 011* (week 8)				Study 050** (week 12)				Study 065** (week 12)			
	Black		non-Black		Black		Non-Black		Black		Non-Black	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
enalapril 20 mg od	7	.8	75	-6.2								
losartan 10 mg od	10	.5	70	-2.8								
losartan 25 mg od	14	2.5	68	-2.0					21	-1.5	84	-4.4
losartan 25 mg bid									10	-.3	91	-6.7
losartan 50 mg od	10	-3.2	68	-4.7	14	.3	111	-4.1	16	-1.0	85	-5.3
losartan 50/100 mg ¹					16	-1.6	102	-4.7				
losartan 50 mg bid												
losartan 100 mg od	17	-2.8	72	-4.7								
losartan 150 mg od	11	-2.3	73	-4.5								

¹ = once a day dosing, dose titration permitted at four weeks; * change in sDBP; ** change in siDBP; bid = twice a day dosing

Table E.5. Diastolic Blood Pressure by Age (All Patients Treated Data)

Dose	Study 011* (week 8)				Study 050** (week 12)				Study 065** (week 12)			
	< 65		≥ 65		< 65		≥ 65		< 65		≥ 65	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
enalapril 20 mg od	71	-6.1	11	-3.5								
losartan 10 mg od	68	-3.3	12	2.6								
losartan 25 mg od	64	-1.3	18	0					89	-3.6	16	-4.0
losartan 25 mg bid									90	-5.5	11	-8.3
losartan 50 mg od	66	-5.4	12	.2	106	-3.1	19	-6.3	85	-4.0	16	-5.0
losartan 50/100 mg ¹					90	-4.2	28	-5.1				
losartan 50 mg bid												
losartan 100 mg od	72	-4.6	17	-2.7								
losartan 150 mg od	71	-5.1	13	.7								

¹ = once a day dosing, dose titration permuted at four weeks, * change in suDBP, ** change in aiDBP; bid = twice a day dosing

Only study 011 suggests that black patients had a minimal response (approximately 50% of the decrease of non-black patients). During the process of validating this data, it becomes apparent that the response of black patients in study 011 is influenced by the small number of patients in the placebo group. Table E.6 lists the change in DBP (placebo subtracted) when only the week 8 data is included in the analysis. The placebo subtracted decrease in DBP is less than 1 mm for losartan 50 - 150 mg. Both analysis are greatly influenced by the size of the placebo group and the effect of the single dropout on the mean blood pressure change.

Table E.6. Change in supine DBP in black patients at week 8

Treatment	N	Change in suDBP (S.D.) [mm Hg] (non-carry forward analysis)*	Placebo Subtracted Change in suDBP [mm Hg] (non-carry forward analysis)	N	Change in suDBP (S.D.) [mm Hg] (carry forward analysis)**	Placebo Subtracted Change in suDBP [mm Hg] (carry forward analysis)
placebo	4	-7.5 (4.5)	-	5	-5.2	-
enalapril	7	-4.4 (8.3)	3.1	7	-4.4	.8
losartan 10 mg	9	-4.3 (7.8)	3.2	10	-4.7	.5
losartan 25 mg	12	-3.7 (7.2)	3.8	14	-2.7	2.5
losartan 50 mg	10	-8.4 (6.0)	-0.9	10	-8.4	-3.2
losartan 100 mg	13	-8.0 (6.6)	-0.5	17	-8.0	-2.8
losartan 150 mg	9	-8.3 (9.8)	-0.8	11	-7.5	-2.3

* obtained from the CANDAs database by eliminating carry-forward data

** obtained from the sponsor's clinical summary report page 48, table 13

The failure of losartan to convincing lower DBP in black patients is supported by categorical response Diastolic Blood Pressure (6 hours Post -Dosing)

Protocols 005, 011, 050 and 065 measured diastolic blood pressures at approximately 6 hours post dose. Table E.7 lists the mean change in peak diastolic blood pressure (placebo subtracted). Trough to peak ratios can be found in the summaries of the individual studies. Losartan 100 mg did not appear to provide a greater response compared to 50 mg of losartan based on the results of study 011 and 050.

Table E.7. Placebo Subtracted Mean Change in DBP at Peak (6 hours post dose).

Dose	Study 005* (day 5)		Study 011* (week 8)		Study 050** (week 12)		Study 065** (week 12)	
	N	Mean	N	Mean	N	Mean	N	Mean
enalapril 10 mg od	18	-11.0						
enalapril 20 mg od			82	-11.0				
losartan 10 mg od			79	-2.6				
losartan 25 mg od			80	-5.2			95	-4.7
losartan 25 mg bid							94	-6.9
losartan 50 mg od	20	-9.7	77	-7.2	108	-5.6	94	-5.7
losartan 50/100 mg ¹					111	-4.8		
losartan 50 mg bid								
losartan 100 mg od	18	-6.3	87	-5.7				
losartan 150 mg od	19	-12.0	81	-8.4				

¹ = once a day dosing, dose titration permuted at four weeks, * change in suDBP, ** change in aiDBP; bid = twice a day dosing (All-Patients-Treated Approach)

Diastolic Blood pressure (Multiple Measurements During the 24 Hours Post Dosing)

Protocol 021 measured ambulatory blood pressure for 24 hours. Protocol 005 measured DBP at 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 23, 23.5 and 24 hours post-dosing by Dinamap. Protocol 043 measured supine diastolic blood pressure during the final visit (week 6) at 30 min, 1 hour, 1.5, 2, 3, 4, 6, 8, 12, 24, 2E, 32, 36, 48 and 72 hours after dosing. Refer to the individual study summaries for the results from these measurements.

Rebound Hypertension

Studies 011 and 050 evaluated patients for rebound hypertension by measuring DBP after the final double-blind treatment visit while the patients were off of treatment. Study 065 had post-DB visits for only three patients (does not pertain to open label period) and as such does not contribute much information. Table E.8a and E.8b lists the number of patients who had measurements during the post-DB period. In study 011, only 51% of the patients had post-DB treatment visits. Consequently, it would be difficult to conclude anything from this data since half the data was not obtained. In study 050, 87% of patients had post-double-blind treatment visits. The percent of patients with post double-blind siDBP measurements greater than baseline is greatest in the placebo group. When the post-double-blind measurements for each treatment group are compared to baseline or to the last double-blind measurement or the number of patients with post-DB measurement > 110 mmHg are considered, there does not appear to be a significant difference between losartan and placebo. It is not unreasonable to conclude that rebound hypertension is not a problem.

Table E.8a. Patients with Post-DB Visits and BP Measurements in Study 011

Treatment	N ^a	N with post-DB Visit	N with suDBP Change ^c > 0 mmHg	Range of Changes ^c in suDBP during Post-DB Period (mmHg)
Placebo	78	42	6	-21 to 9
Losartan 10 mg	80	41	7	-24 to 6
Losartan 25 mg	82	45	6	-20 to 5
Losartan 50 mg	79	36	0	-29 to 0
Losartan 100 mg	90	43	5	-40 to 12
Losartan 150 mg	84	44	4	-27 to 6
Enalapril 20 mg	83	41	1	-30 to 1
Total	576	297 (51%) ^b	29 (10%) ^d	

a = number of patients randomized; b = percent of patients randomized;
c = Change equals Post-DB suDBP minus baseline suDBP; d = as a percent of patients with post-DB visit.

Table E.8b. Patients with Post-DB Visits and BP Measurements in Study 050

Treatment	N ^a	N with post-DB Visit	N with suDBP Change ^c > 0 mmHg	Range of Changes ^c in siDBP during Post-DB Period (mmHg)	Mean Change ^c from Baseline (mmHg)	Mean Change ^e from Last DB siDBP (mmHg)	N with siDBP Change ^c > 10 mmHg	N with Post-DB siDBP > 110 mmHg
Placebo	116	97	32 (33%) ^d	-20 to 20	-3.4	1.7	5	7
Losartan 50/P	127	115	26 (23%) ^d	-29 to 12	-5.5	2.7	1	4
Losartan 50/100	123	106	23 (22%) ^d	-28 to 18	-5.6	3.0	3	2
Total	366	318 (87%) ^b	81 (22%) ^d					

a = number of patients randomized; b = percent of patients randomized;
c = Change equals Post-DB siDBP minus baseline siDBP (> 0 mmHg indicates that post-DB measurement is greater than baseline);
d = as a percent of patients with post-DB visit; e = Change equals First Post-DB siDBP minus Last DB siDBP

Active Control Studies

Eight studies in hypertensive patients included an active control. Three of the studies (011, 005, 043) included a placebo group and were discussed previously. One study (056) evaluated hypertensive patients with a previous history of ACE inhibitor induced cough for the incidence of cough while receiving losartan. In this study, patients with lisinopril induced cough were randomized to losartan, HCTZ or lisinopril. Losartan had significantly fewer patients complain of cough compared to lisinopril. Four studies (044, 045, 055, 064) compared the anti-hypertensive response of losartan to captopril, atenolol, felodipine and enalapril. All four studies were 12 weeks of double blind therapy. Studies 044, 045 and 055 were performed outside of the United States, did not have efficacy data available from all investigative sites and allowed for doubling of the randomized dose if DBP ≥ 90 mmHg after 6 weeks of therapy. Study 064 was performed in the United States in patients with severe hypertension (siDBP 115 - 130 mmHg) and permitted dose titration of randomized medications plus the addition of either HCTZ, atenolol and/or a dihydropyridine calcium channel blocker if blood pressure was not controlled. For the most part, these studies were powered to detect a difference in blood pressure response from baseline after 6 or 12 weeks of treatment and not a difference between treatments. They contribute safety data.

Clinical Pharmacology Summary

Three trials (001, 002, 006) examined the ability of losartan to suppress the pressor response to intermittent infusions of angiotensin I (001) or angiotensin II (002, 006). Losartan (2.5 mg - 120 mg) was administered to healthy male subjects in open label trials. Losartan doses of 10 mg or greater blunted the pressor response. This effect appeared to persist despite non-detectable levels of losartan in plasma. This suggests that the active metabolite of losartan, E-3174, which has a longer terminal elimination half-life than losartan could have a clinically relevant effect on prolonging an anti-hypertensive response. In study 001, pre-angiotensin infusion SBP was increased after losartan dosing which raised a concern that losartan may have agonist properties. In study 006, pre-angiotensin infusion SBP did not increase after losartan therapy.

ACE activity was measured in study 005 at trough and at 5 hours after dosing. Mean ACE inhibitor activity decreased with enalapril therapy. Placebo, losartan 50 mg, 100 mg, and 150 mg had minimal effect on ACE activity. Renin activity and angiotensin II levels increase with losartan (study 004, 007). Aldosterone levels either decreased or remained unchanged within 24 hours after single doses of losartan (study 004, 007, 019).

The metabolism of losartan to the primary metabolite, E-3174 (L-158,641; see page 1 for structure) involves oxidation of an alcohol side chain to form the carboxylic acid derivative, a reaction demonstrated *in vitro* to be carried out by several cytochrome P450 mixed-function oxidases, CYP 3A4 and CYP 2C. Losartan has an absolute bioavailability of 23% (study 022) and an elimination half-life of approximately 2 hours (studies 003, 004, 007, 013). E-3174 has an elimination half-life of approximately 9 hours (study 007; arithmetic mean). The harmonic mean half-life of E-3174 ranges from 3.9 hours to 6.9 hours (studies 003, 004, 013, 017). Several subjects in the NDA produced minimal or no E-3174 after losartan therapy. Please refer to Dr. Fadiran's biopharm review for details on these patients. In patients who do not metabolize losartan to E-3174, the duration of anti-hypertensive effect is likely to be shortened. Female patients ≥ 65 years of age had an increased losartan AUC, absolute bioavailability and C_{max} compared to male patients ≥ 65 years of age.

Urine sodium and potassium excretion did not change after losartan with or without a depleted sodium diet (study 004, 007, 023, 034). Urine uric acid increased slightly during the first 6 hours after single doses (study 023).

Food decreased the losartan AUC by 19% and the C_{max} by 52% compared to the fasted period (study 015). E-3174 AUC decreased by 13%. Cimetidine (study 24) caused the C_{max} and AUC for losartan to increase by 23% and 36% respectively. However, cimetidine did not affect the AUC for E-3174. There was minimal interaction between a single intravenous or oral dose of digoxin on top of losartan therapy. Losartan increased oral digoxin C_{max} (13%) and AUC (5%) with losartan therapy (study 063). Phenobarbital administration caused the AUC of losartan and E-3174 to decrease by approximately 20% (study 72). An interaction study was performed between warfarin and losartan which suggested that there is not a pharmacokinetic interaction between warfarin and losartan (study 070). However, the study design is inadequate to conclude that there is not a pharmacodynamic interaction. This is discussed further in the summary of study 070 and the safety summary that follows.

Safety Summary

Before summarizing the safety of losartan, it is worthwhile to comment on the quality of the safety data. Due to the size of the database under review, each individual case report form cannot be reviewed by the medical reviewer. The accuracy of the safety database depends on the inclusion of all adverse events, the accurate coding of the adverse event and an accurate summary of adverse events by the sponsor. Information in the clinical summary report for the trials should be consistent with the CANDAs database. For this the medical reviewer is dependent on the sponsor to accurately document and summarize adverse events. The medical reviewer depends on the sponsor to be forthright in the presentation of data. There are occasions that the presentation of the adverse events data is less than satisfactory. For example, patient #783 is listed as withdrawing on relative day 286 secondary to diarrhea. A summary of the adverse event (patient summaries are provided only for serious adverse events in this report) for patient #783 explains that the patient also had hemorrhoidal bleeding and was found to have a large fungating mass in the rectum (? bleeding due to mass). When the CANDAs database is queried for this patient, the only adverse events listed are diarrhea and headache. Hemorrhoidal bleeding and rectal cancer are not listed in the database for this patient.

It is important to note that not all of the laboratory data for each patient is included in the CANDAs. The storage capacity of the system was insufficient to include all of the data. Thus, if there are deficiencies in the review, it is most likely to occur in the evaluation of laboratory data.

Patient Exposure

Tables SS.1 and SS.1b lists the number of patients exposed to losartan monotherapy. Two thousand five-hundred and thirty-three patients received losartan monotherapy. This includes patients from protocols 048, 054, and 073 which are not included in this review (These studies have been reviewed by Dr. Knudson. Patients who received losartan monotherapy at some time during the long term open label periods of protocols 011, 021, 049, 050 and 054 are also included. Patients from 057 are included even though the study was not complete at the time the database was closed. The majority of patients received losartan 50 mg per day

Table SS.1 Losartan Monotherapy Duration of Therapy by Total Daily Dose

Days of Therapy	Number of Patients						
	0-9 mg	10 mg	25 mg	50 mg	100 mg	150 mg	>150 mg
1 - 7	1	0	40	152	99	26	6
8 - 30	0	2	16	674	319	109	1
31 - 91	0	78	186	997	421	95	0
92 - 183	0	0	6	202	21	22	0
184 - 274	0	0	0	42	16	7	0
275 - 365	0	0	0	50	18	2	0
366 - 457	0	0	0	20	1	3	0
458 - 548	0	0	0	17	5	0	0
549 - 639	0	0	0	1	0	0	0
>639	0	0	0	1	1	0	0

Table SS.1a.

Total Number of Patients	2533
Total Patient Days on Drug	218957
Range of Duration on Drug	1 to 677
Mean Duration on Drug	86.4

Deaths

Table SS.1b lists twelve patients who died while enrolled in clinical trials for losartan. Six of the patients were enrolled in heart failure trials and five patients in hypertension trials. Nine of the patients received losartan and two patients received placebo.

Table SS.1b. Deaths in Losartan Trials

Study	Patient #	Treatment	Day of Death	Days in Study	Days on Treatment	Cause of Death
16*	154	Losartan 5 mg	7	7	1	MI / Cardiogenic Shock
16*	512	Losartan 150 mg	12	12	1	Not Reported
47*	1128	Losartan 2.5 mg	85	85	84	Ventricular fibrillation
47*	1133	Losartan 2.5 mg	21	21	21	Ventricular fibrillation
47*	1139	Losartan 10 mg	18	18	10	Ventricular fibrillation
47*	1195	Losartan 10 mg	115	115	85	MI / Cardiac Arrest/ Anoxic Encephalopathy
65	1330	placebo	85	85	85	Accident
65	1373	placebo	39	39	4	MI / CVA
65	1596	Losartan 25 mg BID	68	68	41	Malignant hypertension / CVA
L11	174	Losartan 50 mg	90	27	26	CVA
L50	2414	Losartan 50 mg/ HCTZ 6.25 mg	244	153	153	Cerebral Aneurysm
55	8856	Los 50/H12.5/Fel5	193	193	193	Trauma Death

* Heart Failure Trial. [Study 16 is a single dose trial.]

Patient #154 in study 016 was a 66 year-old Caucasian male with an ejection fraction of 29%, NYHA Class II heart failure and a history of myocardial infarction. He was randomized and received a single oral dose of losartan 5 mg on 4/7/91. On April 11, 1991, he had a myocardial infarction and suffered cardiogenic shock with bradycardia. He was admitted to the hospital and treated with atropine, dopamine, and streptokinase and his heart rate was maintained with a pacemaker. The patient was stable for 48 hours then subsequently had episodes of ventricular tachycardia which were followed by ventricular fibrillation. On April 13, 1991 the patient died. Autopsy demonstrated left ventricular myocardial infarction and extensive sclerosis of the coronary arteries. A thrombus was found in the circumflex artery. The investigator felt the myocardial infarction and ventricular fibrillation were not related to study drug.

Patient #512 in study 016 was a 62 year-old Caucasian male with an ejection fraction of 16% and NYHA Class III heart failure. The etiology of heart failure in this patient was ischemic cardiomyopathy. The patient had a myocardial infarction in 1977. The patient was randomized and received a single oral dose of losartan 150 mg on 6/19/91. On 6/20/91, prestudy therapy of furosemide, quinidine, isosorbide dinitrate, diltiazem, aspirin, and enalapril was reinstated. On 6/30/91, the patient was found dead in bed.

Patient #1128 in study 47 was a 68-year-old Caucasian male with an ejection fraction of 29%, NYHA functional class IIa heart failure, angina, peripheral vascular disease and a history of 2 myocardial infarctions and coronary artery bypass graft was randomized to receive single daily doses of losartan 2.5 mg. The etiology of heart failure in this patient was ischemic heart disease. His last dose of study drug was on Day 84. He was concomitantly treated with dipyridamole. On Day 85, he

experienced a cardiac arrest and was hospitalized. On admission, the patient was found to be in ventricular fibrillation and died that day.

Patient #1133 in study 47 was a 71-year-old Caucasian male with an ejection fraction of 14%, NYHA Class IIb heart failure, atrial fibrillation, diabetes, and a history of 3 myocardial infarctions was randomized to receive single daily doses of losartan 2.5 mg. The etiology of heart failure in this patient was ischemic heart disease. Concomitant medications included digitoxin, furosemide, spironolactone, glyburide, and warfarin. On Day 21, the patient died suddenly - attempts at resuscitation failed. The investigator identified the cause of death as ventricular fibrillation.

Patient #1139 in study 47 was a 65-year-old Caucasian male with an ejection fraction of 23%, NYHA Class IIb heart failure, atrial fibrillation and a history of myocardial infarction and coronary artery bypass graft surgery was randomized to receive single daily doses of losartan 10 mg. The etiology of heart failure in this patient was ischemic heart disease. Concomitant medications included digoxin, furosemide, spironolactone, dipyridamole, and aspirin. On Day 10, the patient suffered ventricular fibrillation and cardiac arrest. He was resuscitated and was hospitalized, but remained unconscious. On Day 15, the patient developed pneumonia. On Day 17 life-sustaining measures were withdrawn. On Day 18, the patient died. Autopsy confirmed pneumonia as the cause of death.

Patient #1195 in study 47 was a 67-year-old Caucasian male with an ejection fraction of 22%, NYHA Class IIb heart failure, angina, and a history of myocardial infarction, and ventricular tachycardia was randomized to receive single daily doses of losartan 10 mg. The etiology of heart failure in this patient was ischemic heart disease. The patient completed the study and losartan was discontinued on Day 85. Twelve days following completion of the study, the patient suffered cardiac arrest and was resuscitated. He was hospitalized and was found to have suffered a myocardial infarction. These episodes caused serious cerebral degeneration which led to the patient's death thirty days after completion of the study.

Patient # 1596 (losartan 25 bid) in study 65 was a 78-year-old hypertensive male patient had a blood pressure reading of 211/143 and numbness and tingling of the right leg on Day 41 of treatment with losartan 25 mg b.i.d. He was hospitalized and diagnosed with a cerebral vascular accident secondary to malignant (177/111, 157/110, 170/113, 176/118, 174/105 mmHg readings) hypertension. Therapy was discontinued. Seven days later he had a cardiac arrest and was resuscitated. Eighteen days later he developed an arrhythmia, respiratory failure, and seizures. On Study Day 68 he had a second cardiac arrest and died.

Patient #0174 in study 011 was a 70 year old hypertensive male was hospitalized on 4/30/91 for what appeared to be a stroke. A CT scan of the brain showed a hemorrhagic infarct of the mid-brain. The patient did not recover consciousness and was kept alive via life-support (respirator) until 5/1/91. An EEG done on 5/1/91 showed extremely depressed brain function. It was the opinion of the consulting neurologist that the patient was beyond recovery and advised the family accordingly. The family chose to discontinue life-support at that time. No spontaneous respiratory activity was noted, and the patient died at 7:45 PM on 5/1/91. The patient had been treated for moderately severe hypertension since 1975. He had no other known complications from hypertension; his only abnormal findings were an S4 on physical examination and a LAHB and RBBB on EKG. At the time of the adverse event, the patient was taking losartan 100 mg q.d. and was last seen in the clinic on 22APR91 (Supine BP = 167/100 mmHg, standing BP = 162/110 mmHg). The patient was taking no other concomitant medication.

Patient #2414 in study 050 was a 46-year-old hypertensive male with ankylosing spondylitis, hypercholesterolemia, and back pain, and a history of cigarette smoking, who collapsed at home on 12/7/92. Despite medical intervention, he was pronounced dead. The cause of death was found to be a ruptured cerebral aneurysm. At the time of the event the patient was receiving losartan/HCTZ 50/6.25 mg, and ibuprofen.

Patient #8856 was a 54-year-old hypertensive male who fell asleep "at the wheel" while driving his car at night and subsequently had a motor vehicle accident. The patient died as a result of the impact. At the time of the accident the patient was receiving losartan 50 mg, HCTZ 12.5 mg and felodipine 5 mg.

Adverse Events in Studies 011, 050 and 065.

Adverse events incidence rates are reported for each protocol in the review of each trial. Studies 011, 050 and 065 were the primary randomized, double-blind, parallel, placebo-controlled trials of at least 6 weeks duration. The combined randomization in these trials was 1370, of whom, 1287 were randomized to either placebo or losartan alone. Eighty-seven were randomized to enalapril in study 011. Table SS.2 lists the number of patients by study and treatment with at least one adverse event. Of the patients randomized to placebo and losartan, six-hundred and ninety-three patients experienced at least 1 adverse event during the double blind treatment period. There was no difference between the losartan and placebo incidence rate of patients experiencing at least one adverse event. The incidence of patients with at least one adverse event does not appear to increase with losartan dose.

SS.2. Patients with at Least One Adverse Event during Acute Phase

[% equals percent of total on treatment regimen in study]

	Study 011 (%)	Study 050 (%)	Study 065 (%)	Total Patients (%)
losartan 10 mg	41	0	0	41 (51%)
losartan 25 mg	43	0	60	103 (54%)
losartan 50 mg	36	74	61	171 (54%)
losartan 100 mg	36	0	0	36 (40%)
losartan 150 mg	47	0	0	47 (56%)
losartan 25mg BID	0	0	60	60 (57%)
losartan 50mg/100mg	0	69	0	69 (56%)
losartan TOTAL	203 (49%)	143 (57%)	181 (57%)	527 (54%)
Placebo TOTAL	41 (53%)	59 (51%)	66 (61%)	166 (55%)

Table SS.2a lists the number of patients who experienced adverse events while receiving losartan alone (various doses) or placebo in studies 011, 050 and 065. It includes adverse events that have an incidence > 1% in at least one treatment group, have potential serious clinical implications, are characteristic with ACE Inhibitors or may have clinical relevance based on the mechanism of action of losartan. There are several hundred different adverse event descriptors in the data base. Table SS.2a includes only a fraction of them. The pitfalls associated with multiple comparison testing make it difficult to interpret any statistical analysis comparing treatments. This is compounded by the low incidence rate of individual adverse events. With that being said, the following adverse events warrant additional comment

The incidence of cough was 3.6 % in losartan treated patients and 3.0 % in placebo patients. Cough may be reported as other adverse events involving the respiratory system. Combining the adverse events cough, bronchitis, respiratory infection, upper respiratory infection and lower respiratory infection may include all patients with cough as a symptom. When this is done, 11.9 % of losartan patients and 10 % of placebo patients had one or more of these adverse events. These results, in conjunction with the results of protocol 056, would be sufficient evidence for excluding from labeling references to cough that are found in ACE inhibitor labeling

Patient #488 (losartan) from study 011 experienced eyelid and facial edema. This presumably is angioedema.

Patient #1251(losartan) in study 065 experienced anosmia.

Decreased libido was only experienced in patients receiving losartan (6 vs. 0).

Hemoglobinuria was reported in three patients on losartan in study 065 (#1127, #1479, #1582). With this adverse event, the primary concern is to rule out a hemolytic anemia secondary to drug. The sponsor submitted additional information on these patients (document 20-386/BM submitted 12/8/94). All of the patients were reported to have urine rbc's based on a dipstick test. It is not clear that this test can differentiate between red blood cells and hemoglobin in the urine. Patient #1127 had a urinary tract infection and cystoscopy performed. Patients #1479 and #1582 did not have decreases in hemoglobin. It does not appear that these cases are associated with a hemolytic anemia.

Despite evidence that mean uric acid levels of patients receiving losartan decreased in some clinical trials, the incidence of gout and hyperuricemia did not appear to decrease. Thus, there may not be a clinical benefit.

Vertigo occurred in 6 losartan patients and none of the placebo patients.

Table SS.2a. Adverse Event Incidence of Combined Studies 011, 050 and 065. (Includes adverse events that have a incidence > 1% in at least one treatment group, have potential serious clinical implications, are characteristic in ACE Inhibitors or may have clinical relevance based on the mechanism of action of losartan.)

	Losartan	Placebo	Total
Number Randomized	985	302	1287
Adverse Experience			
HEADACHE	14.2%	15.9%	14.6%
URI	7.8%	6.3%	7.5%
ASTHENIA/FATIGUE	3.4%	5.0%	3.7%
COUGH	3.6%	3.0%	3.4%
DIZZINESS	3.2%	2.0%	3.0%
ALT INCREASED	2.8%	1.7%	2.6%
DIARRHEA	2.3%	2.0%	2.3%
NAUSEA	1.7%	3.6%	2.2%
PHARYNGITIS	1.8%	3.0%	2.1%
EDEMA/SWELLING	1.8%	2.0%	1.9%
PAIN, ABDOMINAL	1.5%	2.3%	1.7%
PAIN, BACK	1.8%	1.3%	1.7%
PAIN, CHEST	1.3%	1.7%	1.4%
AST INCREASED	1.5%	0.7%	1.3%
DYSPEPSIA	1.1%	1.0%	1.1%
MYALGIA	0.9%	1.0%	0.9%
PROTEINURIA	0.8%	1.3%	0.9%
CRAMP, MUSCLE	1.0%	0.3%	0.9%
CONGESTION, RESPIRATORY	0.6%	0.7%	0.6%
HEMATURIA	0.7%	0.3%	0.6%
IMPOTENCE	0.7%	0.3%	0.6%
ORTHOSTATIC EFFECTS	0.8%	0.0%	0.6%
EPISTAXIS	0.7%	0.0%	0.5%
GOUT	0.5%	0.3%	0.5%
HYPERURICEMIA	0.5%	0.3%	0.5%
LIBIDO DECREASED	0.6%	0.0%	0.5%
VERTIGO	0.6%	0.0%	0.5%
TINNITUS	0.5%	0.0%	0.4%
URTICARIA	0.2%	0.7%	0.3%
ALOPECIA	0.3%	0.0%	0.2%
ANGINA PECTORIS	0.3%	0.0%	0.2%
ASTHMA	0.3%	0.0%	0.2%
HEMOGLOBINURIA	0.3%	0.0%	0.2%
PAIN, FLANK	0.3%	0.0%	0.2%
TOTAL SERUM BILIRUBIN INCREASE	0.3%	0.0%	0.2%
CONGESTION, PULMONARY	0.2%	0.0%	0.2%
PERVERSION, TASTE	0.1%	0.3%	0.2%
SYNCOPE	0.2%	0.0%	0.2%
ALTERATION, RETINAL PIGMENT	0.1%	0.0%	0.1%
ANOSMIA	0.1%	0.0%	0.1%
ARRHYTHMIA	0.1%	0.0%	0.1%
EDEMA, EYELID	0.1%	0.0%	0.1%
EDEMA, FACIAL	0.1%	0.0%	0.1%
HEARING LOSS	0.1%	0.0%	0.1%
HYPERKALEMIA	0.1%	0.0%	0.1%

A complete list of adverse event incidence rates for studies 011, 050 and 065 combined is included in the appendix.

The incidence of adverse events within subgroups are reported for each protocol in the review of each clinical trial. Generally, individual studies are under powered to conclude a significant difference between subgroups. In an effort to examine this issue, the adverse event data from the randomized, double-blind, controlled clinical trials in hypertensive patients with a double-blind treatment duration of at least 4 weeks were combined. Trials that enrolled patients with renal insufficiency or congestive heart failure were not included. The following trials were included in this analysis: 011, 021, 043, 044, 045, 050, 055, 064 and 065. The database included only patients receiving losartan alone. Table SS.4 lists the demographics of the patients treated with losartan alone in the nine trials. The nine studies randomized 1,492 patients to losartan alone. Approximately two-thirds were female, one-tenth were black and four-fifths were less than 65 years of age.

Table SS.4. Demographic Characteristics of the Losartan Treated Patients in the Nine Trials. [% = % of total randomized]

Study	Losartan Dose									Total
	10 mg	25 mg	50 mg	100 mg	150 mg	Variable	25 mg BID	50/100 mg	50 mg BID	
011 Outpatient Dose Response	80	82	79	90	84	-	-	-	-	415
021 ABPM (QD vs. BID)	-	-	29	30	-	-	-	-	31	90
043 RAAS Effects	-	11	-	14	-	-	-	-	-	25
044 Captopril Comparison	-	-	-	-	-	109	-	-	-	109
045 Atenolol Comparison	-	-	-	-	-	134	-	-	-	134
050 Mild to Moderate HTN	-	-	127	-	-	-	-	123	-	250
055 Felodipine in Elderly	-	-	-	-	-	89	-	-	-	89
064 Double Blind Severe HTN	-	-	-	-	-	50	-	-	-	50
065 BID vs. QD	-	108	106	-	-	-	106	-	-	320
TOTAL	80 (5%)	201 (14%)	341 (23%)	134 (9%)	84 (6%)	382 (26%)	106 (7%)	123 (8%)	31 (2%)	1482
Study	Race				Sex		Age (years)		Total	
	Caucasian	Black	Hispanic	Other	Female	Male	< 65	> 65		
011 Outpatient Dose Response	310	63	40	2	135	280	343	72	415	
021 ABPM (QD vs. BID)	89	0	0	1	32	58	74	16	90	
043 RAAS Effects	24	0	0	1	8	17	19	6	25	
044 Captopril Comparison	97	3	0	9	45	64	94	15	109	
045 Atenolol Comparison	112	3	16	3	59	75	118	16	134	
050 Mild to Moderate HTN	205	30	12	3	88	162	202	48	250	
055 Felodipine in Elderly	52	0	10	27	48	41	0	89	89	
064 Double Blind Severe HTN	25	22	2	1	19	31	45	5	50	
065 BID vs. QD	250	40	13	8	113	207	277	43	320	
TOTAL	1164 (79%)	170 (11%)	93 (6%)	55 (4%)	547 (37%)	935 (63%)	1172 (79%)	310 (21%)	1482	

Fifty-eight percent of the female and fifty percent of the male subjects experienced at least one adverse event. There was no difference in the overall incidence of patients experiencing adverse events based on age. Blacks had a slightly higher incidence of patients with adverse experiences compared to non-blacks, 58% versus 52%. Tables SS.5a. and SS.5b. lists the incidence of individual adverse events for subgroups based on age, sex, race and treatment group. In general, there appear to be little difference in the incidence of adverse events between subgroups. Gout, hemoglobinuria, insomnia decreased libido and flank pain occurred only in non-black patients. Headache, upper respiratory infection, dizziness and asthenia/fatigue were the most common adverse events reported with losartan occurring in 13.6%, 7.4%, 4.2% and 4.0% respectively. Cough occurred in 3.4% of patients.

SS.5a. Adverse Event Incidence from Nine Studies by Sex, Race and Age. (Includes adverse events that have a incidence > 1% in at least one treatment group, have potential serious clinical implications, are characteristic in ACE Inhibitors or may have clinical relevance based on the mechanism of action of losartan.)

	Sex		Race		Age		TOTAL
	F	M	Black	Non-Black	< 65	>64	
Patients Randomized	547	935	170	1312	1172	310	1482
Patients with at Least 1 AE	318	468	99	687	621	165	786
Percent with at least 1 AE	58%	50%	58%	52%	53%	53%	53%
Adverse Experience							
HEADACHE	15.50%	12.50%	17.60%	13.10%	14.70%	9.70%	13.60%
URI	7.90%	7.20%	6.50%	7.50%	7.80%	6.10%	7.40%
DIZZINESS	4.90%	3.70%	5.30%	4.00%	4.60%	2.60%	4.20%
ASTHENIA/FATIGUE	4.60%	3.70%	3.50%	4.10%	4.20%	3.50%	4.00%
COUGH	3.70%	3.30%	3.50%	3.40%	2.90%	5.50%	3.40%
ALT INCREASED	1.30%	2.90%	1.80%	2.40%	2.60%	1.30%	2.30%
DIARRHEA	2.40%	1.90%	0.60%	2.30%	2.00%	2.60%	2.10%
NAUSEA	3.30%	1.30%	1.80%	2.10%	1.60%	3.50%	2.00%
EDEMA/SWELLING	2.60%	1.50%	4.10%	1.60%	1.60%	2.90%	1.90%
PAIN, BACK	2.40%	1.60%	1.80%	1.90%	1.60%	2.90%	1.90%
CONGESTION, NASAL	1.60%	1.80%	2.40%	1.70%	1.80%	1.60%	1.80%
PHARYNGITIS	2.60%	1.40%	1.80%	1.80%	1.70%	2.30%	1.80%
PAIN, ABDOMINAL	2.90%	1.00%	2.40%	1.60%	1.70%	1.60%	1.70%
AST INCREASED	0.70%	1.60%	1.20%	1.30%	1.50%	0.60%	1.30%
DYSPEPSIA	1.60%	1.10%	1.80%	1.20%	1.10%	1.90%	1.30%
PAIN, CHEST	1.50%	1.20%	2.40%	1.10%	1.40%	1.00%	1.30%
SINUS DISORDER	1.50%	1.10%	1.80%	1.10%	1.30%	1.00%	1.20%
INSOMNIA	1.50%	1.00%	0.00%	1.30%	1.00%	1.60%	1.10%
PAIN, LEG	1.30%	0.70%	0.60%	1.00%	1.00%	0.60%	0.90%
HEMATURIA	0.70%	0.50%	1.20%	0.50%	0.50%	1.00%	0.60%
GOUT	0.20%	0.60%	0.00%	0.50%	0.60%	0.00%	0.50%
LIBIDO DECREASED	0.20%	0.50%	0.00%	0.50%	0.50%	0.00%	0.40%
CREATININE INCREASED	0.40%	0.40%	0.60%	0.40%	0.30%	0.60%	0.40%
HYPOKALEMIA	0.50%	0.20%	0.00%	0.40%	0.30%	0.60%	0.30%
PAIN, FLANK	0.00%	0.40%	0.00%	0.30%	0.30%	0.00%	0.30%
HEMOGLOBINURIA	0.40%	0.10%	0.00%	0.20%	0.20%	0.30%	0.20%
EDEMA, EYELID	0.20%	0.00%	0.00%	0.10%	0.00%	0.30%	0.10%
EDEMA, FACIAL	0.40%	0.00%	0.00%	0.20%	0.10%	0.30%	0.10%
HYPERKALEMIA	0.20%	0.10%	0.00%	0.20%	0.20%	0.00%	0.10%

SS.5b. Adverse Event Incidence from Nine Studies by Dose. [Includes adverse events that have a incidence > 1% overall, have potential serious clinical implications, are characteristic in ACE Inhibitors or may have clinical relevance based on the mechanism of action of losartan]

	10 mg	25 mg	50 mg	100 mg	150 mg	variable	25 mg bid	50/100 mg	50 mg bid	Total
Patients Randomized	80	201	341	134	84	382	106	123	31	1482
Patients with at Least 1 AE	41	112	181	58	47	201	60	69	14	786
Percent with at least 1 AE	51%	56%	61%	43%	56%	53%	57%	56%	45%	
Adverse Experience										
HEADACHE	13.80%	17.40%	12.30%	12.70%	13.10%	12.00%	17.00%	15.40%	9.70%	13.60%
URI	1.30%	9.50%	7.00%	6.00%	8.30%	7.10%	10.40%	8.10%	9.70%	7.40%
DIZZINESS	2.50%	4.50%	4.10%	0.70%	2.40%	6.50%	3.80%	3.30%	3.20%	4.20%
ASTHENIA/FATIGUE	3.80%	2.50%	3.50%	3.00%	4.80%	6.00%	5.70%	1.60%	3.20%	4.00%
COUGH	6.30%	4.00%	2.60%	3.00%	3.60%	3.10%	2.80%	4.90%	3.20%	3.40%
ALT INCREASED	3.80%	3.00%	1.50%	3.70%	3.60%	1.00%	0.00%	4.90%	6.50%	2.30%
DIARRHEA	3.80%	2.00%	2.90%	1.50%	2.40%	1.30%	1.90%	1.60%	3.20%	2.10%
NAUSEA	1.30%	2.00%	2.60%	0.70%	0.00%	2.90%	0.00%	2.40%	3.20%	2.00%
EDEMA/SWELLING	1.30%	1.50%	2.90%	0.70%	0.00%	2.60%	0.00%	2.40%	0.00%	1.90%
PAIN, BACK	3.80%	2.00%	2.10%	1.50%	2.40%	2.10%	0.80%	0.00%	0.00%	1.90%
CONGESTION, NASAL	0.00%	1.50%	2.60%	2.20%	3.60%	0.30%	2.80%	1.60%	6.50%	1.80%
PHARYNGITIS	1.30%	2.00%	4.10%	0.70%	0.00%	1.60%	0.00%	0.00%	3.20%	1.80%
PAIN, ABDOMINAL	3.80%	1.00%	2.10%	1.50%	1.20%	2.40%	0.00%	0.80%	0.00%	1.70%
AST INCREASED	2.50%	2.00%	1.20%	0.70%	1.20%	0.50%	0.00%	2.40%	6.50%	1.30%
DYSPEPSIA	1.30%	1.00%	0.90%	0.70%	1.60%	1.60%	1.90%	0.80%	0.00%	1.30%
PAIN, CHEST	1.30%	2.00%	1.20%	0.70%	1.20%	1.60%	1.90%	0.00%	0.00%	1.30%
SINUS DISORDER	2.50%	1.00%	1.50%	1.50%	2.40%	0.30%	0.90%	2.40%	0.00%	1.20%
INSOMNIA	1.30%	1.50%	1.80%	0.70%	0.00%	1.30%	0.90%	0.00%	0.00%	1.10%
PAIN, LEG	2.50%	1.00%	1.50%	0.70%	0.00%	0.50%	0.00%	1.60%	0.00%	0.90%
HEMATURIA	0.00%	0.00%	0.90%	1.50%	1.20%	0.30%	0.00%	0.80%	3.20%	0.60%
GOUT	0.00%	0.00%	0.60%	0.70%	1.20%	0.30%	0.90%	0.80%	0.00%	0.50%
LIBIDO DECREASED	1.30%	0.50%	0.60%	0.00%	0.00%	0.00%	1.90%	0.00%	0.00%	0.40%
CREATININE INCREASED	0.00%	0.00%	0.30%	0.00%	0.00%	1.30%	0.00%	0.00%	0.00%	0.40%
HYPOKALEMIA	1.30%	0.00%	0.30%	0.00%	0.00%	0.80%	0.00%	0.00%	0.00%	0.30%
PAIN, FLANK	0.00%	0.00%	0.30%	1.50%	1.20%	0.00%	0.00%	0.00%	0.00%	0.30%
HEMOGLOBINURIA	0.00%	1.00%	0.00%	0.00%	0.00%	0.00%	0.90%	0.00%	0.00%	0.20%
EDEMA, EYELID	0.00%	0.00%	0.00%	0.00%	1.20%	0.00%	0.00%	0.00%	0.00%	0.10%
EDEMA, FACIAL	0.00%	0.00%	0.00%	0.00%	1.20%	0.30%	0.00%	0.00%	0.00%	0.10%
HYPERKALEMIA	0.00%	0.00%	0.00%	0.00%	1.20%	0.30%	0.00%	0.00%	0.00%	0.10%

A complete listing of all adverse events in these nine trials can be found in the appendix.

Table SS.6 lists the number of subjects receiving losartan therapy who were withdrawn prematurely from the clinical trials and the reason for withdrawal. This does not include patients in long term follow-up studies. One hundred and ninety patients on losartan monotherapy withdrew prematurely from the clinical trials. Seventy-four withdrew for clinical or laboratory adverse events. Fifty-three patients withdrew as lost to follow-up or "patient withdrew".

Table SS.6. Reasons for Premature Discontinuations from Clinical Trials in Patients Treated with Losartan (Does not include Studies 048, 049, 054, 073 and long term follow-up studies. See Dr. Knudson's Review.) (Reviewer's Note: Studies 002, 004, 007, 012, 022, 023, 024, 033, 034, 060, 063, 067, 072, 074 and 075 did not have any premature withdrawals) (doc. excel file discall.exe)

Study	Clinical AE	Lab AE	Lost To Followup	Protocol Deviation	Patient Uncooperative	Therapy Ineffective	Did Not Meet Eligibility	Clinical and Lab AE	Clinical and ECG AE	Patient Withdrew	Clinical AE/Continuing	Therapy Ineffective/Continuing	Protocol Violation/Continuing	Total
001 Dupont Angiotensin II Infusion	0	0	0	0	0	0	0	0	0	0	0	0	0	0
003 Dupont Single Dose Safety	2	1	0	0	0	0	0	0	0	0	0	0	0	3
005 Inpatient Multiple Dose	1	0	0	0	0	0	0	0	0	0	0	0	0	1
006 Dupont High Dose Angiotensin II Infusion	1	0	0	0	0	0	0	0	0	0	0	0	0	1
011 Outpatient Dose Response	7	1	3	3	1	9	0	1	0	8	1	1	0	35
014 Urinary Protein Excretion	1	0	0	0	0	0	0	0	0	0	0	0	0	1
015 Food Interaction	0	0	2	1	0	0	0	0	0	0	0	0	0	3
016 HF Hemodynamics	0	0	0	0	0	0	0	0	0	0	0	1	0	1
018 12 Week Prostaglandin Synthesis	0	0	0	1	0	0	0	0	0	0	0	0	0	1
019 Low Sodium Diet	1	0	0	1	0	0	0	0	0	1	0	0	0	3
021 ABPM (QD vs. BID)	4	0	0	2	0	0	0	0	0	0	0	0	0	6
035 Forearm Blood Flow	0	0	0	0	1	0	0	0	0	0	0	0	0	1
043 RAAS Effects in Hypertensives	1	0	0	0	0	0	0	0	0	0	0	0	0	1
044 Captopril Comparison	10	0	1	1	0	0	0	0	0	1	0	0	0	13
045 Atenolol Comparison	2	0	2	1	0	4	0	0	0	2	0	0	0	11
047 HF Hemodynamics	13	0	0	0	0	1	0	0	0	0	1	0	0	15
050 Mild to Moderate Hypertension	7	0	4	3	1	2	0	0	0	3	0	5	1	26
055 Felodipine in Elderly	3	0	1	0	0	1	0	0	0	0	0	0	0	5
056 Multicenter Cough	1	0	0	0	0	0	0	0	0	0	0	0	0	1
058 Renal Impairment	2	0	0	1	0	2	1	0	0	6	0	0	0	12
059 Open Severe Hypertension	5	0	1	0	0	1	0	0	1	1	0	0	0	9
064 Double Blind Severe Hypertension	0	0	3	2	1	0	0	0	0	0	0	0	0	6
065 BID vs. QD	4	2	4	5	0	9	0	0	0	7	0	0	0	31
070 Coumadin Interaction	0	0	0	0	0	0	0	0	0	1	0	0	0	1
079 Digoxin Interaction	0	1	0	0	0	0	0	0	0	1	0	0	0	2
TOTAL	65	5	22	21	4	29	1	1	1	31	2	7	1	190

(In reasons for discontinuation, continuing means that despite withdrawal prematurely, patients entered open label losartan study.)

At the request of the FDA, the sponsor submitted (document 20-38c/BM submitted 12/8/94) additional information on the 53 patients withdrawn because of "lost to follow-up" or "patient withdrew". Table SS.7 provides details of the information included in the submission. Twenty-four patients had adequate explanations for discontinuing. Eighteen patients had no additional information. Four patients could have been listed as treatment failures (inadequate response to therapy as determined by the patient). Four patients could have been listed as experiencing adverse events. Four patients could be listed as adverse events or treatment failures.

Table SS.7. Reason for Discontinuation in Patients Withdrawn as Patient Withdrew or Lost to Follow-up.

	Study # / Patient #					
	No Additional Information	11/192	11/496	45/4058	50/2291	50/2394
	59/5528	64/4518	64/4559	65/1676	65/1685	65/1407
	65/1628	44/3092	50/2284	50/2119	58/373	11/552
Therapeutic Failure (TF)	64/462	65/1386	65/1420	65/1351		
Adverse Event (AE)	50/2110	64/4617	45/4167	65/1310		
AE or TF	58/463	58/552	59/5517			

A complete list of losartan treated hypertensive patients withdrawn from clinical trials due to adverse experiences is located in the appendix. There was one healthy subject in study 007 worth noting. Patient #13 experienced hemolytic anemia, palmar desquamation and increased creatinine while receiving losartan. A relationship between losartan and this adverse event has not been ruled out. A complete description of this adverse event can be found in the summary for study 007.

Adverse Events - Open Label Trials

The CANDA contains the data for the long term follow-up studies 011, 021, 049, 050 and 054. This is summarized in the review of these trials. The integrated summary of safety includes additional information on long term follow-up studies 063, 073, 018 and 059. Table SS.7a is a partial list of adverse events in patients enrolled in open label trials. However, the sponsor can not identify time point up to which this data was collected. As noted earlier, the CANDA and paper NDA submission only contain data for long term follow-up of studies 011, 021, 049, 050 and 054 reportedly because these were the only studies with CRF's in house by the NDA cut-off date of 3/31/93. Serious adverse events from the sponsors WAES data base were included up to 6/30/93. Thus, it is not clear where and when the data for long term follow-up for studies 063, 073, 018 and 059 is derived. [Reviewer's Note: Compare this table with data in the summary of the long term follow-up of studies 011, 021, 049, 050 and 054. (summary is located in open label trials section)]

Table SS.7a. Clinical Adverse Experiences (%)^a Hypertensive Patients by Treatment Group (Open-Label)

	Losartan (n=831)	Losartan Plus HCTZ (n=601)	Losartan Plus HCTZ Plus Other Antihypertensive Agents (n=212)
Body System			
Body as a Whole			
Asthenia/Fatigue	3.4	2.8	1.9
Edema/Swelling	1.9	1.3	6.6
Flu-Like Illness	0.4	1.3	0.5
Pain, Abdominal	2.3	2.3	0.5
Pain, Chest	2.0	3.0	0.9
Digestive System			
Diarrhea	3.1	2.0	1.4
Dyspepsia	1.1	1.3	1.4
Nausea	1.9	1.3	0.5
Musculoskeletal System			
Cramp, Muscle	0.4	1.3	1.4
Myalgia	1.2	0.5	0.5
Pain, Back	2.2	2.7	1.4
Pain, Leg	1.0	0.3	0.0
Pain, Shoulder	0.6	1.5	0.5
Nervous System and Psychiatric			
Anxiety	0.8	0.8	1.9
Depression	1.2	0.2	0.5
Dizziness	3.7	5.8	4.2
Headache	12.5	8.5	7.5
Insomnia	1.3	1.0	0.0
Paresthesia	0.7	1.3	0.0
Respiratory System			
Bronchitis	0.7	1.5	0.5
Congestion, Nasal	1.1	2.0	0.9
Cough	2.5	2.7	1.9
Infection, Respiratory, Upper	9.1	6.7	6.6
Influenza	0.5	1.0	0.9
Pharyngitis	2.5	2.0	1.4
Sinus Disorder	1.3	0.8	0.0
Sinusitis	1.8	0.7	0.5
Skin and Skin Appendage			
Flushing	0.2	0.5	2.8
Rash	2.0	1.5	3.9
Urogenital System			
Impotence	0.6	1.2	1.4
Infection, Urinary Tract	1.7	1.5	0.9

^a Occurring in $\geq 1\%$ hypertensive patients in at least one of the losartan treatment groups.

Fifty-seven patients withdrew due to adverse events from open-label trials while being treated with losartan +/- combination. A listing of these patients can be found in the appendix.

Adverse Events - Cough

Angiotensin converting enzyme inhibitors (ACEI) cause cough possibly related to its interaction with the bradykinin system. Since losartan acts on the RAAS system but not the bradykinin system, it is of interest to determine whether losartan increases the risk for cough in patients. Study 056 exams this in patients who have a previous history of lisinopril induced cough. In this study, losartan significantly decreased the incidence of cough in patients with ACEI induced cough. The limitation of the study is the short duration of exposure, up to 4 weeks, and the likelihood that the dose of lisinopril and losartan used in this trial were not equipotent (in terms of lowering DJP). The latter limitation may be irrelevant if ACEI induced cough is not a dose dependent phenomena.

Four double-blind, controlled clinical trials of 6 to 12 weeks in duration included an ACEI and losartan as treatment groups. These trials were 011, 043, 044 and 064. Table SS.8 lists the number of patients randomized to each group in these trials, the number of patients with cough as an adverse event and the number of patients with cough or other adverse events that probably presented with cough (cough, bronchitis, respiratory infection, upper respiratory infection, lower respiratory infection) as an adverse event. The rationale for looking at this is that in the ACEI's initially approved, cough was not known to be a side effect. It became apparent post-marketing. One possible reason it was not found to be a problem in the NDA controlled data base is that patients with cough were classified as having a respiratory infection. In the four studies, the overall incidence of cough reported as an adverse event was 2.2%, 4.6% and 7.4% for placebo, losartan and ACEI respectively (not significantly different; Chi-square Test: losartan vs. placebo $p = 0.292$, losartan vs. ACEI, $p = .148$). If respiratory infection adverse events, that are likely to cause cough, are included with cough, 13.3% of placebo, 13.9% of losartan and 15.9% of ACEI patients respiratory adverse events or cough.

Table SS.8. Number of Patients Randomized in Studies 011, 043, 044 and 064, Incidence with Cough and Incidence with Cough or Other Respiratory Infections.

	Placebo	Losartan	ACEI
Study 011. # Randomized	78	415	83
Study 043. # Randomized	12	51	14
Study 044. # Randomized	-	109	54
Study 064. # Randomized	-	50	25
Total Randomized	90	625	176
# With Cough as and Adverse Event	2	29	13
% with Cough	2.2%	4.6%	7.4%
# With cough or bronchitis or respiratory infection or lower respiratory infection or upper respiratory infection as an adverse event	12	87	28
% With cough or bronchitis or respiratory infection or lower respiratory infection or upper respiratory infection	13.3%	13.9%	15.9%

Adverse Events - Cancer

Thirteen patients were diagnosed with cancer while enrolled in losartan or losartan/HCTZ clinical trials. Table SS.9 lists the patients and the type of cancer. Twelve of the patients were on losartan or losartan combination therapy. One patient in the WMA database is listed with renal cancer. A complete review of the relationship between losartan and renal cell cancer is summarized in a separate review and in a consultation by Dr. Greg Burkhart from the Division of Epidemiology.

Table SS.9. Patients Diagnosed with Cancer in Losartan Trials

Study	Patient #	Sex	Age	Race	Day Discontinued	AE Drug Dose	Adverse Experience	AE Start Day
L11 LT	666	F	58	Caucasian	22	100 mg Losartan	SKIN, MALIGNANT	66
49	7418	M	64	Caucasian	57	100 mg Losartan/25 mg HCTZ	INTESTINAL, MALIGNANT	42
L11 LT	508	M	66	Caucasian	476	150 mg Losartan/12.5 mg HCTZ	MELANOMA	498
L11 LT	27	M	57	Caucasian	343	150 mg Losartan/25 mg HCTZ	SKIN, MALIGNANT	403
49	7280	M	62	Black	54	25 mg Losartan/25 mg HCTZ	LUNG, MALIGNANT	48
65	1421	M	66	Caucasian	43	Placebo	INTESTINAL, METASTATIC	43
65	1194	M	64	Caucasian	84	50 mg Losartan	MALIGNANT NEOPLASM	15
L11 LT	71	M	49	Caucasian	458	50 mg Losartan	SKIN, MALIGNANT	237
L49 LT	7279	M	52	Caucasian	254	50 mg Losartan	TONGUE, MALIGNANT	267
L50 LT	2022	M	66	Caucasian	279	50 mg Losartan/12.5 mg HCTZ/5 mg Felodipine	PROSTATE, MALIGNANT	336
49	7288	F	34	Black	84	50 mg Losartan/25 mg HCTZ	UTERINE, BENIGN	38
L11 LT	828	M	65	Caucasian	373	50 mg Losartan	SKIN, MALIGNANT	133
L49 LT	7411	M	61	Caucasian	287	50 mg losartan/ 25 mg HCTZ	KIDNEY, MALIGNANT	293

Laboratory - Mean Changes

There was no clinically significant change in mean laboratory values in the acute (12 weeks or less), double blind, placebo controlled studies except for a consistent decrease in mean uric acid levels. There were some trends in mean values that are worth noting (Table SS.10.). Mean uric acid levels tended to decrease with losartan therapy. It is unclear that this is clinically important since there did not appear to be a decrease in the incidence of acute attacks of gout with losartan treatment. Mean serum potassium increased slightly and mean urine pH decreased slightly.

Table SS.10. Mean Change in Labs

	Placebo Change	Losartan Change (range)
Uric Acid (mg/dl)		
Study 011	.05	.1 to -.33
Study 050	.18	-.08 to -.12
Study 065	-.16	-.24 to -.35
Urine pH		
Study 011	.12	.04 to -.32
Study 050	-.2	.01 to -.23
Study 065	.06	-.16 to -.39
Serum Potassium (mEq/l.)		
Study 011	-.14	.01 to -.12
Study 050	-.02	.05 to .09
Study 065	-.03	0 to .13

Laboratory Adverse Experiences

There was not a clinically significant change in mean creatinine in the controlled clinical studies. However, there are instances where serum creatinine increased in some individuals. Table SS.11 lists three patients from study 044 (2 losartan, 1 captopril) that experienced elevated creatinine during therapy. In the both losartan cases, baseline BUN was increased.

Table SS.11. Patients With Increased Creatinine from Study 044

Patient	Treatment	Baseline Creatinine (mg/dl)	Maximum Creatinine (mg/dl)	Comment
3181	losartan	1.4	2.3	Creatinine decreased, but not to baseline, after losartan discontinued. Baseline BUN = 61 mg/dl, Maximum BUN = 72 mg/dl
3238	losartan	1.1	1.5	Creatinine decreased, but not to baseline, after losartan discontinued. Baseline BUN = 26 mg/dl, Maximum BUN = 53 mg/dl.
3023	captopril	1.25	2.4	Creatinine decreased, but not to baseline, after captopril discontinued. Baseline BUN = 17 mg/dl, Maximum BUN = 32 mg/dl.

There are three patients in long term follow-up studies who experienced elevations in serum creatinine while receiving losartan in combination with HCTZ. Patient #2212 in study L50 had a baseline creatinine of 1.2 mg/dl. On study day 198, the creatinine was 2.8 mg/dl (BUN = 35 mg/dl, baseline BUN = 10 mg/dl). The patient received losartan/HCTZ until day 191.

The database does not provide any creatinines between days 191 and 198. Thus, until shown otherwise, one must presume that the elevated creatinine and BUN is due to losartan/HCTZ. On day 209, the creatinine was 1.4 mg/dl. Patient #646 in study L011 had a creatinine of 2.4 mg/dl on day 134 (losartan 150 mg/ HCTZ 12.5 mg). The creatinine was 1.4 mg/dl on day 119 and 1.2 mg/dl at baseline. Patient #594 in study L011 had an elevated creatinine of 2.4 mg/dl on day 377 (Losartan 150 mg/HCTZ 25 mg). Baseline creatinine was 1.2 mg/dl. The creatinine improved after the HCTZ was discontinued. Patient #5274 in study 055 had a creatinine of 1.6 mg/dl on day 83 (losartan 100 mg). These examples provide evidence that losartan with or without HCTZ can cause reversible elevations in serum creatinine.

There were no patients with serious laboratory adverse experiences who died. Two patients had non-fatal serious adverse events. Patient # 0548, a 52-year-old male, developed elevations of total serum bilirubin, AST, ALT, serum LDH, serum GGT while participating in protocol 011 and was subsequently found to be serologically positive for acute hepatitis A. Patient # 5188, a 68-year-old female, developed hypokalemia (3.0 mmol/L) while participating in protocol 055. Previous serum potassiums were in the normal range. The patient had developed minor flu complaints and headache with reduced appetite.

Table SS.12 provides a detailed listing of the laboratory adverse experiences leading to patient discontinuation in losartan-treated patients during the double-blind phase of clinical trials with hypertensive patients.

Table SS.12. Discontinuations Due to Laboratory Adverse Experiences in Losartan-Treated Hypertensive Patients (Double-Blind)

Protocol #/ Study #	Patient #	Age/Sex	Treatment	Daily Dose (mg)	Relative Day of Onset	Relative Day Discontinued	Adverse Experience
011/006	0115	76/M	Losartan	25	14	22	Platelet Count Decrease
065/003	1599	44/F	Losartan	50	84	84	AST Increased
			Losartan	50	84	84	ALT Increased
048/001	0193	53/M	Losartan	50	28	28	Eosinophilia
			Losartan	50	28	28	Hemoglobin Decreased
			Losartan	50	28	28	Hematocrit Decreased
048/001	0194	55/M	Losartan	50	14	13	Proteinuria
048/018	6336	68/M	Losartan	50	10	11	Hyperglycemia
065/023	1750	45/M	Losartan	50	90	90	Hyperglycemia
011/027	0548	52/M	Losartan	150	28	34	Total Serum Bilirubin Increased*
			Losartan	150	28	34	AST Increased
			Losartan	150	28	34	ALT Increased
			Losartan	150	34	34	GGT Increased
			Losartan	150	34	34	LDH Increased
			Losartan	150	34	34	Hepatitis A Antibody Positive
			Losartan	150	34	34	Total Serum Bilirubin Increased
			Losartan	150	34	34	AST Increased
			Losartan	150	34	34	ALT Increased
			Losartan	150	35	34	Total Serum Bilirubin Increased
			Losartan	150	35	34	AST Increased
			Losartan	150	35	34	ALT Increased
			Losartan	150	35	34	GGT Increased

* Serious Adverse Event

Brief narratives describing the events in these seven patients follow :

Patient # 0115, a 76-year-old male, developed "thrombocytopenia" ($118,000/\text{mm}^3$, normal range $130,000$ to $400,000/\text{mm}^3$) after approximately 5 weeks of participation in protocol 011. The platelet count at baseline (prior to randomization) was normal, $198,000/\text{mm}^3$. The patient was noted to have had a platelet count that was at the lower limit of normal ($139,000/\text{mm}^3$, normal range $130,000$ to $394,000/\text{mm}^3$) approximately 5 months prior to entering the study. The patient subsequently recovered (platelet count $168,000/\text{mm}^3$) approximately 3 weeks after discontinuation of the study drug.

Patient # 1599, a 44-year-old female, developed mild elevations of ALT (56 U/L, normal range 6-34 U/L) and AST (73 U/L range 9-34 U/L) while participating in protocol 065. The patient was discontinued. A follow-up evaluation revealed persistent mild elevation of these laboratory parameters (ALT 68 U/L and AST 78 U/L).

Patient # 0193, a 53-year-old male, developed a decreased hemoglobin (13.7 gm/dL and hematocrit 40.0%) and increased eosinophils (4.5%) while participating in protocol 048. The decreased hemoglobin and hematocrit was felt to be due to bleeding hemorrhoids, there was no evidence of a bleeding diathesis. The increased eosinophils which resolved on discontinuation of the study drug were felt to be drug related.

Patient # 0194, a 55-year-old male, developed worsening proteinuria (from 2 units at baseline to 3 units during the study) while participating in protocol 048. The patient was a known insulin-dependent diabetic with mild renal insufficiency at baseline (creatinine 1.3 mg/dL).

Patient # 6336, a 68-year-old male, developed hyperglycemia (12.1 mmol/L) while participating in protocol 048. The patient was a known diabetic at baseline.

Patient # 1750, a 45-year-old male, developed hyperglycemia (326 mg/dL, range 70-115 mg/dL) while participating in protocol 065. The patient was a known diabetic at baseline with an elevated baseline glucose 268 mg/dL.

Patient # 0548, a 52-year-old male, developed elevations of total serum bilirubin, AST, ALT, serum LDH, serum GGT while participating in protocol 011 and was subsequently found to be serologically positive for acute hepatitis A.

Drug Interaction - Warfarin

Clinical pharmacology trials assessing the effect of phenobarbital and cimetidine on the pharmacokinetics of losartan were performed and are discussed in the clinical pharmacology summary. Additionally, the sponsor studied the effect of losartan on the pharmacokinetics of warfarin in study 70. Study 70 does not provide sufficient information on the pharmacodynamics of warfarin to conclude that no interaction with losartan occurs. In the NDA, fifty-seven patients received concomitant anti-coagulants while receiving losartan. Sixteen patients received single doses of losartan in study 016. Forty-one patients received multiple doses of losartan while on anti-coagulants. Prothrombin and partial thromboplastin times were not obtained on case report forms as part of the laboratory parameters collected (as per submission 20-386/BM; received 10/7/94). Patient 1031 in study 047 experienced gingival bleeding on losartan 2.5 mg and warfarin. Apparently the prothrombin time was increased to 29.4 seconds at the time of bleeding (day 22). Baseline prothrombin times are not provided. In addition to losartan, lovastatin was the only other medication started after randomization and continued through the time of the gingival bleeding. It is not clear whether losartan played a role in the increase in the prothrombin time in this patient. Unless the sponsor provides additional information, a pharmacodynamic interaction between warfarin and losartan can not be ruled out.

Placebo Controlled Multi-Dose Trials in Hypertensive Patients						
Study #	Design/ Patient Population	Treatment Groups	N	Primary Endpoint	Other Measures	Page
005	- r, db, pc, ac, 5 day Rx period - non-black hypertensives	- placebo - losartan 50 mg - losartan 100 mg - losartan 150 mg - enalapril 10 mg	23 20 18 20 19	- change in suDBP	- 6 hour post dose DBP - plasma renin - aldosterone - Angiotensin II - withdrawal BP	24
011*	- r, db, pc, p, mc, 8 wk Rx period - hypertensives (limited to $\leq$ 25% black) - open label extension optional	- placebo - losartan 10 - losartan 25 - losartan 50 - losartan 100 - losartan 150 - enalapril 20 mg	78 80 82 79 90 84 83	- Trough sup DBP at week 8	- losartan levels - peak blood pressure (6 hours post-dose) - response rate - PRA	34
050*	- r, db, pc, p, mc, dose titration, 12 wk Rx period - hypertensives (limited to $\leq$ 30% black) - open label extension optional	- placebo - losartan 50/100 mg - losartan 50/P	116 123 127	- Trough si DBP at week 12	- peak blood pressure (5 - 8 hours post-dose) - response rate - PRA	47
065*	- r, db, pc, 12 wk Rx period - hypertensive, no more than 30% black, 30% with moderate hypertension - open label extension optional	- placebo - losartan 25 mg daily - losartan 25 mg bid - losartan 50 mg daily	108 108 106 106	- Trough siDBP at week 12	- Response Rate - BP change at peak - Difference in BP change between losartan 50 od and 25 bid	57
021	- r, db, pc, p, 6 wk Rx period - non-black hypertensives - Ambulatory Blood Pressure Monitoring (ABPM) - open label extension	- placebo - losartan 50 mg - losartan 100 mg - losartan 50 mg bid	32 29 30 31	- change in ABPM blood pressure at 4 weeks		69
043*	- r, db, pc, ac, 6 wk Rx period - non black hypertensives	- losartan 25 mg od - losartan 100 mg od - placebo - enalapril 20 mg od	11 14 12 14	- plasma renin - plasma angiotensin II	- losartan levels - E-3174 levels - plasma and urine aldosterone - plasma and urine NE and Epi. - supine DBP and SBP - rebound hypertension	128

* Summarized in Clinical Pharmacology Section

wk = week, db = double-blind, ol = open label, od = once a day, bid = twice a day, r = randomized, ac = active control, pc = placebo control, nc = no control, p = parallel, co = crossover, hx = history, HTN = hypertension, ACEI = angiotensin converting enzyme inhibitor, NE = norepinephrine, Epi = epinephrine, PRA = plasma renin activity

* = designated pivotal by the sponsor. ** = does not include data from 1 of 17 centers due to cut-off date restrictions.

Study 005. A Multicenter, Double-Blind, Placebo-Controlled, Two Panel, Parallel Group, Inpatient Study to Investigate the Safety and Antihypertensive Efficacy of Multiple Doses of An Antagonist Losartan in Patients with Mild-to-Moderate Essential Hypertension

Protocol

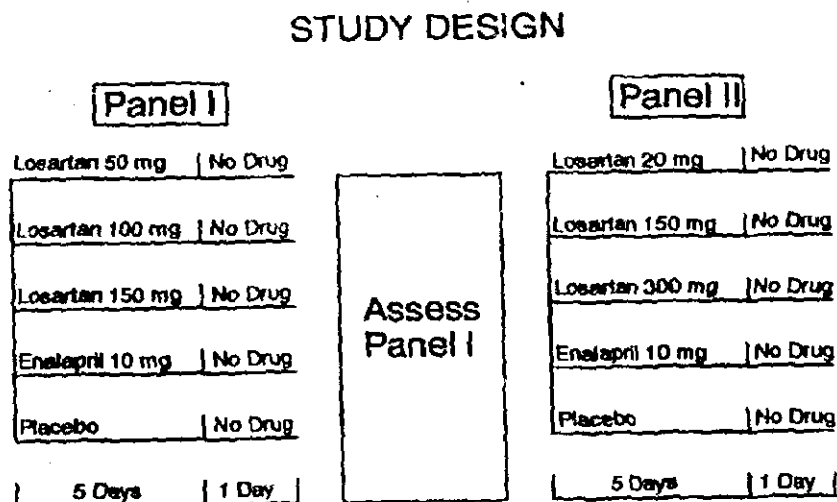
This was a multicenter, randomized, double-blind, placebo-controlled, two-panel, parallel, multiple-dose study in mild to moderate hypertensive patients. The objectives of this phase II study were to establish safety, obtain preliminary dose response data, estimate the duration of effect, assess the withdrawal effect and measure various metabolic parameters. The study enrolled non-black patients, age 21 - 70 years, within 30% of ideal body weight and with no other active medical problems. The study consisted of a 2 week single-blind, outpatient, placebo baseline period, a 2 day in-patient placebo baseline period, a 5 day in-patient double-blind treatment period and a 1 day in-patient withdrawal period.

Following discontinuation of all antihypertensive medications for at least 1 week, patients were eligible to enter a 2-week outpatient, single-blind placebo period to document blood pressure, provided their supine diastolic blood pressure (suDBP) was ≥ 90 mmHg. After 1 and 2 weeks of placebo therapy, a patient's suDBP had to be in the range of 95-120 mmHg with the two readings not differing by more than 7 mmHg in order for the patient to continue in a 2-day in-patient placebo period. In addition, supine systolic blood pressure (suSBP) could not exceed 200 mmHg on more than 2 successive visits. Patients who were eligible were to return to the clinic within 5 days for inpatient placebo screening.

During the 2-day in-patient screening period, blood pressure readings were obtained at various intervals between 0.5 - 24 hrs post-dose. Readings with an automated device were also obtained only if the procedure did not interfere with the quality or timing of the mercury sphygmomanometer readings. In order to be randomized to receive double-blind drug, the suDBP at Hours 23, 23.5 and 24 on the second inpatient day had to be between 95-120 mmHg without varying by more than 7 mmHg from the mean. In addition, on both placebo days, 6 of the first 9 mercury measurements of suDBP (Hours 5-12) as well as Hours 23, 23.5 and 24 on the second placebo day, had to be in the range of 95-120 mmHg. None of the first 9 readings could be < 90 mmHg. Also, a blood sample for the measurement of plasma renin activity, aldosterone, angiotensin II and safety was drawn at various time points on the second day of placebo.

Patients who met all the eligibility criteria during the placebo days were randomized at the completion of the second placebo day to 1 of the 5 parallel groups as shown in Figure 5.1. Each patient was to participate in 1 panel only.

Figure 5.1



Note: n=20/Group, 100/Panel ...

Patients received 5 days of therapy and then participated in an off-drug day while remaining inpatients to assess whether there were any major shifts in blood pressure. After the 1-day off-drug period, patients could resume conventional antihypertensive therapy.

The second panel was to be initiated upon the completion of Panel I after the clinical safety and preliminary efficacy data had been assessed by the clinical monitor. Upon completion of Panel I it was determined that a maximum efficacy dose had been found, and that it was not appropriate to proceed with the second panel.

Table 5.1 identifies the clinical and laboratory measurements that were obtained during the study and the time at which they were obtained.

Table 5.1 Clinical Observations and Laboratory Measurements

	Pre-study	Outpatient				Inpatient						Off Drug Day 6	Follow-Up 3 - 7 days after discharge	
		Baseline		Baseline		Double-Blind								
		Start of Outpatient Placebo Period	Week -1	Week -2	Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5			
Medical History	X													
Physical Exam	X											X	X	
Body Weight	X		X	X										
Body Height	X													
BP and HR ¹	X		X	X	X ²	X ³	X ³	X ⁶	X ⁶	X ⁶	X ³	X ¹¹		
ECG	X			X		X ⁵	X ¹⁰			X ⁵		X ¹³		
Laboratory Screen	X			X		X		X			X	X ¹²	X	
Stool Sample	X					X				X	X	X		
Discontinue Anti-hypertensive Meds	X													
Urine Drug Screen, HIV and Hepatitis Screen		X		X ¹⁴										
Blood Draw (PRA, All and Aldosterone)						X ⁴	X ⁸				X ⁴	X ¹²		
Measurement Urine Volume					X	X ⁹	X ⁹	X	X	X	X ⁹	X ⁹		
Bleeding Time						X				X				
Blood Draw (ACE Activity)							X ⁷				X ⁷			
Determination of Electrolytes, Creatinine, Total Protein, Cortisol and Aldosterone						X	X				X	X		

¹Measurements made in both the supine and standing positions

²Hours -1, -0.5, 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 23, 23.5 and 24=Dinamap, Hours 0, 6, 8, 12, and 24=mercury sphygmomanometer

³Hours 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 23, 23.5 and 24=Dinamap, Hours 6, 8, 12 and 24=mercury sphygmomanometer

⁴Hours -1, 5, 13, and 23

⁵Hours 0, 16 and 24

⁶Hours 1, 2, 4, 6, 8, 12, 16, 20, 23 and 24=Dinamap, Hours 6, 8, 12 and 24=mercury sphygmomanometer

⁷Hours -1 and 5

⁸Hours 5, 13 and 23

⁹pH of Urine Immediately after Voiding

¹⁰Hours 6 and 24

¹¹Hours 1, 2, 4, 6, 8, 12, 16, 20, 23 and 24=Dinamap, Hours 6, 12, and 24=mercury sphygmomanometer

¹²After rising (Hour 23)

¹³Hours 0 and 24

¹⁴Repeat Screen within 5 days of Inpatient Period

When evaluated as inpatients, the mercury sphygmomanometer was used as the primary measurement device. A comparison between the Dinamap® automated blood pressure monitor (only if measurement's did not interfere with the quality or timing of the mercury sphygmomanometer readings) and the mercury sphygmomanometer was to be made. [Note: Due to inaccuracies in blood pressure readings taken with the automated device when compared to readings taken with the mercury sphygmomanometer obtained at the same time, results obtained with the automated device were not analyzed.]

The statistical analysis performed are outlined in table 5.2. The Type I error rate was set at $\alpha=0.05$ for all formal hypothesis testing.

Table 5.2. Statistical Analysis.

Parameter	Statistical Analysis
Blood Pressure and Heart Rate Change (within group mean changes)	Paired t-test
Blood Pressure Change (between group mean changes)	Least significant difference procedure Linear and Quadratic Dose Response Evaluations
Signed Area of change Maximum decrease in first 12 hours postdosing Time to maximum decrease in blood pressure	Pairwise comparison Dose Response
Laboratory Tests (outside pre-defined limit of change)	Fisher's Exact Test (2 tailed)
Bleeding Time	ANOVA with respect to least square mean changes

Results

Demographics

One hundred non-black patients, 60 males and 40 females, mean age 54.3 ± 9.8 years from 10 clinics entered this study. The number of patients per treatment group ranged from 18 to 23. The number of patients randomized per center ranged from 3 to 16. No more than 3 patients in any one treatment group received an ACE inhibitor prior to entering this trial. Variations in between-clinic baseline measurements did differ significantly for mean blood pressures, pulse (except standing pulse 24-hour), serum aldosterone, plasma renin activity, and in serum potassium. There were no statistically significant differences (overall F-test) between the treatment groups with respect to mean blood pressure, heart rate, weight, serum aldosterone, plasma renin activity, serum potassium, serum creatinine, and serum uric acid levels as recorded for the patients on Day -1.

Disposition

Four of the 100 patients who entered the study did not complete the study as "per protocol". They are listed in Table 5.3.

Table 5.3. Patients Who Did Not Complete The Study As "Per Protocol"

Patient	Treatment	Study Day	Reason
118	Placebo	4	Clinical Adverse Experience (discontinued)
39	losartan 150 mg	2	Clinical Adverse Experience (discontinued)
124	Enalapril	1	Clinical Adverse Experience (discontinued)
168	Enalapril	6	Received one extra (sixth) dose of treatment, completed study

Efficacy [Note: Efficacy data for study 005 was not included in the CANADA.]

On study Days -1, 1, 2, 3, 4, 5, and 6, supine diastolic and systolic blood pressures, standing diastolic and systolic blood pressures, and supine and standing heart rates were collected over 24 hours following a single morning dose of the allocated treatment. Timepoint-by-timepoint changes from Day -1 were calculated at the 14 timepoints (0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 23, 23.5, 24 hours) postdosing over which 24-hour blood pressure and heart rate readings were taken on Days 1, 2, 3, 4, 5, 6. Hours 6 and 24 were chosen by the sponsor as clinically meaningful timepoints to evaluate. [Note: The sponsor contends that "the 24-hour blood pressure lowering effect is smooth and not associated with an excessive reduction in blood pressure at the peak time of efficacy"....and "because of this smooth profile, first-dose hypotension is rarely seen".]

Table 5.4 shows the mean change in suDBP from baseline for days 1, 5 and 6. Significant changes from baseline for all treatment groups at 6 and 24 hours post dosing are noted. A dose response is not present among losartan treatment groups unless placebo is included (model and time post dosing dependent). Figure 5.2 depicts the change in suDBP at each timepoint post-dosing day 1 and 5. The placebo subtracted decline from baseline at trough on day 5 ranged from 6.7 mmHg to 8.1 mmHg for losartan therapy. The changes in blood pressure between losartan groups are indistinguishable.

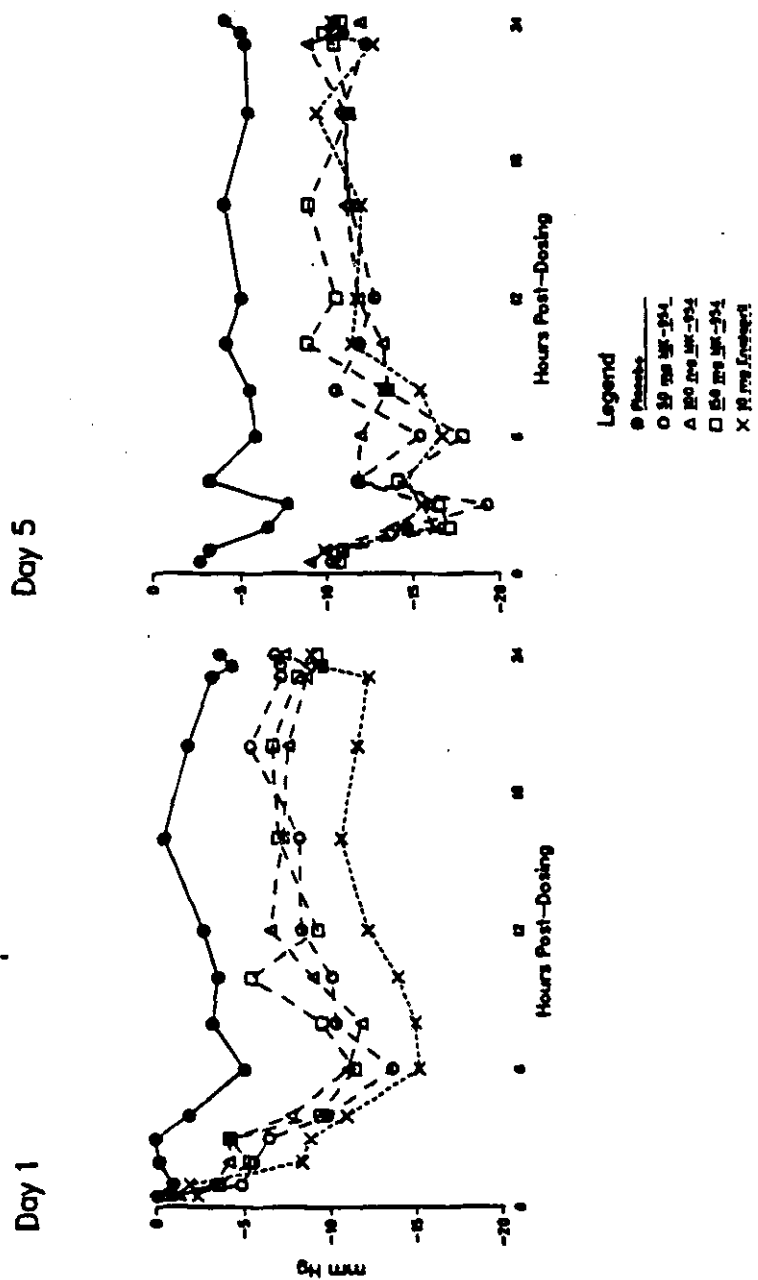
Table 5.4. Supine Diastolic Blood Pressure (mmHg). Mean^(a) Changes from Day -1

Treatment	Day 1		Day 5		Day 6		Day 6 - 5									
	Hr 6	Hr 24	Hr 6	Hr 24	Hr 6	Hr 24	Hr 6	Hr 24								
	N	Mean	N	Mean	N	Mean	N	Mean								
Placebo	23	-5.2**	22	-4.2**	23	-5.9**	23	-4.3**	23	-6.4**	23	-4.4**	23	-0.5	23	-0.1
Losartan 50 mg	20	-13.9**	20	-7.8**	20	-15.6**	20	-11.0**	20	-9.7**	20	-7.0**	20	+5.9**	20	+4.0**
Losartan 100 mg	18	-11.6**	18	-8.4**	18	-12.2**	18	-12.4**	18	-10.3**	18	-9.1**	18	2	18	+3.3*
Losartan 150 mg	20	-11.7**	20	-10.0**	19	-17.9**	19	-11.3**	19	-9.8**	19	-9.2**	19	+8.1**	19	2.1
10 mg Enalapril	19	-15.4**	18	-9.6**	18	-16.9**	18	-10.2**	18	-10.9**	18	-8.5**	18	+6.0**	18	1.7
p values																
Day 1																
Day 5																
Day 6																
Day 6 - 5																
Dose Response																
Pbo 50 100 150 L																
Pbo 50 100 150 Q																
50 100 150 L																
50 100 150 Q																
Pairwise vs. Placebo																
Pbo 150																
Pbo 100																
Pbo 50																

L = Linear Component, Q = Quadratic Component

Δ = .05 < p ≤ .10, * = p ≤ .05, ** = p ≤ .01, (a) Least Squares Means

Figure 5.2. Mean^a Changes from Day -1 Supine Diastolic Blood Pressure



From the change curves in figure 5.2, signed area about zero over 24 hours, maximum decrease in the first 12 hours postdosing, and the time of the maximum decrease in the first 12 hours were calculated. The results for these measurements are listed in table 5.5.

Table 5.5. Supine Diastolic Blood Pressure (mmHg)

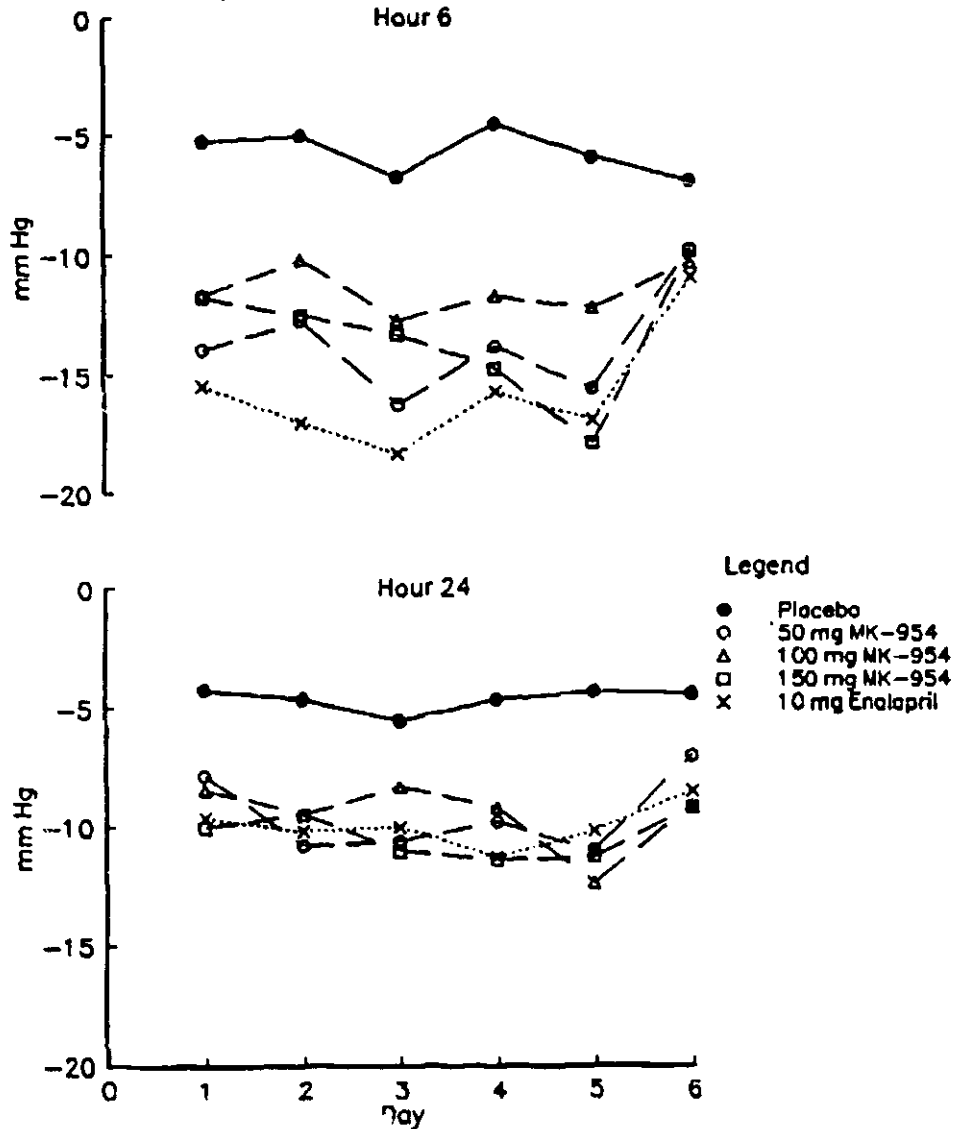
Treatment	Changes from day -1											
	Mean ^(a) Area ^(b) About Zero				Mean ^(a) Maximum Decrease in First 12 Hours Postdosing				Mean ^(a) Hours Post Dosing of Maximum Decrease			
	Day 1		Day 5		Day 1		Day 5		Day 1		Day 5	
N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	
Placebo	23	-45.7*	23	-111.9**	23	-10.8**	23	-14.5**	23	7.0**	23	5.1**
Losartan 50 mg	20	-189.2**	20	-282.9**	20	-18.9**	20	-23.5**	20	7.4**	20	4.7**
Losartan 100 mg	18	-174.9**	18	-266.7**	18	-17.0**	18	-22.8**	18	7.1**	18	5.8**
Losartan 150 mg	20	-167.9**	19	-260.3**	20	-17.2**	19	-24.2**	20	7.3**	19	3.7**
10 mg Enalapril	19	-268.6**	18	-283.0**	19	-21.2**	18	-22.9**	19	7.3**	18	5.6**

(a) Least Squares Means; (b) Over 24 Hours.
* = $p \leq 0.05$, ** = $p \leq 0.01$

The sponsor contends that the area under the curve below (or above) zero was analyzed, revealing that after the first dose of losartan potassium, total reduction in measured blood pressure was not as great with the three losartan potassium doses as with enalapril 10 mg. After 5 days, there was no obvious difference between the groups and all were significantly different from placebo. They claim that this data suggests that losartan potassium has a slower onset of action in lowering BP than enalapril 10 mg, but that after 5 days the effects are equivalent in these patients. This could be interpreted as losartan potassium 50, 100 and 150 mg potentially having less first-dose hypotension when compared to enalapril 10 mg. It is difficult to conclude this from the data for the following reasons. First, area under the curve data is clinically meaningless. Second, five mg and not ten mg of enalapril is the recommended starting dose for enalapril. Since anti-hypertensive medications are titrated from the lowest effective dose, one can not consider this conclusion unless the initial recommended starting doses of enalapril and losartan are compared, and they are not in this trial. Third, the definition of first dose hypotension is subjective but is usually not assessed by measuring mean changes in blood pressure or mean area under the curve. First dose hypotension is better measured by defining what constitutes first dose hypotension and determining the incidence for each therapy. They have not shown anything with this data.

Figure 5.3 shows the 6 and 24 hour post dose changes in suDBP for each treatment group. The changes in blood pressure appear to be stable within the first five days of therapy.

Figure 5.3. Mean^(a) Change from Day -1: Supine Diastolic Blood Pressure
Hour 6



(a) Least Squares Means

Table 5.6 lists the mean changes in suSBP at days 1, 5 and 6. Figure 5.4 depicts the change in suSBP over day 1 and day 5 for each treatment group.

Table 5.6. Supine Systolic Blood Pressure (mmHg). Mean^(a) Changes from Day -1

Treatment	Day 1				Day 5				Day 6				Day 6 - 5			
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Placebo	23	-3.5	22	-7.6**	23	-1.6	23	-10.2**	23	-6.1*	23	-4.7	23	-4.5*	23	+5.5*
losartan 50 mg	20	-14.8**	20	-12.4**	20	-19.7**	20	-11.2**	20	-11.1**	20	-6.0*	20	+8.6**	20	+5.2*
losartan 100 mg	18	-12.3**	18	-10.3**	18	-14.8**	18	-17.5**	18	-14.4**	18	-10.6**	18	0.4	18	+6.9**
losartan 150 mg	20	-12.1**	20	-15.3**	19	-18.9**	19	-18.4**	19	-10.5**	19	-13.6**	19	+8.4**	19	+4.8*
Enalapril 10 mg	19	-19.6**	18	-14.8**	18	-18.2**	18	-15.4**	18	-10.9**	18	-10.3**	18	+7.4*	18	+5.1*

(a) Least Squares Means, $\Delta = .05$ $q \leq 10$, * = $p \leq 0.05$, ** = $p \leq 0.01$

Figure 5.4. Mean Changes from Day -1: Supine Systolic Blood Pressure

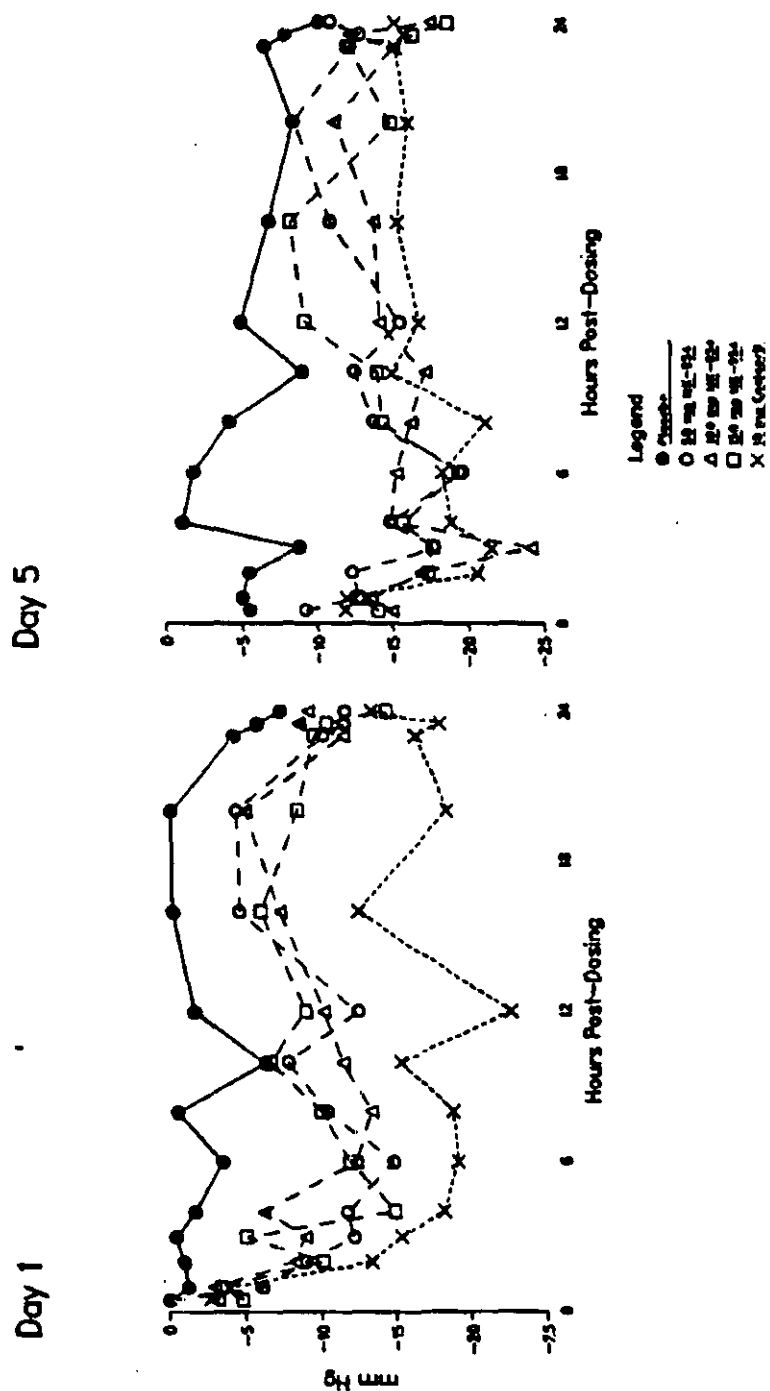


Table 5.8 and 5.9 show the standing DBP for the treatment groups. The difference from placebo is not as pronounced as for suDBP. The effect for each losartan dose at trough on day 5 are not different.

Table 5.8. Standing Diastolic Blood Pressure (mmHg). Mean^(a) Changes from Day -1

Treatment	Day 1				Day 5				Day 6				Day 6-5			
	Hr. 6		Hr. 24		Hr. 6		Hr. 24		Hr. 6		Hr. 24		Hr. 6		Hr. 24	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Placebo	23	-4.5*	22	-3.8*	23	-4.8*	23	-5.3**	23	-7.7**	23	-2.8Δ	23	-2.9	23	2.5
losartan 50 mg	20	-10.6**	20	-5.6**	20	-15.1**	20	-8.5**	20	-8.5**	20	-5.8**	20	+6.6**	20	2.7
losartan 100 mg	18	-9.8**	18	-7.8**	18	-12.6**	18	-10.2**	18	-9.9**	18	-7.8**	18	2.7	18	2.4
losartan 150 mg	20	-11.0**	20	-7.7**	19	-14.3**	19	-8.4**	19	-10.2**	19	-6.0**	19	+4.1Δ	19	2.4
Enalapril 10 mg	19	-13.7**	18	-7.9**	18	-15.0**	18	-9.2**	18	-8.2**	18	-6.7**	18	+6.9**	18	2.5

Δ = .05 < p ≤ .10, * = p ≤ .05, ** = p ≤ .01; a = least Square means

Table 5.9. Standing Diastolic Blood Pressure (mmHg). Mean^(a) Changes from Day -1

Treatment	Day 2				Day 3				Day 4			
	Hr. 6		Hr. 24		Hr. 6		Hr. 24		Hr. 6		Hr. 24	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Placebo	23	-6.4**	23	-3.1*	23	-7.3**	23	-6.4**	23	-6.0**	23	-5.4**
Losartan 50 mg	20	-13.5**	20	-9.3**	20	-14.2**	20	-9.1**	20	-11.3**	20	-6.9**
Losartan 100 mg	18	-10.2**	18	-7.6**	18	-11.6**	18	-6.7**	18	-10.3**	18	-7.3**
Losartan 150 mg	20	-12.7**	20	-5.0**	20	-11.3**	20	-7.8**	20	-13.1**	20	-7.4**
10 mg Enalapril	18	-14.0**	18	-7.5**	18	-16.1**	18	-7.1**	18	-10.8**	18	-5.3**

Δ = .05 < p ≤ .10, * = p ≤ .05, ** = p ≤ .01, a = least Square means

Pulse rate is not significantly affected by losartan.

Plasma renin was increased in the losartan groups on day 1 and day 5 as illustrated in table 5.10.

Table 5.10. Plasma Renin Activity (ng/ml/hr)

Treatment	Mean ^(a) Changes from Day -1							
	Day 1				Day 5			
	Hr. 5		Hr. 23		Hr. 5		Hr. 23	
	N	Mean	N	Mean	N	Mean	N	Mean
Placebo	23	+0.35	23	-0.02	22	-0.11	23	+0.45
50 mg LOSARTAN	19	+1.9*	20	+1.3*	19	+4.9*	19	+1.8*
100 mg LOSARTAN	18	+1.5	18	+1.4*	18	+3.9Δ	18	+2.0*
150 mg LOSARTAN	20	+2.3*	20	+1.5**	19	+4.5Δ	20	+1.7Δ
10 mg Enalapril	18	+2.3*	18	+1.4*	17	+7.7**	16	+2.7**
P-Values								
Dose Response	Hr. 5		Hr. 23		Hr. 5		Hr. 23	
Pbo 50 100 150 L	13		042		16		24	
Pbo 50 100 150 Q	62		27		28		30	
50 100 150 L	76		74		89		95	
50 100 150 Q	56		97		78		79	
Pairwise vs. placebo	Hr. 5		Hr. 23		Hr. 5		Hr. 23	
Pbo 150	084		015		11		24	
Pbo 100	32		062		16		16	
Pbo 50	16		073		08		23	
(a) Least Squares Means								
L = Linear Component								
Q = Quadratic Component								
Δ = .05 < p ≤ .10								
* = p ≤ .05								
** = p ≤ .01								

Aldosterone levels generally decreased with losartan and enalapril treatment as table 5.11 illustrates. The magnitude of the change from baseline was less on day 5 as opposed to day 1.

Table 5.11. Serum Aldosterone (pg/mL)

Treatment	Mean ^(a) Changes from Day -1								
	Day 1				Day 5				
	Hr 5		Hr 23		Hr 5		Hr 23		
	N	Mean	N	Mean	N	Mean	N	Mean	
Placebo	23	-3.9	23	+9.1	22	+31.1	23	+55.7Δ	
50 mg LOSARTAN	18	-96.9**	19	-16.5	19	-42.5Δ	18	-8.7	
100 mg LOSARTAN	18	-87.4**	18	-49.0*	18	-36.6	18	-25.0	
150 mg LOSARTAN	20	-53.8**	20	-39.8Δ	19	+7.7	20	-15.7	
10 mg Enalapril	18	-76.1	19	-32.3	17	-21.6	16	-30.9	
P-Values									
Dose Response				Hr 5	Hr 23	Hr 5	Hr 23		
Pbo	50	100	150	L	.081	.047	.49	.088	
Pbo	50	100	150	Q	.0009	.40	.0066	.24	
	50	100	150	L	.10	.43	.098	.88	
	50	100	150	Q	.60	.42	.47	.74	
Pairwise vs. Placebo									
Pbo			150		.048	.082	.43	.092	
Pbo		100			.0016	.046	.026	.065	
Pbo	50				.0005	.37	.014	.14	
Pairwise vs. Enalapril									
			150	E	.40	.80	.35	.74	
		100		E	.67	.58	.63	.90	
	50			E	.44	.59	.50	.64	
Pbo				E	.0061	.15	.087	.057	
Mean Squared Error					6,407.7	8,141.6	8,472.0	18,155.5	
(a) Least Squares Means					L = Linear Component		Δ = .05 < p ≤ .10		
					Q = Quadratic Component		* = p ≤ .05		
							** = p ≤ .01		

Serum uric acid tended to decrease with losartan treatment as shown in Table 5.12. It is unclear whether this is a clinically meaningful change.

Table 5.12. Mean Uric Acid Labs

Variable	Treatment	Mean ^(a) Changes from Day -1						P-Values Pairwise		
		Day 2		Day 5		Day 6		vs. Placebo		
		N	Mean	N	Mean	N	Mean	Day 2	Day 5	Day 6
S. Uric Acid (mg/dl)	Placebo	23	-0.103	23	-0.153	23	-0.053			
	Losartan 50 mg	19	-.367**	19	-.945**	17	-.769**	0.0019	0.003	0.016
	Losartan 100 mg	17	-.289*	18	-1.133**	18	-.742**	0.27	0.0004	0.0019
	Losartan 150 mg	19	-.618**	19	-.944**	19	-.581**	0.1	0.0029	0.0017
	10 mg Enalapril	17	0.111	17	-0.129	16	-0.146	0.2	0.93	0.68
Dose Responses							P-Values			
S. Uric Acid (mg/dl)	Pbo	50	100	150	L		Day 2	Day 5	Day 6	
	Pbo	50	100	150	Q		0.78	0.011	0.0062	
		50	100	150	L		0.14	0.99	0.41	
		50	100	150	Q		0.18	0.43	0.74	
Pairwise vs. Enalapril										
			150				<.0001	0.0051	0.067	
		100					0.027	0.0007	0.014	
	50						0.007	0.0048	0.011	
Mean Squared Error							0.2613	0.6633	0.4563	

(a) Least Squares Means, (b) Over 24 Hours, L = Linear Component, Q = Quadratic Component, Δ = .05 < p ≤ .10, * = p ≤ .05, ** = p ≤ .01

ACE activity was measured before patients received their first dose of study medication on day 1 and then five hours after the dose. Measurements were taken again on day 5, at one hour before and five hours after patients received their dose. Table 5.13 shows that the mean ACE activity after enalapril decreased and that there was essentially no change after losartan.

Table 5.13. ACE Activity

		Mean Changes from Baseline (Hr -1)						P-Values: Pairwise		
		Day 1		Day 5				vs Placebo		
		Hour 5		Hour -1		Hour 5		Day 1	Day 5	Day 5
		N	Mean	N	Mean	N	Mean	Hour 5	Hour -1	Hour 5
ACE Activity (U/L)	Placebo	21	-4.1	21	-1.5	20	-3.3			
	Losartan 50 mg	18	-3.2	18	-1.9	18	-2.2	0.838	0.932	0.819
	Losartan 100 mg	17	-3	17	-0.6	17	-0.7	0.808	0.852	0.61
	Losartan 150 mg	20	-2.7	19	1.8	19	-4.3	0.737	0.467	0.842
	10 mg Enalapril	15	-30.9**	15	-31.9**	15	-35.9**	0	0	0
	Mean Square Error		191.1		200.4		229.7			

(a) Least Squares Means

Within Treatment Change equal to zero. # = .010 < p < .100, * = p < .050, ** = p < .010

Safety

Table 5.14 lists three patients discontinued from the study due to adverse experiences. Patient #118 had standing heart rates generally in the 80's and 90's until day 4. The majority of standing heart rates on day 4 were greater than 100 with a maximum as high as 136 beats per minute. There was not a significant decline in blood pressure that could precipitate this increase in heart rate. Patient #039 had standing SBP on day -1 range from 117 to 180 and standing DBP range from 95 to 111 mmHg. On the day the patient complained of lightheadedness on standing, the standing DBP was as low as 72 mmHg and the standing SBP was as low as 112 mmHg. Standing blood pressures were not lower than supine blood pressures. Patient 124 had baseline standing blood pressures range from 141/89 to 191/108. On the first day of treatment with 10 mg of enalapril, the standing blood pressure was as low as 87/59 mmHg. Day 2 blood pressure data is not provided.

Table 5.14. Patients Discontinued Due to a Clinical Adverse Experience

Patient Allocation	Sex/Age	Drug	Relative Day of Onset	Adverse Experience	Duration	Severity	Outcome
0118	M/69	Placebo	4	Orthostatic tachycardia	12 hrs	Moderate	Recovered
0039	F/68	Losartan 150 mg	2	Lightheadedness on standing	23 8 hrs	Moderate	Recovered
0124	F/72	enalapril	1	Postural Hypotension	6 hrs	Mild	Recovered

Table 5.15 lists the incidence of adverse experiences reported during the 6 day treatment period. Forty-eight percent of placebo and fifty-five to sixty percent of losartan patients complained of

Table 5.15. Clinical Adverse Experience Summary

Number (%) of Patients	Placebo (N=23)	Losartan 50 mg (N=20)	Losartan 100 mg (N=18)	Losartan 150 mg (N=20)	Enalapril 10 mg (N=19)
With any Clinical AE	11 (48)	12 (60)	10 (56)	11 (55)	12 (63)

A summary of clinical adverse experiences by body system, along with individual adverse experiences reported in at least two patients are summarized in Table 5.16. The most common adverse experience reported was headache. The incidence of headache was significantly higher in the losartan potassium 150 mg group (40%) than in the placebo group (13%). Dizziness was also common in the active treatment groups, with the losartan potassium 100 mg (28%) and enalapril 10 mg (37%) groups reporting significantly higher incidence than the placebo group (0%).

Table 5.16. Clinical Adverse Experiences by Body System and Individual Adverse Experiences Occurring in at Least Two Patients. () - % of patients with AE, [] - indicates number of Drug-Related Adverse Experiences

Adverse Experience	Placebo (N=23)			Losartan 50 mg (N=20)			Losartan 100 mg (N=18)			Losartan 150 mg (N=20)			Enalapril 10 mg (N=19)		
Body as a Whole	4	(17)	[2]	5	(25)	[1]	2	(11)	[2]	4	(20)	[3]	4	(21)	[3]
Asthenia	1	(4)	[0]	1	(5)	[0]	2	(11)	[2]	4	(20)	[2]	3	(16)	[2]
Cardiovascular	3	(13)	[3]	1	(5)	[1]	3	(17)	[3]	0	(0)	[0]	1	(5)	[0]
Tachycardia	3	(13)	[3]	1	(5)	[1]	3	(17)	[3]	0	(0)	[0]	0	(0)	[0]
Digestive	0	(0)	[0]	4*	(20)	[0]	2	(11)	[1]	3 [#]	(15)	[1]	1	(5)	[0]
Nausea	0	(0)	[0]	1	(5)	[0]	1	(6)	[1]	2	(10)	[1]	1	(5)	[0]
Musculoskeletal	3	(13)	[1]	2	(10)	[0]	1	(6)	[0]	1	(5)	[0]	1	(5)	[0]
Nervous System/															
Psychiatric	4	(17)	[2]	8	(40)	[4]	7	(39)	[4]	9 [#]	(45)	[5]	9*	(47)	[7]
Dizziness	0	(0)	[0]	0	(0)	[0]	5*	(28)	[4]	2	(10)	[2]	7**	(37)	[5]
Headache	3	(13)	[1]	7	(35)	[4]	5	(28)	[2]	8 [#]	(40)	[4]	7	(37)	[5]
Respiratory	1	(4)	[0]	0	(0)	[0]	2	(11)	[1]	1	(5)	[0]	2	(11)	[0]
Skin and Skin															
Appendage	2	(9)	[0]	2	(10)	[0]	2	(11)	[2]	1	(5)	[0]	3	(16)	[2]
Special Senses	1	(4)	[0]	0	(0)	[0]	1	(6)	[0]	1	(5)	[1]	2	(11)	[2]
Urogenital	0	(0)	[0]	1	(5)	[0]	1	(6)	[1]	0	(0)	[0]	0	(0)	[0]

[#]Difference from placebo noted, p<0.100, *, ** Significant difference vs. placebo, p<0.050, p<0.010 respectively.

Note: This table contains counts of patients. If a patient reported a particular adverse experience more than once, the patient was counted only once with that adverse experience. If a patient had more than one adverse experience in a body system category, the patient was counted only once in the body system total.

Excluding mean changes in uric acid (see efficacy summary for study 005), there were no significant differences in mean changes of laboratory parameters from baseline. There is no trend in the number of patients with laboratory parameters outside pre-defined limits. There was no significant effect on ECG intervals at trough.

Study 011. A Double-Blind Randomized, Parallel, Placebo-Controlled Study to Investigate the Antihypertensive Efficacy and Safety of Different Doses of Losartan

Protocol

Design

This was a multicenter, randomized double-blind, placebo-controlled, parallel study in patients with mild to moderate essential hypertension (supine diastolic blood pressure 100-115 mmHg). The primary objective of the trial was to evaluate the antihypertensive efficacy of the AII antagonist losartan at different doses (10, 25, 50, 100 or 150 mg) as compared to placebo and 20 mg enalapril.

Inclusion Criteria

1. Mild to moderate uncomplicated essential hypertension characterized by an untreated supine diastolic blood pressure (suDBP) 100 to 115 mmHg. The patient's Prestudy (Day -29) suDBP must be >90 mmHg, Week -3 suDBP must be ≥95 mmHg, and the means of the Week -3 and Week -1 suDBP readings cannot vary from each other by more than 7 mmHg.
2. The patient is at least 21 years of age at the time of entrance into the baseline period.
3. The patient is within 30% of ideal weight for his/her height and body build 4. The patient has no active medical problems other than essential hypertension, that might of themselves or their treatment affect blood pressure.
5. The patient is receiving no drug therapy that might affect blood pressure.
6. The patient's prestudy laboratory screen shows no clinically important abnormalities.
7. No more than 25% of the patient population studied at each site can be Black (3 of 14 patients).

Exclusion Criteria

1. Prior exposure to losartan.
2. Secondary hypertension of any etiology, such as unilateral or bilateral renal disease, coarctation of the aorta or pheochromocytoma. History of malignant hypertension. Supine systolic blood pressure >210 mmHg.
3. History of cerebrovascular accident (stroke) or history of transient ischemic attacks.
4. Documented history of myocardial infarction or angina pectoris (prior or active).
5. Clinically significant AV conduction disturbance, i.e., second- or third-degree AV block, or left bundle branch block. Sick-sinus syndrome or clinically significant bradycardia (resting heart rate <45 beats/minute).
6. Atrial flutter or atrial fibrillation and an accessory bypass tract (e.g., Stokes-Adams Syndrome or Wolff-Parkinson-White Syndrome).
7. History of congestive heart failure or a known left ventricular ejection fraction <40%.
8. Prior known sensitivity to ACE inhibitors.
9. Concomitant use of β-blockers (excluding ophthalmic preparations) or digitalis, or any agent that may cause a lowering of blood pressure (e.g. diuretics, angiotensin converting enzyme inhibitors, nitrates, calcium channel blockers) is not permitted

during the study. Patients taking major psychotropic agents or anti-depressants will be excluded. Regular use of nonsteroidal anti-inflammatory agents (NSAIDs) and high-dose aspirin are not permitted. Acetaminophen is permitted. One or two aspirins taken regularly as a cardioprotective agent is permitted.

10. Evidence of significant renal or hepatic dysfunction as indicated by history or recent laboratory:

BUN	>35 mg/dl
Serum Creatinine	>1.7 mg/dl
Proteinuria	>TRACE
SGPT/SGOT	>50% above normal

11. Clinically significant laboratory values outside of the established normal range including but not limited to any of the following parameters: hematocrit, hemoglobin, platelet count or white blood count.

12. White blood count below 3000 mm³, platelet count below 100,000 mm³.

13. Serum potassium <3.5 or >5.5 mEq/L.

14. Known positive test for AIDS (positive HIV) or Hepatitis B surface antigen.

15. History of clinically important malabsorption or gastrointestinal resection.

16. Patients being treated for acute ulcer disease. The H₂-antagonists, famotidine or ranitidine are allowed on a PRN basis.

17. History of chronic liver disease.

18. Actively treated diabetes mellitus. Fasting glucose levels up to 150 mg/dl will be permitted.

19. Other concurrent severe disease, such as neoplasm which could preclude participation or survival.

20. Any known bleeding or platelet disorder.

21. The absence of one kidney.

22. Women of childbearing potential or who are currently breastfeeding, i.e., those who are not postmenopausal or have not been surgically sterilized; (postmenopausal women receiving chronic estrogen treatment are allowed. The dose should be kept constant).

23. The patient is currently abusing or has a history of alcoholism, drug addiction, or abuse of other substances.

24. Mentally or legally incapacitated patients.

25. Patient has participated in another drug trial, including one using marketed drugs, within the 28 days prior to initiation of placebo baseline.

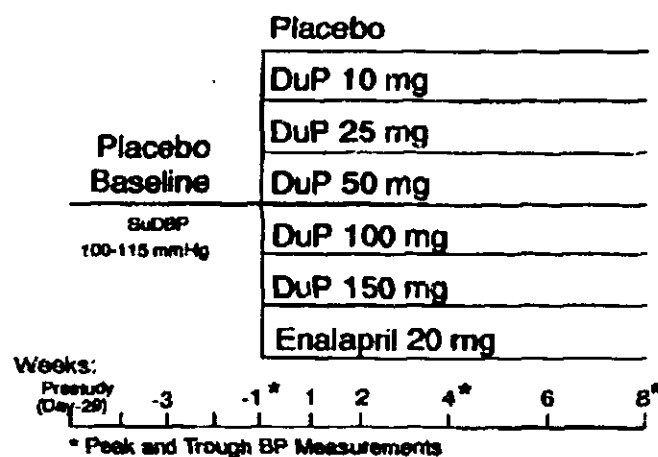
26. Patients who, in the opinion of the investigator, will not cooperate fully, keep appointments or are generally unreliable.

27. Patients who will not be able to complete the study due to economic or social problems.

Study Description

The trial consisted of a two to four week single-blind placebo period and a double-blind 8 week treatment period. Prior to entry into the study, the patient's prestudy (Day -29) supine diastolic blood pressure (suDBP) had to be > 90 mmHg. All antihypertensive medications were discontinued, and the patients were given placebo for 2 weeks (Weeks -4 through -3). After 2 weeks of placebo therapy, the patient's Week -3 suDBP had to be ≥ 95 mmHg in order for the patient to continue with the final 2 weeks of placebo baseline therapy (Weeks -2 through -1). If at the end of the 4-week placebo baseline period a patient's suDBP was 100 to 115 mmHg and the means of the Week -3 and Week -1 suDBP readings did not vary from each other by more than 7 mmHg, the patient entered the 8-week treatment period (Weeks 1 through 8). If during the placebo baseline period the patient's suDBP exceeded 115 mmHg at any visit, then the investigator could enter the patient into the active-treatment period. Patients were randomized to one of seven possible treatment groups as outlined in figure 11.1.

FIGURE 11.1 Study Outline (DuP = Losartan).



Patients could, at the investigator's discretion, be randomized after 2 weeks of placebo provided there are at least 2 sets of blood pressure data within the acceptable range (suDBP 110-115 mmHg), not less than 3 days apart, and the difference between the readings is ≤ 7 mmHg. If during the placebo baseline period the patient's suDBP exceeds 115 mmHg at any visit, the patient should not be entered into the active-treatment period. If during the active-treatment period the supine DBP is inadequately controlled (supine DBP >120 mmHg or a rise of >15 mmHg from baseline on two successive measurements separated by at least 3 days), the investigator could discontinue the patient from the study and provide alternative therapy. At the end of the 8-week double-blind treatment phase, centers could elect to participate in an open-label extension phase of the study, which was ongoing. Results from the open-label extension will be presented as a separate clinical study report.

Primary Objectives

A. To investigate the antihypertensive efficacy, safety (clinical and laboratory), and dose response relationship of Losartan compared to placebo. Week 8 supine diastolic blood pressure 24 hours postdose results will be used as primary efficacy determinants.

Secondary Objectives

- B. To investigate the length of time (weeks) on drug necessary to establish a stable reduction in blood pressure.
- C. To investigate the safety and antihypertensive efficacy of Losartan at various doses in the following subsets of the patient population studied:
- Elderly (≥ 65 years) vs. young (<65 years)
 - Non-black vs. Black
 - Male vs. Female
 - Mild (100-105 mmHg suDBP) vs. Moderate (106-115 mmHg suDBP)
- D. To investigate the antihypertensive efficacy of various doses of Losartan in the patient population studied stratified by the patients' predose ambulatory renin status (PRA levels).
- E. To investigate the effects of Losartan on metabolic parameters (glucose, sodium, potassium, creatinine, uric acid, HDL and total cholesterol).
- F. To investigate the trough to peak ratio of antihypertensive efficacy.
- G. To investigate the safety and efficacy of Losartan compared to enalapril (20 mg).
- H. To determine an ineffective dose of Losartan.

Statistical Analysis

Efficacy Analyses was performed using the "All-Patients-Treated" and "Per-Protocol" analysis. The "all patients treated" analysis included all patients with at least one treatment period measurement. The last measurements of withdrawn patients were carried forward to subsequent timepoints. For patients with data missing from a visit, the missing data is estimated by carrying forward data from the last visit at which it was available (excluding the baseline visit). For the "per protocol" analysis, patients with protocol violations are excluded. Patients who withdraw prior to an analyzed timepoint are not included.

The sample size estimation provided in the protocol is quite confusing and difficult to interpret as illustrated in table 11.1.

Table 11.1. Sample Size Estimation

Approximately 40 sites will be used to enter a total of up to 840 patients; at least 357 (51 per treatment group) are expected to complete the study. Assuming a standard deviation of 9 mmHg or less, 51 patients per treatment group will be sufficient to detect a 5 mmHg difference between the treatments with the highest and lowest responses; i.e., in mean reduction in suDBP with 80% probability at the 5% level of significance (two-sided test).

If 420 (504) patients complete the study, 60 (72) patients per treatment group will be sufficient to detect a 5 mmHg difference in mean reduction in suDBP between the treatments with the highest and lowest responses with 86% (92%) probability at the 5% level of significance (two-sided test).

The sample size (51 per group) will also provide approximately 95% power for detecting a slope of -2 mmHg for the regression of change from baseline in suDBP on the log of Losartan dose; i.e., to detect a 2 mmHg decrease with each doubling of the dose. This statement assumes a standard deviation in change from baseline in suDBP of 9 mmHg for a one-sided, 5% level of significance test. It is believed that a slope of this magnitude would indicate a dose-response relationship.

Outline of Procedures

Table 11.1a outlines the procedures performed during the trial.

Table 11.1a. Clinical and Laboratory Measurements

Procedure	Study Week							
	Baseline			Treatment				
	Prestudy	-3	-1	1	2	4	6	8
Medical History	X							
Complete Physical Exam	X							X
Body Weight	X	X	X	X	X	X	X	X
Trough BP and HR ¹	X	X	X	X	X	X	X	X
Peak BP and HR ¹			X			X		X
Chest X-ray ²		X						
Fasting Laboratory		X			X	X		X
12-lead ECG		X			X			X
"Peak time" PRA			X					X
Plasma Drug Levels								X

1 = Measurements made in both the supine and standing positions. 2 = Unless x-ray from 1 year period prior to study participation was available for review

Trough supine and standing blood pressure and heart rate were measured at the beginning of every clinic visit, 22-26 hours post the previous day's dose of medication. Peak supine and standing blood pressure and heart rate were also measured 5-6 hours post that day's dose of study medication at Weeks -1, 4 and 8, as indicated in Table 1.

The pulse rate over at least 30 seconds was taken after 5 minutes in the supine position and again after 2 minutes in the standing position, prior to blood pressure measurement.

Ambulatory plasma renin activity (PRA) was measured in samples obtained from patients at peak clinic visits at Weeks -1 and 81. Prior to venipuncture, the patient had to remain ambulatory for at least 30 minutes.

Results

A planned interim analysis of this study consisting of data summarizations was performed when approximately 40% of the patients in the final analysis had completed the double-blind phase. This analysis was for the purpose of selecting doses for future hypertension studies and included summarizations of blood pressure, adverse experience information and laboratory test results. Two additional blood pressure summarizations [Reviewer's Note: These additional analysis were not pre-specified.] occurred for the same purpose as noted above when approximately 60% and 90% (study was complete at this point, but not all data were available) of the double-blind data were available. The study remained blinded (patient-treatment assignments were not reported) until validation of the data was complete. No adjustments to final statistical p-values were made. [Reviewer's Note: Enrollment for this trial was complete by the time the first interim analysis was performed. (Information obtained from Larry Bell on 1/11/95)]

Demographics/Patient Disposition

Five hundred and seventy-six patients were randomized to 41 centers. A listing of investigators can be found in the appendix. The number of patients screened during the baseline period is not provided. The number of patients randomized per treatment group ranged from 78 - 90. Table 11.2 summarizes the demographic parameters among treatment groups. The mean age was 53 years. Two-thirds of the patients were male. The percentage of black patients in each treatment group ranged from 6% to 19%. The percentage of hispanic patients ranged from 6% to 14% per treatment group.

Table 11.2. Baseline Patient Demographic Characteristics

	PBO (N=78)	Losartan						ENAL 20 (N=83)	Total (N=576)
		10 (N=80)	25 (N=82)	50 (N=79)	100 (N=90)	150 (N=84)			
Sex									
Female	31 (40%)	29 (36%)	27 (33%)	26 (33%)	31 (34%)	22 (26%)	27 (33%)	193 (34%)	
Male	47 (60%)	51 (64%)	55 (67%)	53 (67%)	59 (66%)	62 (74%)	56 (67%)	383 (66%)	
Age (Years)									
Mean	52.3	53.9	52.8	52.8	54.0	53.9	51.9	53.1	
S.D.	11.6	12.3	12.2	10.3	10.2	10.8	11.1	11.2	
Median	53.0	55.0	53.0	53.0	52.5	56.0	53.0	53.0	
Range	28-77	22-88	25-76	27-73	29-75	29-77	27-73	22-88	
Racial Origin									
Caucasian	64 (82%)	60 (75%)	63 (77%)	57 (72%)	66 (73%)	64 (76%)	64 (77%)	438 (76%)	
Black	5 (6%)	10 (13%)	14 (17%)*	11 (14%)	17 (19%)*	11 (13%)	7 (8%)	75 (13%)	
Hispanic	9 (12%)	9 (11%)	5 (6%)	11 (14%)	7 (8%)	8 (10%)	10 (12%)	59 (10%)	
Other	0	1 (1%)	0	0	0	1 (1%)	2 (2%)	4 (1%)	
Duration of Hypertension (years)									
<1	3 (4%)	5 (6%)	2 (2%)	3 (4%)	2 (2%)	3 (4%)	5 (6%)	23 (4%)	
1-5	11 (14%)	13 (16%)	27 (33%)	25 (32%)	22 (24%)	24 (29%)	23 (28%)	145 (25%)	
5.01-10	29 (37%)	21 (26%)	21 (26%)	17 (22%)	26 (29%)	19 (23%)	24 (29%)	157 (27%)	
>10	35 (45%)	41 (51%)	32 (39%)	33 (42%)	39 (43%)	38 (45%)	31 (37%)	249 (43%)	
Unknown	0	0	0	1 (1%)	1 (1%)	0	0	2 (0%)	
Mean	11.9	11.6	10.0	10.1	10.7	9.8	9.8	10.5	
S.D.	8.8	8.4	7.4	7.8	7.1	6.7	7.5	7.7	
Median	10.0	10.3	8.3	7.5	10.0	10.0	8.5	10.0	
Range	0.5-44	0.1-46	0.6-30	0.1-35	0.5-32	0.1-28	0.1-36	0.1-46	
Supine Diastolic Blood Pressure (mmHg)									
<105 (mild)	61 (78%)	57 (71%)	64 (78%)	58 (73%)	65 (72%)	66 (79%)	68 (82%)	439 (76%)	
>105 (moderate)	17 (22%)	23 (29%)	18 (22%)	21 (27%)	25 (28%)	18 (21%)	15 (18%)	137 (24%)	
Mean	103.3	104.3	103.3	104.0	104.1	103.4	103.1	103.7	
S.D.	3.8	3.9	3.7	3.7	4.2	3.4	3.7	3.8	
Median	102.0	103.0	102.0	103.0	103.0	102.0	101.0	102.0	
Range	100-113	100-115	100-114	100-115	99-115	100-114	100-115	99-115	

* Statistically significantly different from PLACEBO treatment group, p<0.05

Fifty patients withdrew prematurely during the 8 weeks of double blind therapy. The number of dropouts ranged from 3 to 11 per treatment group. Discontinuations due to adverse experiences are divided into clinical adverse experience, laboratory adverse experience and both. A total of 14 patients withdrew due to adverse experiences. Eleven patients are listed as simply "patient withdrew". Six withdrew in the losartan 100 mg group for this reason. Six patients were lost to follow-up. Three hundred and seven patients continued into the open label follow-up study. A listing of patients withdrawn prematurely can be found in the appendix. Table 11.3 lists the number of patients discontinued based on treatment.

Table 11.3. Patient Accounting

	PBO (N=78)	Losartan						ENAL 20 (N=83)
		10 (N=80)	25 (N=82)	50 (N=79)	100 (N=90)	150 (N=84)		
		n (%)	n (%)	n (%)	n (%)	n (%)		
Completed DB/No OL	28 (35.9)	31 (38.7)	37 (45.1)	33 (41.8)	32 (35.6)	30 (35.7)	31 (37.3)	
Completed DB/ Entered OL	39 (50.0)	41 (51.3)	38 (46.3)	43 (54.4)	48 (53.3)	47 (56.0)	48 (57.8)	
Discontinued DB Prematurely	11 (14.1)	8 (10.0)	7 (8.5)	3 (3.8) ^a	10 (11.1)	7 (8.3)	4 (4.8)	
Clinical Adverse Experience	0	2 (2.5)	1 (1.2)	1 (1.3)	1 (1.1)	3* (3.6)	1* (1.2)	
Laboratory Adverse Experience	2 (2.6)	0	1 (1.2)	0	0	0	1 (1.2)	
Clinical & Laboratory AE	0	0	0	0	0	1 (1.2)	0	
Therapy Ineffective	3 (3.8)	5* (6.3)	2 (2.4)	0	0 ^b	3 (3.6)	0 ^b	
Patient Uncooperative	2 (2.6)	0	0	0	1 (1.1)	0	0	
Patient Withdrew	2 (2.6)	1 (1.3)	1 (1.2)	0 ^c	6 (6.7)	0 ^c	1 (1.2)	
Protocol Deviation	0	0	1 (1.2)	1 (1.3)	1 (1.1)	0	0	
Lost to Follow-up	2 (2.6)	0	1 (1.2)	1 (1.3)	1 (1.1)	0	1 (1.2)	

* One patient in this treatment group continued into the extension period of the study after discontinuing the double-blind phase.

^a: Statistically significantly different from PBO treatment group, p<0.05; DB = Double Blind Phase^b: Statistically significantly different from LOS 10 treatment group, p<0.05; OL = Open Label Phase^c: Statistically significantly different from LOS 100 treatment group, p<0.05.

Supine Blood Pressure Changes - Trough and Peak

Three patients, # 376 (losartan 50 mg; lost to follow up), #190 (losartan 100 mg; protocol deviation) and #124 (enalapril; patient withdrew), did not have any treatment period blood pressure measurements and could not be included in the "all-patients-treated" analysis.

The mean change in trough supine diastolic blood pressure at week 8 is listed in table 11.4. [NOTE: Adjusted means (for baseline DBP and clinic) are provided in this table since baseline was included as a covariate in the model and the pairwise comparisons were based upon these adjusted means] Although losartan 10 mg showed a significant difference from placebo, the relative change was only 2.3 mmHg. This difference was numerically greater than the difference between losartan 25 mg and placebo. There is no difference in treatment effect between losartan 50 mg, 100 mg and 150 mg. Enalapril was not significantly different from the three highest doses of losartan.

Table 11.4. Mean Change in Trough Supine Diastolic Blood Pressure at Week 8 (All-Patients-Treated Approach)

Treatment	N	Baseline		Treatment		Change		Change Adj Mean	Comparison					
		Mean	S.D	Mean	S.D.	Mean	S.D.		VS. B	VS. C	VS. D	VS. E	VS. F	VS. G
Placebo (A)	78	103.3	3.8	97.8	8.8	-5.6	7.8	-5.3	*	NS	**	**	**	**
LOS 10 (B)	80	104.3	3.9	96.3	9.7	-7.9	7.6	-7.8	--	NS	*	NS	NS	**
LOS 25 (C)	82	103.3	3.7	96.5	9.5	-6.8	7.9	-6.4	--	--	**	**	**	**
LOS 50 (D)	78	104.1	3.7	94	8.5	-10.1	7	-10.1	--	--	--	NS	NS	NS
LOS 100 (E)	89	104.1	4.3	94.2	8	-9.9	6.9	-9.9	--	--	--	--	NS	NS
LOS 150 (F)	84	103.4	3.4	93.7	9.4	-9.7	8	-9.5	--	--	--	--	--	NS
ENAL 20 (G)	82	103.1	3.8	91.9	8.2	-11.2	6.7	-10.8	--	--	--	--	--	--

NS -- Not statistically significant; * -- Treatment difference statistically significant, $p \leq 0.05$; ** -- Treatment difference statistically significant, $p \leq 0.01$

Table 11.5 lists the change in supine systolic blood pressure. Losartan doses greater than 25 mg are significantly different from placebo. There is no dose response with losartan.

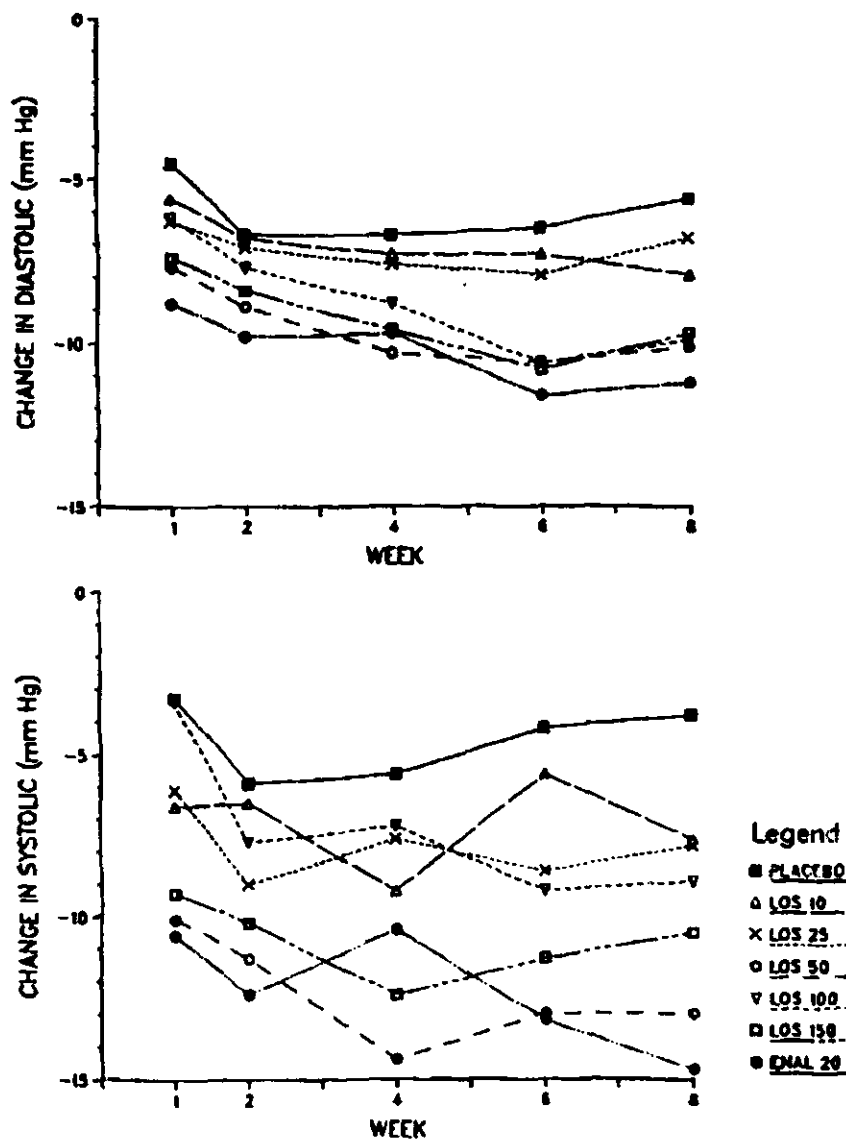
Table 11.5. Mean Change in Trough Supine Systolic Blood Pressure at Week 8 (All-Patients-Treated Approach)

Treatment	N	Baseline		Treatment		Change		Change Adj Mean	Comparison					
		Mean	S.D	Mean	S.D.	Mean	S.D.		VS. B	VS. C	VS. D	VS. E	VS. F	VS. G
Placebo (A)	78	157.9	14.5	154.1	17.7	-3.8	11.7	-3.9	NS	*	**	**	**	**
LOS 10 (B)	80	160.7	16.7	153.1	19.2	-7.6	12.6	-6.7	--	NS	**	NS	NS	**
LOS 25 (C)	82	158.7	16.2	151	18.7	-7.8	13.8	-7.9	--	--	**	NS	NS	**
LOS 50 (D)	78	158.3	14.9	145.3	15.4	-13	12.7	-13.2	--	--	--	NS	NS	NS
LOS 100 (E)	89	156.3	16.6	147.4	16.7	-8.9	13.6	-9.4	--	--	--	--	NS	**
LOS 150 (F)	84	158.6	16	148	18.5	-10.5	13.3	-10.5	--	--	--	--	--	*
ENAL 20 (G)	82	155.4	14.9	140.7	17.3	-14.7	13.6	-15.4	--	--	--	--	--	--

NS -- Not statistically significant; * -- Treatment difference statistically significant, $p \leq 0.05$; ** -- Treatment difference statistically significant, $p \leq 0.01$

The maximum effect on suDBP appears to stabilize after 6 weeks of therapy as shown in figure 11.2. The effect on suSBP stabilizes after 4 weeks of therapy.

Figure 11.2. Mean Change in Trough Supine Blood Pressures by Week (All-Patients-Treated Approach)



The "per-protocol" analysis for trough suDBP at week 8 was similar to the "all-patients-treated" approach.

Peak supine and standing blood pressures were obtained approximately 6 hours post dosing. Tables 11.6 and 11.7 list the mean change in peak supine DBP and SBP at week 8. Enalapril had a significantly greater effect on week 8 supine DBP at peak compared to any dose of losartan. Paradoxically, losartan 150 mg had a significantly greater effect on week 8 supine DBP than losartan 100 mg but not losartan 50 mg.

Table 11.6. Mean Change in Peak Supine Diastolic Blood Pressure at Week 8 (All-Patients-Treated Approach)

Treatment	N	Baseline		Treatment		Change		Change Adj Mean	Comparison					
		Mean	S.D	Mean	S.D	Mean	S.D		VS B	VS C	VS D	VS E	VS F	VS G
Placebo (A)	75	99.0	5.5	94.4	8.9	-4.7	8.7	-4.7	NS	**	**	**	**	**
LOS 10 (B)	79	99.8	6.0	92.5	10.3	-7.3	9.4	-7.3	--	NS	**	*	**	**
LOS 25 (C)	80	100.2	5.4	90.3	10.3	-9.9	8.5	-9.7	--	--	NS	NS	*	**
LOS 50 (D)	77	100.1	6.4	88.3	10.3	-11.9	9.2	-12.0	--	--	--	NS	NS	**
LOS 100 (E)	87	100.5	6.7	90.1	9.2	-10.4	8.9	-10.3	--	--	--	--	*	**
LOS 150 (F)	81	99.9	6.4	86.8	10.7	-13.1	9.0	-13.1	--	--	--	--	--	*
ENAL 20 (G)	82	100.4	6.2	84.2	10.1	-16.2	10.4	-16.0	--	--	--	--	--	--

NS – Not statistically significant; * – Treatment difference statistically significant, $p < 0.05$; ** – Treatment difference statistically significant, $p < 0.01$.

Table 11.7. Mean Change in Peak Supine Systolic Blood Pressure at Week 8 (All-Patients-Treated Approach)

Treatment	N	Baseline		Treatment		Change		Change Adj Mean	Comparison					
		Mean	S.D	Mean	S.D	Mean	S.D		VS B	VS C	VS D	VS E	VS F	VS G
Placebo (A)	75	152.1	12.9	151.3	15.9	-0.8	12.0	-1.2	**	**	**	**	**	**
LOS 10 (B)	79	157.4	15.3	148.9	18.1	-8.5	14.5	-7.6	--	NS	**	*	**	**
LOS 25 (C)	80	155.0	16.1	143.4	17.3	-11.6	14.5	-11.5	--	--	NS	NS	NS	**
LOS 50 (D)	77	154.6	13.6	139.9	15.1	-14.7	11.8	-14.6	--	--	--	NS	NS	*
LOS 100 (E)	87	154.5	15.4	142.2	16.8	-12.3	14.4	-12.2	--	--	--	--	NS	**
LOS 150 (F)	81	152.1	15.1	138.6	18.0	-13.5	11.9	-14.2	--	--	--	--	--	*
ENAL 20 (G)	82	152.9	15.8	134.2	16.6	-18.7	15.4	-18.9	--	--	--	--	--	--

NS – Not statistically significant; * – Treatment difference statistically significant, $p < 0.05$; ** – Treatment difference statistically significant, $p < 0.01$.

The trough/peak ratio was obtained by using the mean adjusted change in supine DBP at week 8 (placebo subtracted; carry forward analysis; from table 10 and 17 of the clinical summary report). The results are depicted in figure 11.3 and table 11.8. The ratio for 50 - 150 mg of losartan is $\geq$ to .5.

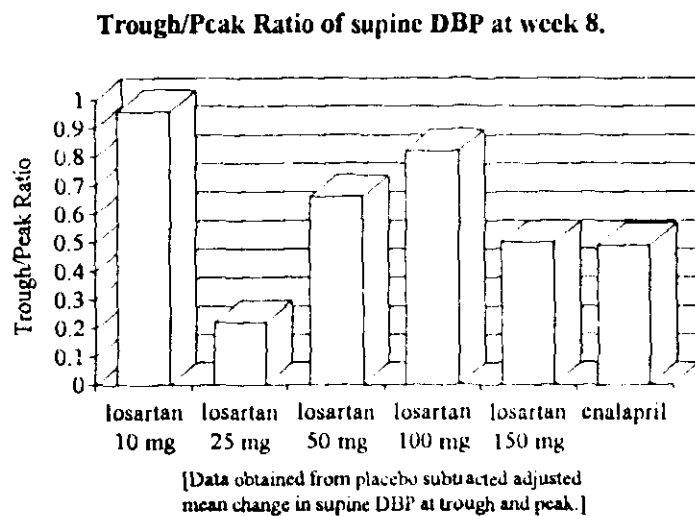
Figure 11.3. Supine DBP Trough/Peak Ratio at week 8.

Table 11.8. Trough-to-Peak Ratios for Supine Diastolic Blood Pressure at Week

N	Treatment	Mean Change (mmHg)		T:P Ratio	T:P Ratio (PBO Adjusted)
	Group	Trough	Peak		
75	Placebo	-5.8	-4.7	125%	~
79	LOS 10	-7.9	-7.3	108%	78%
80	LOS 25	-7.0	-9.9	71%	23%
77	LOS 50	-10.2	-11.9	86%	60%
86	LOS 100	-10.0	-10.5	95%	72%
81	LOS 150	-10.0	-13.1	76%	49%
82	ENAL 20	-11.2	-16.2	69%	47%

NOTE: Only patients with both trough and peak measurements were included in this table.

Mean changes in peak blood pressures for the "per-protocol" approach were similar to those obtained for the "all-patients-treated" approach.

Subgroup Analysis - Supine DBP

Subgroup analysis of suDBP was performed on patients based on gender, age and race. In figure 11.4 and table 11.9, the carry forward analysis of suDBP (placebo subtracted) based on gender suggests that in female patients the 100 and 150 mg doses of losartan are less effective than the 50 mg dose. However, these results are not statistically different. Each treatment group was comprised of approximately one-third women. The carry forward result is similar to the non-carry forward analysis (Reviewer's Note: The non-carry forward analysis includes only suDBP measurements available at week 8.).

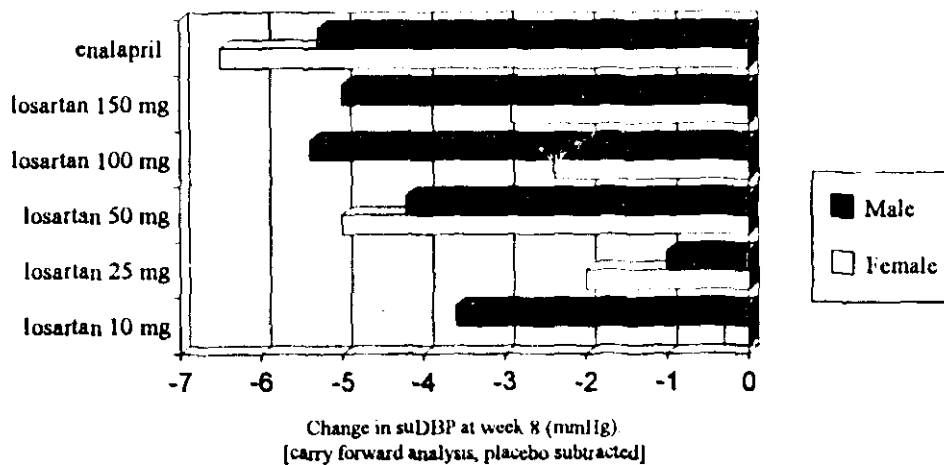
Figure 11.4**Mean Change in suDBP by gender at week 8.**

Table 11.9. Mean Change in Trough Supine Diastolic Blood Pressure at Week 8 by Sex (All-Patients-Treated Approach)

Sex	Treatment	N	Baseline Mean	Treatment Mean	Change Mean	95% Confidence Interval for Mean Change
Female	Placebo	31	102.4	96.0	-6.5	(-9.0, -4.0)
	LOS 10	29	104.7	97.9	-6.8	(-9.2, -4.4)
	LOS 25	27	102.8	94.3	-8.5	(-11.5, -5.5)
	LOS 50	25	103.2	91.6	-11.5	(-14.0, -9.0)
	LOS 100	31	103.1	94.2	-8.9	(-11.6, -6.2)
	LOS 150	22	103.0	93.6	-9.4	(-12.4, -6.4)
Male	ENAL 20	27	102.8	89.8	-13.0	(-15.8, -10.2)
	Placebo	47	104.0	99.0	-5.0	(-7.4, -2.6)
	LOS 10	51	104.0	95.4	-8.6	(-10.8, -6.4)
	LOS 25	55	103.6	97.6	-6.0	(-8.1, -3.9)
	LOS 50	53	104.5	95.1	-9.4	(-11.3, -7.5)
	LOS 100	58	104.5	94.2	-10.4	(-12.0, -8.8)
	LOS 150	62	103.5	93.7	-9.8	(-11.9, -7.7)
	ENAL 20	55	103.3	93.0	-10.3	(-12.0, -8.6)

The mean change in suDBP (placebo subtracted, carry forward analysis) at week 8 based on race is depicted in figure 11.5. The analysis is limited by the small number of patients in some black and hispanic patient treatment groups. The black treatment groups ranged in size from 5 to 17 patients. The hispanic treatment group ranged in size from 7 to 11 patients. An analysis that did not include carry forward data showed even less of a treatment effect in black patients. Table 11.9a shows the non-carry forward analysis of the change from baseline in suDBP at week 8 in black patients compared to the carry forward analysis. Losartan therapy is essentially no different from placebo. The major limiting factor in concluding anything from the race subgroup analysis is that only 5 black patients were randomized into the placebo group.

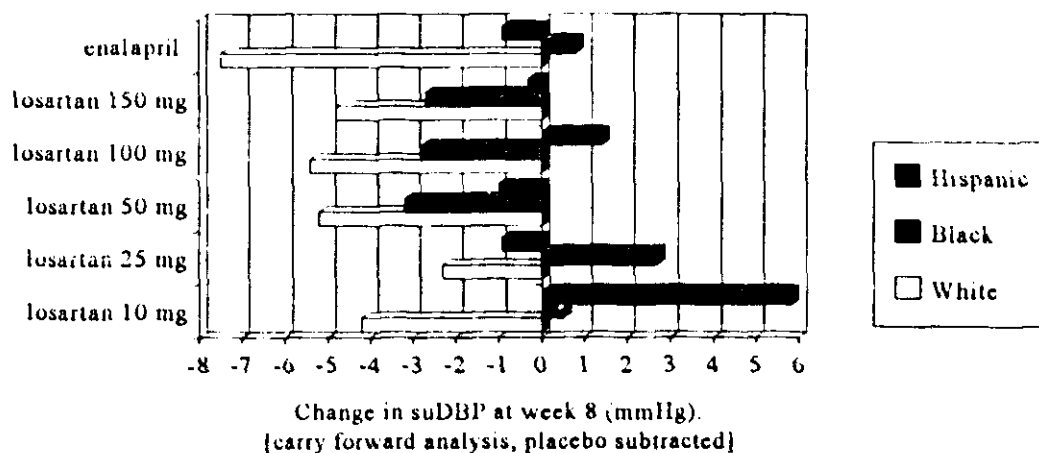
Figure 11.5.**Change in suDBP by Race at week 8.**

Table 11.9a. Change in supine DBP in black patients at week 8

Treatment	N	Change in suDBP (S.D.) [mm Hg] (non-carry forward analysis)*	Placebo Subtracted Change in suDBP [mm Hg] (non-carry forward analysis)	N	Change in suDBP (S.D.) [mm Hg] (carry forward analysis)**	Placebo Subtracted Change in suDBP [mm Hg] (carry forward analysis)
placebo	4	-7.5 (4.5)	-	5	-5.2	-
enalapril	7	-4.4 (8.3)	3.1	7	-4.4	.8
losartan 10 mg	9	-4.3 (7.8)	3.2	10	-4.7	.5
losartan 25 mg	12	-3.7 (7.2)	3.8	14	-2.7	2.5
losartan 50 mg	10	-8.4 (6.0)	-0.9	10	-8.4	-3.2
losartan 100 mg	13	-8.0 (6.6)	-0.5	17	-8.0	-2.8
losartan 150 mg	9	-8.3 (9.8)	-0.8	11	-7.5	-2.3

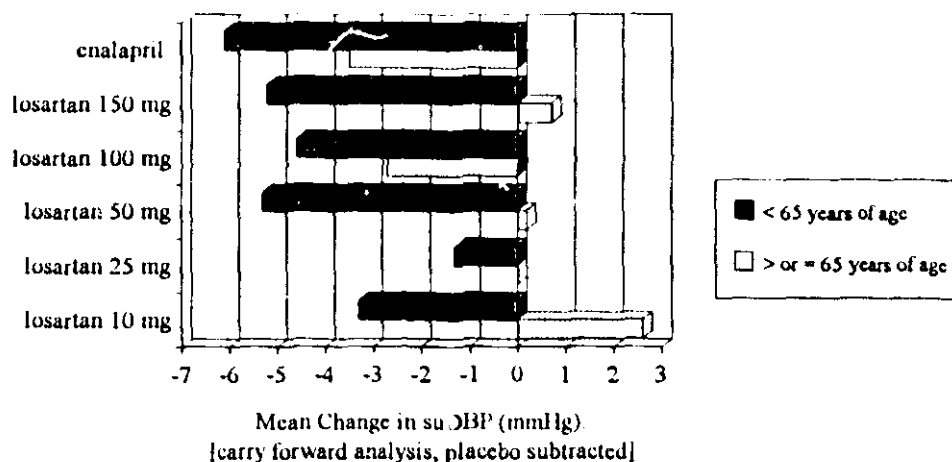
* obtained from the CANDAs database by eliminating carry-forward data

** obtained from the sponsor's clinical summary report page 48, table 13

Figure 11.6 depicts the change in suDBP based on age. For patients ≥ 65 years of age, 11 to 18 were present in each treatment group. Patients ≥ 65 years of age responded poorly to losartan in this study.

Figure 11.6.

Mean Change in suDBP by Age at Week 8.



In general, patients with moderate hypertension (DBP > 105 mmHg) had less of an anti-hypertensive effect compared to patients with mild hypertension (DBP < 105 mmHg) in all treatment groups (placebo excluded).

Adverse Experience

No patients died during this phase of the study. A summary of overall clinical adverse experiences (AEs) is given in Table 11.10. There appeared to be no dose-related trend for losartan with respect to the percentage of patients with one or more AE.

Table 11.10. Clinical Adverse Experience Summary

	PHO	Losartan 10	Losartan 25	Losartan 50	Losartan 100	Losartan 150	ENAL 20
Number of Patients Randomized	N=78	N=80	N=82	N=79	N=90	N=84	N=83
With One or More AE	40 (51%)*	38 (48%)	40 (49%)	32 (41%)	32 (36%)	46 (55%)*	39 (47%)
With Serious AE	1 (1%)	1 (1%)	0	0	0	2 (2%)	0
Withdrawn Due to AE	0	2 (3%)	1 (1%)	1 (1%)	1 (1%)	4** (5%)	1 (1%)

* Statistically significantly different from LOSARTAN 100 treatment group, $p < 0.05$, ** AN 548 discontinued due to a clinical and a laboratory adverse experience.

Interpretation of each individual adverse event is difficult. Table 11.10a list the adverse events that occurred in greater than 1% of the patients randomized. Cough occurred most often in patients on enalapril (8%) compared to losartan (4%) and placebo (1%). Patient #667 (enalapril) was discontinued due to cough. Dizziness and vertigo was not reported in the placebo patients but was reported by 8 (2%) and 6 (1%) of losartan patients respectively.

Table 11.10a. Adverse Events in > 1% of Patients Randomized

	losartan 10 mg	losartan 25 mg	losartan 50 mg	losartan 100 mg	losartan 150 mg	enalapril 20 mg	placebo	total
ALT INCREASED	3	2	0	5	3	1	3	17
AST INCREASED	2	2	0	1	1	1	1	8
ASTHENIA/FATIGUE	3	2	3	3	4	5	5	25
CONGESTION, NASAL	1	1	4	1	3	0	0	9
COUGH	5	2	2	2	3	7	1	22
DIARRHEA	3	0	3	1	2	4	2	15
DIZZINESS	2	1	2	0	2	0	2	9
DYSPEPSIA	1	0	0	1	3	1	0	6
FLUSHING	0	0	0	1	3	1	1	6
HEADACHE	11	15	10	8	11	8	10	73
HEMATURIA	0	0	2	2	1	2	0	7
URI	1	9	2	7	7	9	7	42
INSOMNIA	1	2	2	1	0	0	0	6
NAUSEA	1	1	0	1	0	2	5	10
ORTHOSTATIC EFFECTS	0	0	2	3	3	0	0	8
PAIN, ABDOMINAL	3	0	1	2	1	1	2	10
PAIN, BACK	3	0	2	0	2	1	2	10
PAIN, CHEST	1	2	0	1	1	1	3	9
PAIN, LEG	2	1	2	0	0	1	0	6
PHARYNGITIS	1	1	1	1	0	2	2	10
PROTEINURIA	1	0	2	1	0	2	2	8
PYURIA	1	1	0	1	2	0	1	6
VERTIGO	1	1	0	2	2	0	0	6

Table 11.10b. lists several other adverse events that are worth discussing. Five patients had decreased leukocytes but in no case was the total count less than 2900/mm³. Total serum bilirubin was increased in three losartan patients. Data for this lab is not available in the CANADA.

Table 11.10 b. Adverse Events

	losartan 10 mg	losartan 25 mg	losartan 50 mg	losartan 100 mg	losartan 150 mg	enalapril 20 mg	placebo	total
EDEMA, EYELID	0	0	0	0	1	0	0	1
EDEMA, FACIAL	0	0	0	0	1	0	0	1
EDEMA/SWELLING	1	1	1	1	0	0	0	4
LEUKOCYTES DECREASED	0	2	0	1	1	0	1	5
TOTAL SERUM BILIRUBIN INCREASED	1	0	0	0	2	0	0	3

Four patients had adverse clinical experiences that were considered serious. Table 11.11 lists the serious clinical adverse experiences which occurred in this study. These adverse events are further described in the narrative paragraphs which follow:

Table 11.11. Serious Clinical Adverse Experiences

Patient #	Sex	Age	Dosage	Rel Day Of Onset	Adverse Experience(s)	Duration (Days)	Severity	Outcome
0649	F	66	PlbO	21	Asthenia/Fatigue	12	Moderate	Recovered
0399*	M	64	LOS 10 mg	32	Angina Pectoris	5	Moderate	Still Present**
				15	Edema	22	Moderate	Still Present**
				32	Exertional Dyspnea	5	Moderate	Still Present**
0033*	M	56	LOS 150 mg	1	Chest Pain	20	Mild	Recovered
0548*	M	52	LOS 150 mg	28	Hepatitis A Infection	139	Moderate	Recovered

* Discontinued, ** Information obtained after correction cutoff date indicated Ah was resolved as of July 9, 1991. Patient recovered.

Patient AN 0649 was a 66-year-old hypertensive female patient was treated with placebo for 21 days during the double-blind portion of the study when she was hospitalized for moderate **asthenia/fatigue** secondary to her development of hypokalemia. The patient was discontinued from the study due to the development of hypokalemia and recovered after receiving potassium replacement therapy.

Patient AN 0399 was a 64-year-old male hypertensive patient had been treated for 32 days with losartan (10 mg) when he was hospitalized for moderate **angina pectoris, edema and exertional dyspnea**. The patient was discontinued from the study. The day after discontinuation from the study, the patient underwent cardiac catheterization. A diagnosis of a high grade obstruction of the left main coronary artery was made from the test. Bypass surgery was performed 13 days after discontinuation, the patient recovered.

Patient AN 0033 was a 56-year-old male hypertensive patient had been treated for 17 days with losartan (150 mg) when he was discontinued from the study due to **chest pain** and a positive thallium stress test result. The patient had a documented history of chest pain due to both gastroesophageal reflux and ischemic heart disease, which had resulted in angioplasty in 1987. After 2 weeks of participation in the placebo baseline phase of this study, the patient began to experience mild burning chest pain, which continued into the double-blind treatment phase. This was initially attributed to epigastric

reflux. However, due to the patient's history of ischemic heart disease, the investigator performed the thallium stress test, which was positive. The patient was discontinued from the study. Angioplasty was performed 10 days after the patient's discontinuation; the chest pain resolved.

Patient AN 0548 was a 52-year-old male hypertensive patient had been treated for 28 days with losartan (150 mg) when he was diagnosed as having contracted an acute moderate hepatitis A infection. The patient was discontinued from the study after 34 days of double-blind therapy and eventually recovered.

A total of 10 patients were discontinued for clinical adverse experiences. Table 11.12 lists pertinent data for these patients. There appeared to be no dose-related trend for losartan with respect to the percentage of patients withdrawn for a clinical adverse experience, although the largest number of patients (n=4) were discontinued from the losartan 150 mg group. Patient 0488 (losartan 150 mg) discontinued for what appears to be angioneurotic edema.

Table 11.12. Patients Discontinued for Clinical Adverse Experiences

Patient	Age (Yrs)	Sex	Dose (mg/Day)	Adverse Reaction	Onset (Day)	Duration (Days)	Relative Day of Discontinuation	Intensity	Outcome
0033	56	M	LOS 150	Chest Pain	1	20	17	Mild	Recovered
0085	64	F	LOS 50	Asthma	30	6	34	Mild	Recovered
0294	65	M	LOS 100	Hematuria	34	0.5	36	Moderate	Recovered
0399	64	M	LOS 10	Angina Pectoris	32	5	36	Moderate	Still Present ¹
				Exertional Dyspnea	32	5	36	Moderate	Still Present ¹
				Edema	15	22	36	Moderate	Still Present ¹
0488	73	F	LOS 150	Edema, Eyelid	18	8	20	Moderate	Recovered
				Edema, Facial	18	8	20	Moderate	Recovered
0489	69	F	LOS 10	Rash	24	2	25	Severe	Recovered
				Tremor	24	2	25	Moderate	Recovered
				Increased Intraocular Pressure	24	2	25	Moderate	Recovered
0548*	52	M	LOS 150	Hepatitis A	28	139	34	Moderate	Recovered
				Asthma/Fatigue	30	46	34	Moderate	Recovered
				Malaise	30	46	34	Moderate	Recovered
				Fever	30	13	34	Mild	Recovered
0617	43	M	LOS 150	Tachycardia	28	2	28	Moderate	Recovered
0667	56	M	ENAL	Cough	10	38	47	Moderate	Still Present
0684	52	F	LOS 25	Headache	34	15	41	Severe	Recovered

¹ Information obtained after correction cut-off date indicated AE was resolved as of July 9, 1991. Patient recovered.

* Patient also discontinued due to laboratory AE, see Table 10.

Five patients were withdrawn due to adverse laboratory experiences. Pertinent data for these patients is listed in Table 11.13. Three patients experienced elevated AST and ALT > 100 U/L simultaneously. In addition to patients #548 and #802, patient #574 (placebo) had increases in ALT and AST (ALT = 182 U/L (baseline = 77 U/L), AST = 96 U/L (baseline = 44 U/L) on day 56, ALT = 200 U/L, AST = 101 U/L on day 63)

Table 11.13. Patients Discontinued Due to Laboratory Adverse Experiences

Patient #	Age (Yrs)	Sex	Dose (mg/Day)	Adverse Reaction	Normal Range	Baseline Value	Highest (Lowest) Value	Study Day ¹ of Highest (Lowest) Value	Day Discontinued
0115	76	M	LOS 25	Platelet Count Decreased	130-400 ths/mm ³	198	(118)	24	32
0321	53	M	ENAL 20	Hyperglycemia	80-125 mg/dL	114	129	31	41
				Alkaline Phosphatase Increased	20-140 U/L	144	155	31	41
0548*	52	M	LOS 150	Tox. Serum Bilirubin Increased	0.2-1.2 mg/dL	0.80	13.0**	42	34
				AST Increased	0-50 U/L	23.0	3530**	42	34
				ALT Increased	0-55 U/L	27.0	7600**	42	34
				GGT Increased	0-65 U/L	ND	213**	49	34
				LDH Increased	0-250 U/L	ND	629	34	34
				Hepatitis A Antibody Positive	Negative	N/A	Positive	34	34
0649	66	F	Placebo	Hypokalemia	3.5-5.3 mEq/L	3.9	(3.10)	14	28
0802	61	M	Placebo	AST Increased	0-50 U/L	25	129	47	43
				ALT Increased	0-55 U/L	14	124	47	43

¹ = Study day of highest (lowest) value = relative day of test. * Patient was also discontinued due to clinical AE, see Table 26.

** Patient's Day 28 and/or Day 35 laboratory values for these tests also listed as "reason discontinued"

Tot. Serum Bilirubin (Day 28) = 0.9 mg/dL

AST (Day 28) = 113 U/L

ALT (Day 28) = 140 U/L

Tot. Serum Bilirubin (Day 35) = 4.60 mg/dL

AST (Day 35) = 1010 U/L

ALT (Day 35) = 1390 U/L

GGT (Day 35) = 198 U/L

Mean changes in laboratory parameters suggest that with the losartan 100 and 150 mg treatment groups the mean serum uric acid decreased compared to placebo.

Patient 548 (losartan 150 mg) experienced marked elevations of liver function tests that was attributed to hepatitis A infection. Cough occurred in 1.3% of placebo, 3.4% of losartan and 8.4% of enalapril patients.

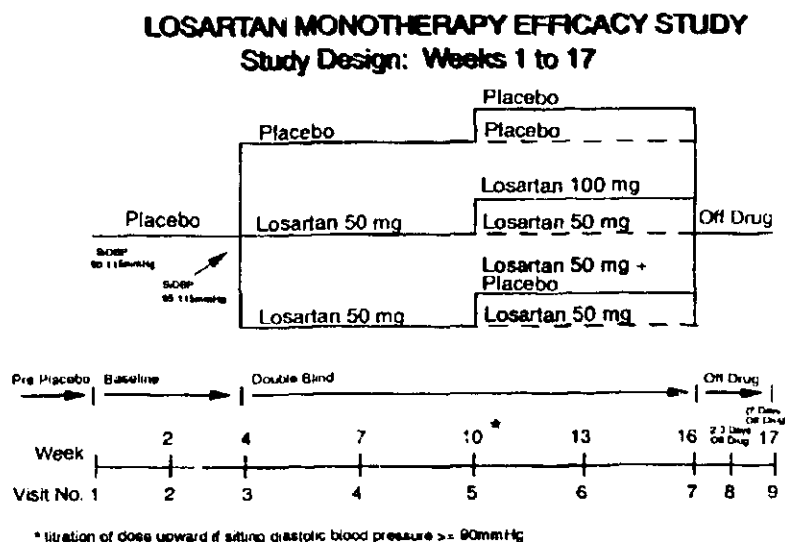
Study 050. A Multicenter, Double-Blind, Randomized, Placebo-Controlled Clinical Study to Evaluate the Antihypertensive Efficacy and Safety of Losartan (MK-954, DuP 753) in Patients with Mild-to-Moderate Hypertension:

Protocol

Design

This is a randomized, double-blind, multicenter, placebo-controlled study of 17 weeks duration. A 4-week baseline period was followed by 12 weeks of double-blind treatment with either placebo or losartan. After 6 weeks of double-blind therapy, patients were titrated as outlined in the figure 50.1 based on blood pressure response. After the double-blind period, there was a 1-week off drug period. Patients then entered an open-label treatment period until Week 56.

Figure 50.1. Study 050 Design



Inclusion/Exclusion Criteria

Patients were excluded from enrollment in the study for pregnancy, history of renal disease, secondary hypertension, siSBP > 210 mmHg, MI within past year, other active medical problems (except for diabetes mellitus), conduction disturbances, CVA or TIA, significant arrhythmia, obstructive valvular disease, heart failure, history of unexplained syncope, concomitant medications as listed in the protocol, abnormal laboratory parameters at baseline and illicit drug use.

Patients were enrolled into the single-blind, 4 week, placebo baseline phase if they were > 21 years of age, were not receiving anti-hypertensive medication and had a siDBP of 90 -115 mmHg at visit 1. Hypertensive patients whose siDBP was 95-115 mmHg at the end of the Week 2 and Week 4 baseline period AND whose siDBP values at Week 2 and Week 4 did not differ by >7 mmHg were randomized (see table 50.1). Randomization was stratified based on the severity of hypertension [mild {95 - 105 mmHg} or moderate {106 - 115mmHg}] and race (Black or non-Black). No more than 30% of the patients enrolled in the trial could be black. Patients were randomized to either placebo (with a placebo titration dose), losartan 50 mg (with a losartan 50 mg titration dose) or losartan 50 mg (with a placebo titration dose). Titration occurred at week 6 of double-blind therapy if the siDBP was >= 90 mmHg. Patients received double-blind therapy for 12 weeks (until Week 16).

Table 50.1
Blood Pressure Criteria for Randomization.

Visit 1	Pre-Placebo	Trough Mean SiDBP*	
Baseline		90-115-mmHg	
Visit 2	(Week 2)	95-115 mmHg	Difference between SiDBP values at Week 2 and Week 4 must be <7 mmHg
Visit 3	(Week 4)	95-115 mmHg	
Period	Early entry into Double-Blind	Week 2: SiDBP 110-115 mmHg AND Reading must be confirmed (i.e., SiDBP 110-115 mmHg) at a second visit at least 3 days later	

* Mean SiDBP. The calculated average of three consecutive readings at 1 minute intervals. All individual readings are to be read to the nearest 2 mmHg. None of the three readings may differ from the average by >5 mmHg.

The procedures performed during the trial are outlined in table 50.2.

Table 50.2 Flowchart of Study Visits For Losartan Monotherapy Efficacy: Pre-Placebo - Week 17

	Screen	Baseline			Double-Blind				Off-Drug	
Visit:	1	2	3	4	5	6	7	8	9	
Day:	1	14	28	49	70	91	112	115	119	
Week:	0	2	4	7	10*	13	16	17	17	
Medical History	X									
Complete Physical Examination	X						X		X	
Pregnancy Test			X ^j							
Sign Informed Consent	X									
Weight	X	X	X	X	X	X	X	X	X	
Clinic Visits ^a		X	X	X	X	X	X	X	X	
Sitting & Standing BP & HR ^c (Trough/Peak)	X ^{e,i}	T ^f	T ^{g,p}	T	T,P	T	T,P	X	X	
Laboratory Safety Tests ^h	X ^b	X			X		X		X ^m	
Additional Blood Draw ^o							T,P			
ECG (12-lead)		X			X		X		X ^m	
Chest X-ray		X ^j								
AE Evaluation		X	X	X	X	X	X	X	X	
Ophthalmology Examination			X ^k				X ^k			
Plasma Renin Activity		X				X	X	X		
Dispense Baseline Medication	X ⁱ	X								
Dispense Double-Blind Medication			X	X	X ⁿ	X				
Discontinue Double-Blind Medication							X			
Dispense Open-Label Medications								X		

a = Clinic Visits will occur as indicated between 6:30 and 10:00 a.m. Patients are to be in the fasted state at all clinic visits (i.e., no food is to be taken during the 8 hours prior to each clinic visit); b = Perform tests if patient does not have known history or if prior tests are not available.

c = Measurements are to be taken 24 hours (range 22 to 26 hours) after the last study dose; d = Repeat labs, if necessary.

e = Mean SiDBP must be 90-115 mmHg or patient cannot continue in the study; f = Mean SiDBP must be 95-115 mmHg or patient cannot continue in study

g = Mean SiDBP must be 95-115 and Week 2 and Week 4 values must be <7 mmHg or patient cannot continue in study

h = Fasting hematology, blood chemistry and urinalysis as described in Appendix 2

i = Patient must be off antihypertension medication at least 7 full days or patient must return for another evaluation when an adequate washout period is achieved (refer to section IX B)

j = Chest x-ray will be performed if one is not available from within the previous 6-month period

k = To be performed by a qualified specialist, arrange appointment ahead of time; l = See Section VIII B 1 for necessity and frequency of pregnancy tests

m = Repeat at Week 17 only to be performed if lab or ECG at Week 16 indicated an AE; n = Dispense Bottles A and B if trough SiDBP <90 mmHg or Bottles C and D if trough SiDBP ≥ 90 mmHg;

o = Patients will also have additional blood drawn at both the Week 16 trough and peak clinic visits for possible future pharmacological and physiological analysis

T = Trough, P = Peak, * = Titration

NOTE: If a patient does not complete the study, all procedures scheduled for treatment Week 16 will be done on the day the patient discontinues treatment. In addition, a complete physical examination will be performed

Sitting and standing blood pressure at peak and trough were measured. Trough BP measurements were performed 22 - 26 hours after dosing. The peak BP measurements were measured at Visits 3, 5 and 7 six hours (range 5 to 8 hrs) after dosing.

Primary Endpoint

The primary endpoint in the trial is the change in siDBP at week 12 of double-blind treatment. The projected enrollment was 300 patients. This assumes that 86 patients per treatment group completes the trial. The power to detect a 5 mm change in siDBP between treatment groups is 95 % (at the .05 significance level).

Results

[In the discussion of the results, the placebo with placebo titration is designated placebo, the losartan with placebo titration is designated losartan 50/P and the losartan with losartan titration is designated losartan 50/100.]

Patient Disposition

Three hundred sixty-six patients (366) were randomized to the three treatment groups at 22 centers (Placebo N = 116, Losartan 50/P N = 127, losartan 50/100 N = 123). A listing of investigators can be found in the appendix. No explanation was provided as to why more patients than projected in the protocol (100 per treatment group) were enrolled. The number of patients randomized at each center ranged from 12 to 30. Table 50.3 outlines the patient disposition throughout the trial. The projected enrollment in the trial was 300 patients. There is no explanation for the increased enrollment.

Table 50.3 Patient Disposition

[Table is from sponsor's summary and is corrected for one error. It has been validated in the CANDa database except that 2 losartan 50/100 patients withdrew because therapy was ineffective. Thus, 14 and not 13 losartan 50/100 patients did not complete the double-blind phase of the study.]

	Losartan		
	PBO	50	50/100
	(N= 116)	(N=127)	(N=123)
	n (%)	n (%)	n (%)
Completed DB/ No OL	16 (13.8)	15 (11.8)	13 (10.6)
Completed DB/ Enter OL	82 (70.7)	100 (78.7)	96 (78.9)
Discontinued Double-Blind Phase	18 (15.5)	12 (9.4)	14 (10.6)
Clinical Adverse Experience	3 (2.6)	0 (0.0)	7 (5.7)
Laboratory Adverse Experience	0 (0.0)	0 (0.0)	0 (0.0)
Clinical & Laboratory AE	0 (0.0)	0 (0.0)	0 (0.0)
Therapy Ineffective	9 ⁺ (7.8)	6 ⁺ (4.7)	2 ⁺⁺ (0.8)
Patient Uncooperative	0 (0.0)	0 (0.0)	1 (0.8)
Patient Withdrew	2 (1.7)	1 (0.8)	2 (1.6)
Protocol Deviation	2 (1.7)	2 (1.6)	1 (0.8)
Lost to Follow-up	2 (1.7)	3 (2.4)	1 (0.8)

⁺ Four patients continued into extension after discontinuing double-blind phase.

⁺⁺ Patient continued into extension after discontinuing double-blind phase.

Forty-four patients did not complete the study. Eighteen placebo patients did not complete the study whereas twelve and fourteen patients did not complete the losartan treatment arms. Patients in the placebo and losartan 50/P group did not complete the study predominately due to lack of effectiveness. The predominate reason patients did not complete the losartan 50/100 treatment was clinical adverse experience. Some of the patients prematurely withdrawn from the double-blind phase continued into the open label extension. A listing of patients withdrawn prematurely can be found in the appendix.

Of the 44 patients discontinued from the study, 9 patients did not have any double-blind period blood pressure data: 2 patients in placebo group (# 2235, # 2385), 2 patients in the losartan 50 group (# 2282, # 2436), and 5 patients in the losartan 50/100 group (# 2160, # 2170, # 2266, # 2394, # 2397). These patients were protocol violators, lost to follow-up, experienced a clinical AE or withdrew prior to an efficacy measurement.

Demographics

Table 50.4 lists the demographic characteristics of the patients in each treatment group.

Table 50.4 Baseline Patient Demographic Characteristics

	Placebo (N=116)	Los 50 (N=127)	Los 50/100 (N=123)	Total (N=366)
Sex				
Female	42 (36%)	44 (35%)	45 (37%)	131 (36%)
Male	74 (64%)	83 (65%)	78 (63%)	235 (64%)
Age (years)				
<35	3 (3%)	7 (6%)	4 (3%)	14 (4%)
35-44	25 (22%)	19 (15%)	17 (14%)	61 (17%)
45-54	33 (28%)	41 (32%)	42 (34%)	116 (32%)
55-64	35 (30%)	41 (32%)	31 (25%)	107 (29%)
>65	20 (17%)	19 (15%)	29 (24%)	68 (19%)
Mean	53.8	53.2	55.1	54
Median	54	53	54	54
Range	26-78	28-75	28-76	26-78
Racial Origin				
Caucasian	92 (79%)	104 (82%)	101 (82%)	297 (81%)
Black	17 (15%)	14 (11%)	16 (13%)	47 (13%)
Hispanic	7 (6%)	8 (6%)	4 (3%)	19 (5%)
Indian	0	1 (1%)	0	1 (0%)
Oriental	0	0	2 (2%)	2 (1%)
Duration of Hypertension (years)				
<1	2 (2%)	3 (2%)	2 (2%)	7 (2%)
1 - 5	39 (34%)	42 (33%)	34 (28%)	115 (31%)
5.01-10	29 (25%)	35 (28%)	32 (26%)	96 (26%)
>10	46 (40%)	47 (37%)	55 (45%)	148 (40%)
Mean	10.3	10	11.8	10.7
Median	9	8	10	9
Range	0.5-41	0.5-52	0.5-48	0.5-52
Severity of Hypertension (sIDBP, mmHg)				
Mild (95-105)	89 (77%)	86 (68%)	85 (69%)	260 (71%)
Moderate (106-115)	27 (23%)	41 (32%)	38 (31%)	106 (29%)
sIDBP (mmHg)				
Mean	101.3	102.2	102.2	101.9
Median	100	101	101	101
Range	95-115	95-113	95-114	95-115

There were no statistically significant differences in baseline variables between treatment groups. The majority of patients enrolled in this trial were caucasian. Thirty-six percent were females and thirteen percent were black. Seventy-one percent of the patients had mild hypertension (95 - 105 mmHg). One hundred and seven patients received ACE inhibitor therapy prior to enrollment in the trial (31 placebo, 43 losartan 50/P, and 33 losartan 50/100).

Blood Pressure Results - Change in sIDBP

Nine patients of the forty-four premature withdrawals did not have any blood pressures measured during the double-blind phase due to discontinuation. Of the remaining 35 premature discontinuations, eighteen did not have a double-blind week 6 visit (titration week). Table 50.5 lists the mean change in sIDBP at weeks 6 and 12 for each treatment using an all patients treated (carry forward) analysis. At week 6, 87% of placebo patients, 68% of losartan 50/P patients and 71% of losartan 50/100 patients had the dose titrated. The placebo subtracted mean change in sIDBP for losartan 50/P is 3.4 mmHg at both weeks 6 and 12. The placebo subtracted mean change in sIDBP for losartan 50/100 is 4.4 and 4.1 mmHg at weeks 6 and 12 respectively. Both treatments significantly changed sIDBP compared to placebo.

Table 50.5 Mean Change In Trough Sitting Diastolic Blood Pressure At Weeks 6 And 12 (mmHg)

All-Patients-Treated Approach

WEEK	TREATMENT	N	Baseline		Treatment		Change		Change Adj Mean	Comparison	
			Mean	S.D.	Mean	S.D.	Mean	S.D.		vs. B	vs. C
6	PLACEBO(A)	114	101.5	4.9	97.8	7.5	-3.5	5.8	-3.5	**	**
	LOS 50 (B)	125	102.1	5.1	95.3	8.6	-6.9	7.0	-6.9	--	NS
	LOS 50/100(C)	118	102.2	5.0	94.3	8.4	-7.9	7.1	-7.9	--	--
12	PLACEBO(A)	114	101.3	4.9	97	7.7	-4.3	6.7	-4.5	**	**
	LOS 50 (B)	125	102.1	5.1	94.2	9.0	-7.9	7.6	-7.9	--	NS
	LOS 50/100(C)	118	102.2	5.0	93.6	8.3	-8.6	7.7	-8.6	--	--

NS -- NOT STATISTICALLY SIGNIFICANT, * -- TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, P<0.05

** -- TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, P<0.01, ANALYSIS SPECS. OVERALL= RANOVA PA

The mean change in siSBP at weeks 6 and 12 are listed in table 50.6. Both losartan treatments caused significant changes in siSBP compared to placebo.

Table 50.6 Mean Change In Trough Sitting Systolic Blood Pressure At Weeks 6 And 12 (mmHg)
All-Patients-Treated Approach

WEEK	TREATMENT	N	BASELINE		POST VALUE		CHANGE		CHANGE	COMPARISON	
			Mean	S.D.	Mean	S.D.	Mean	S.D.	Adj Mean	vs. B	vs. C
6	PLACEBO(A)	114	153.3	16.3	151.8	17.7	-1.5	11.7	-1.7	**	**
	LOS 50 (B)	125	152.8	13.6	145.1	16.0	-7.7	12.0	-8.3	--	NS
	LOS 50/100(C)	118	157.1	18.5	147.3	19.5	-9.8	13.4	-9.4	--	--
12	PLACEBO(A)	114	153.3	16.3	152.5	18.0	-0.8	13.6	-1.2	**	**
	LOS 50 (B)	125	152.8	13.6	144.2	16.7	-8.6	13.9	-9.2	--	NS
	LOS 50/100(C)	118	157.1	18.5	147.4	22.4	-9.7	13.8	-9.4	--	--

NS -- NOT STATISTICALLY SIGNIFICANT

* -- TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, P≤0.05

** -- TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, P≤0.01

ANALYSIS SPECS: OVERALL = RANOVA PAIRWISE = LSMEANS, BASED ON RAW DATA

Subgroup analysis of interest include those based on race, gender and age. Table 50.7 lists the change in siDBP for black and non-black patients. The analysis is limited by the relatively small number of black patients enrolled in the trial. The losartan 50/P treatment in black patients showed no benefit in lowering siDBP compared to placebo at any week. The placebo subtracted mean change in siDBP at week 12 in blacks and non-blacks is listed in table 50.7a.

Table 50.7 Mean Change In Trough Sitting Diastolic Blood Pressure At Week 6 And 12 By Race (mmHg)
All-Patients-Treated Approach

WEEK	RACE	TREATMENT	N	BASELINE MEAN	TREATMENT MEAN	CHANGE MEAN	95% CONFIDENCE INTERVAL FOR MEAN CHANGE
6	BLACK	PLACEBO	17	102.1	98.6	-3.5	(-5.9, -1.2)
		LOS 50	14	103.9	101.2	-2.7	(-6.3, 0.9)
		LOS 50/100	16	103.3	97.4	-5.9	(-10.5, -1.2)
	NON-BLACK	PLACEBO	97	101.2	97.7	-3.5	(-4.6, -2.3)
		LOS 50	111	101.9	94.5	-7.4	(-8.7, -6.1)
		LOS 50/100	102	102.0	93.8	-8.2	(-9.5, -6.9)
12	BLACK	PLACEBO	17	102.1	98.1	-4.0	(-6.3, -1.7)
		LOS 50	14	103.9	100.2	-3.7	(-7.4, 0.0)
		LOS 50/100	16	103.3	97.6	-5.6	(-10.2, -1.1)
	NON-BLACK	PLACEBO	97	101.2	96.8	-4.3	(-5.7, -3.0)
		LOS 50	111	101.9	93.5	-8.4	(-9.8, -7.0)
		LOS 50/100	102	102.0	93.0	-9.0	(-10.4, -7.6)

Table 50.7a. Mean change from baseline in siDBP at week 12. [Placebo Subtracted]

Treatment Group	Black	Non-Black
Losartan 50/P	+ .3 mmHg (N = 14)	- 4.1 mmHg (N = 111)
Losartan 50/100	- 1.6 mmHg (N = 16)	- 4.7 mmHg (N = 102)

Thirty-six percent of the patients enrolled in this trial were female. Table 50.8 lists the change in siDBP based on gender. In female patients, at 6 and 12 weeks of therapy, the change in siDBP was greater in the losartan 50/P group compared to the losartan 50/100 group.

**Table 50.8 Mean Change In Trough Sitting Diastolic Blood Pressure At Weeks 6 And 12 By Sex (mmHg)
All-Patients-Treated Approach**

WEEK	PATIENT SEX	TREATMENT	BASELINE		TREATMENT	CHANGE	95% CONFIDENCE INTERVAL FOR MEAN CHANGE
			N	MEAN	MEAN		
6	FEMALE	PLACEBO	41	100.0	95.2	-4.7	(-6.3, -3.1)
		LOS 50	44	102.1	94.7	-7.4	(-9.8, -5.1)
		LOS 50/100	41	100.1	93.6	-6.6	(-8.8, -4.3)
	MALE	PLACEBO	73	102.1	99.3	-2.8	(-4.1, -1.4)
		LOS 50	81	102.2	95.6	-6.6	(-7.9, -5.2)
		LOS 50/100	77	103.3	94.7	-8.6	(-10.1, -7.0)
12	FEMALE	PLACEBO	41	100.0	94.4	-5.6	(-7.4, -3.8)
		LOS 50	44	102.1	92.5	-9.6	(-12.2, -7.0)
		LOS 50/100	41	100.1	93.5	-6.6	(-9.2, -4.1)
	MALE	PLACEBO	73	102.1	98.5	-3.5	(-5.2, -1.9)
		LOS 50	81	102.2	95.2	-7.0	(-8.4, -5.5)
		LOS 50/100	77	103.3	93.7	-9.6	(-11.2, -8.0)

Table 50.9 lists the change in siDBP for patients < 65 years of age and patients $\geq$ 65 years of age. This analysis is limited by the disproportionate number of patients in the younger age group. At 12 weeks, the placebo subtracted change in siDBP was greater in patients $\geq$ 65 years of age for losartan 50/P (6.3 mmHg vs. 3.1 mmHg) and losartan 50/100 (5.1 mmHg vs. 4.2 mmHg).

**Table 50.9 Mean Change In Trough Sitting Diastolic Blood Pressure At Weeks 6 And 12 By Age Category (mmHg)
All-Patients-Treated Approach**

WEEK	AGE CATEGORY	TREATMENT	BASELINE		TREATMENT	CHANGE	95% CONFIDENCE INTERVAL FOR MEAN CHANGE
			N	MEAN	MEAN		
6	<65 YEARS	PLACEBO	94	101.5	98.1	-3.4	(-4.6, -2.2)
		LOS 50	106	102.3	95.5	-6.8	(-8.2, -5.4)
		LOS 50/100	90	102.5	94.9	-7.6	(-9.0, -6.3)
	$\geq$ 65 YEARS	PLACEBO	20	100.6	96.8	-3.8	(-5.8, -1.8)
		LOS 50	19	101.5	94.2	-7.3	(-9.8, -4.7)
		LOS 50/100	28	101.2	92.5	-8.7	(-11.9, -5.5)
12	<65 YEARS	PLACEBO	94	101.5	96.9	-4.6	(-6.0, -3.3)
		LOS 50	106	102.3	94.6	-7.7	(-9.1, -6.2)
		LOS 50/100	90	102.5	93.7	-8.8	(-10.3, -7.2)
	$\geq$ 65 YEARS	PLACEBO	20	100.6	97.8	-2.8	(-5.7, 0.2)
		LOS 50	19	101.5	92.4	-9.1	(-12.3, -5.9)
		LOS 50/100	28	101.2	93.3	-7.9	(-11.0, -4.8)

Patient response to therapy was divided into three categories as outlined in table 50.9a.

Table 50.9a. Response Categories

Category I:	siDBP <90 mmHg
Category II:	siDBP $\geq$ 90 mmHg and a reduction of 10 mmHg or more
Category III:	neither I nor II

Table 50.9b lists the patient response to therapy at week 12 based on categories I, II and III. The distribution of responses across categories was modeled with Logistic regression including treatment. The percentage of patients in Category I/II in the LOS 50 group and the losartan 50/100 group was significantly greater than the placebo group at both Weeks 6 and 12 ($p \leq 0.01$). The percentage of patients in Category I/II was not significantly different between losartan 50 and losartan 50/100 groups. However, the percentage of patients in Category I/II was higher in the losartan 50/100 group at both Weeks 6 and 12. After 12 weeks, 27.1% of placebo patients, 46.4% of losartan 50/P patients and 51.6% of losartan 50/100 patients were responders.

Table 50.9b. Categories Of Antihypertensive Response (Trough siDBP) At Weeks 6 And 12[†]

WEEK	TREATMENT	ANTIHYPERTENSIVE RESPONSE CATEGORY			COMPARISON TOTAL	VS. B	VS. C
		I	II	III			
6	PLACEBO (A)	14 (12.2%)	8 (7.0%)	92 (80.7%)	114 (100%)	**	**
	LOS 50 (B)	37 (29.6%)	20 (16.0%)	68 (54.4%)	125 (100%)	--	NS
	LOS 50/100 (C)	37 (31.3%)	21 (17.7%)	60 (50.8%)	118 (100%)		
12	PLACEBO (A)	19 (16.6%)	12 (10.5%)	83 (72.8%)	114 (100%)	**	**
	LOS 50 (B)	40 (32.0%)	18 (14.4%)	67 (53.6%)	125 (100%)	--	NS
	LOS 50/100 (C)	37 (31.3%)	24 (20.3%)	57 (48.3%)	118 (100%)		

NS - NOT STATISTICALLY SIGNIFICANT

* - TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, P<0.05

** - TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, P<0.01

[†] - NUMBERS ROUNDED TO NEAREST TENTH, THEREFORE, MAY NOT ADD TO 100%.

Table 50.9c lists the response rates obtained from the database. Responders were defined as patients with week 12 siDBP decline from baseline greater or equal to 10 mmHg or siDBP less than 90 mmHg. Carry forward data was included. If there were more than one visit during week 12, only the last visit was counted in the analysis. There is little improvement in response rate when losartan 50 mg patients are given an additional 50 mg dose of losartan as opposed to placebo. Blacks are generally unresponsive to losartan compared to placebo. It is difficult to assess the response in female patients. One dose of losartan (losartan 50/P) suggests an improved response whereas another dose (losartan 50/100) suggests no difference from placebo. This is consistent with the mean change in siDBP for females. The response rates based on age suggest that patients < 65 years and ≥ 65 years have similar responses to therapy.

Table 50.9c. Responders at Week 12 Based on Demographic Variables. [Patients without any post-randomization blood pressure measurements are counted as treatment non-responders.]

Demographic Group	Placebo (N = 116)	Losartan 50/P (N = 127)	Losartan 50/100 (N = 123)
All Patients	34/116 (29%)	55/127 (43%)	57/123 (46%)
Caucasians	28/92 (30%)	48/104 (46%)	49/101 (49%)
Blacks	5/17 (29%)	3/14 (21%)	4/16 (25%)
Male	19/74 (26%)	32/83 (39%)	40/78 (51%)
Female	16/42 (38%)	24/44 (55%)	17/45 (38%)
≥ 65 years of age	6/20 (30%)	8/19 (42%)	14/29 (48%)
< 65 years of age	28/96 (29%)	47/108 (44%)	43/94 (46%)

Table 50.10 lists the change in peak siDBP (obtained 5 - 8 hours after dosing) at week 6 and 12. Both losartan treatment groups exhibit significant changes in siDBP.

**Table 50.10 Mean Change In Peak Sitting Diastolic Blood Pressure At Weeks 6 And 12 (mmHg)
All-Patients-Treated Approach**

WEEK	TREATMENT	N	BASELINE		POST VALUE		CHANGE		CHANGE		COMPARISON	
			Mean	S.D.	Mean	S.D.	Mean	S.D.	Adj Mean	vs. B	vs. C	
6	PLACEBO(A)	108	98.6	6.3	94.5	7.7	-4.1	6.9	-4.2	**	**	
	LOS 50 (B)	118	99.9	7.1	90.2	10.5	-9.7	8.7	-9.7	--	NS	
	LOS 50/100(C)	111	99.1	5.9	90.3	9.6	-8.9	8.7	-9.0	--	--	
12	PLACEBO(A)	108	98.6	6.3	93.9	8.8	-4.7	7.9	-4.6	**	**	
	LOS 50 (B)	121	99.8	7.1	90.3	10.5	-9.5	9.2	-9.3	--	NS	
	LOS 50/100(C)	113	99.2	6.0	89.1	9.1	-10.1	8.6	-10.1	--	--	

NS - NOT STATISTICALLY SIGNIFICANT

* - TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, $P \leq 0.05$

** - TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, $P \leq 0.01$

ANALYSIS SPECS. OVERALL = RANOVA PAIRWISE = LSMEANS, BASED ON RAW DATA

The placebo adjusted trough/peak ratio ranged from 73% to 78% for losartan groups at week 12 (Table 50.10a.).

Table 50.10a. Trough-To-Peak Ratios For Sitting Diastolic Blood Pressure At Weeks 6 And 12

WEEK	N	TREATMENT GROUP	MEAN CHANGE (mmHg)		T:P RATIO	T:P RATIO (PBO ADJUSTED)
			TROUGH	PEAK		
6	108	PLACEBO	-3.5	-4.1	85%	--
	118	LOS 50	-7.1	-9.7	73%	63%
	111	LOS 50/100	-7.7	-8.9	87%	88%
12	108	PLACEBO	-4.4	-4.7	93%	--
	121	LOS 50	-8.2	-9.5	85%	78%
	113	LOS 50/100	-8.3	-10.1	82%	73%

The claims that there is a correlation (r) between baseline PRA and reduction in trough [peak] sIDBP at Week 12 was significant in the active treatment groups: $r=0.28[-0.30]$, ($p \leq 0.01$) in the LOS 50 group, and $r=0.22[-0.20]$, ($p \leq 0.05$) in the LOS 50/100 group. That is, a higher baseline PRA corresponded with a larger reduction in both trough and peak sIDBP at Week 12. PRA data could not be found in the CANDAs to validate this claim.

There were no significant changes in pulse, weight and ECG measurements with treatment.

Eighty-seven percent of patients had post-double-blind treatment visits. The percent of patients with post double-blind sIDBP measurements greater than baseline is greatest in the placebo group. When the post-double-blind measurements for each treatment group are compared to baseline or to the last double-blind measurement or the number of patients with post-DB measurement > 110 mmHg are considered, there does not appear to be a significant difference between losartan and placebo. It is not unreasonable to conclude that rebound hypertension is not a problem.

Adverse Experience

There was no difference between treatment groups in the incidence of patients reporting at least one adverse experience. The incidence ranged from 52% to 52.8%. Seven losartan 50/100 patients and three of the placebo patients discontinued treatment prematurely due to adverse events. None of the losartan 50/P withdrew due to adverse events. Table 50.11 lists the patients withdrawn prematurely for clinical adverse events.

Table 50.11 Patients Discontinued Due To Clinical Adverse Experiences

Patient #	Age (yr)	Race	Gender	Day Discontinued	Treatment	Adverse Event	AE Start Day	AE Stop Day
2020	75	caucasian	M	36	losartan 50mg/100mg	HEADACHE	-1	20
						ANGINA PECTORIS	36	36
2028	68	black	M	23	placebo	DYSPNEA	-14	-1
						DYSPNEA	1	22
						HEART FAILURE	23	27
2149	78	caucasian	F	39	placebo	EDEMA, FACIAL	-3	17
						RASH	-3	17
						DYSPNEA	37	40
						NAUSEA	37	40
						PAIN, ABDOMINAL	37	40
						PAIN, CHEST	37	40
2160	42	caucasian	F	11	losartan 50mg/100mg	COUGH	-8	-3
						HEADACHE	-8	5
						URI	-8	-3
						FOLLICULITIS	11	12
						HEADACHE	11	12
2170	45	caucasian	F	1	losartan 50. g/100mg	BROWACHE	1	1
						CRAMP, MUSCLE	1	1
						DYSPLASIA	1	1
						DYSPNEA	1	1
						FLUSHING	1	1
						HEMIPARESIS	1	1
						NAUSEA	1	1
						PAIN, ARM	1	1
						VOMITING	1	1
						PARESTHESIA	3	3
						HEMIPARESIS	4	4
						NAUSEA	4	4
						2266	50	caucasian
ANGINA PECTORIS	32	38						
2271	63	caucasian	M	47	losartan 50mg/100mg	DIZZINESS	22	48
						HEADACHE	22	48
						NAUSEA	22	48
2292	59	caucasian	M	72	placebo	BLURRED VISION	8	8
						DYSARTHRIA	8	49
						NAUSEA	8	8
						SOMNOLENCE	28	49
						BLURRED VISION	37	37
						BLURRED VISION	38	38
						ASTHENIA/FATIGUE	70	74
						CONFUSION	70	73
MEMORY IMPAIRMENT	70	74						
2386	65	caucasian	M	21	losartan 50mg/100mg	CONGESTION, NASAL	9	26
						COUGH	9	26
						FEVER	9	26
						PAIN, MUSCULOSKELETAL	9	28
						GLYCOSURIA	26	
						HYPERGLYCEMIA	26	
						LEUKOCYTE COUNT INCREASED	26	
						PLATELET COUNT INCREASED	26	
SINUS TACHYCARDIA	28	28						
2397	75	caucasian	M	9	losartan 50mg/100mg	BRONCHITIS	4	8
						HEART FAILURE	5	9
						MYOCARDIAL INFARCTION	5	13

Eight patients (2.2%) had a clinical adverse experience that was considered serious by the investigator: 1 patient in the placebo group, 1 patient in the losartan 50 group and 6 patients in the losartan 50/100 group. Table 50.12 lists the patients with serious adverse experiences. Patient 2020 experienced a myocardial infarction and not just angina pectoris.

Table 50.12 Serious Clinical Adverse Experiences

Treatment Group	Patient #	Sex	Age	Dose	Day of Onset	Adverse Event	Duration	Resolved
Placebo	2028	M	68	Placebo	1	Dyspnea	22 Days	Yes
				Placebo	23	Heart Failure	4 Days	No
Losartan 50	2161	F	44	Losartan 50 mg	17	Pain, Abdominal	44 Days	Yes
				Losartan 50 mg	17	Menstruation Disorder	2 Days	Yes
Losartan 50/100	2020	M	75	Losartan 50 mg	36	Angin ^a Pectoris	1 Day	No1
	2084	M	54	Losartan 50 mg	36	Tachycardia	1 Day	Yes
	2170	F	45	Losartan 50 mg	1	Dysphasia	30 Mins	Yes
				Losartan 50 mg	1	Hemiparesis	30 Mins	Yes
	2266	F	50	Losartan 50 mg	32	Angina Pectoris	1 Day	Yes
	2289	M	60	Losartan 50 mg	35	Hernia, Inguinal	44 Days	Yes
	2397	M	75	Losartan 50 mg	5	Myocardial Infarction	5 Days	No2
Losartan 50 mg				5	Heart Failure	5 Days	No	

1 Information obtained after correction cutoff date indicated AE was resolved (date unknown) Patient recovered.

2 Information obtained after correction cutoff date indicated AE was resolved (as of 2/24/92) Patient recovered.

Twenty-three adverse experiences had an overall incidence greater than 1%. The incidence of these adverse experiences within each treatment group are provided in table 50.13. For most of these adverse experiences, a causal relationship to losartan is unlikely. However, dizziness occurred in 5 losartan 50/P, 4 losartan 50/100 and only 1 placebo patient. Cough did not appear to be increased in losartan patients compared to placebo. However, upper respiratory infections occurred in 14 losartan 50/P patients, 10 losartan 50/100 patients and 4 placebo patients. Gender does not play a role in predisposing a patient to an adverse event.

Table 50.13 Adverse Experiences in > 1% of the Patients Randomized.

Adverse Experience	losartan 50/P (N=127)	losartan 50/100 (N=123)	Placebo (N=116)	Total (N=366)
ALT increased	1	6	2	9
AST increased	1	3	0	4
Asthma/Fatigue	6	2	8	16
Blurred Vision	1	1	2	4
Bronchitis	0	2	2	4
Nasal Congestion	5	2	2	9
Resp. Congestion	5	2	2	9
Cough	3	6	5	14
Muscle Cramp	1	3	1	5
Diarrhea	2	2	0	4
Dizziness	5	4	1	10
Dyspnea	1	3	3	7
Edema/Swelling	7	3	2	12
Headache	12	19	15	46
URI	14	10	4	28
Nausea	5	3	3	11
Abdominal Pain	1	1	3	5
Arm Pain	1	2	1	4
Back Pain	2	1	1	4
Chest Pain	2	0	2	4
Pharyngitis	4	0	3	7
Rash	2	1	1	4
Sinus Disorder	2	3	0	5

Twenty-five patients (flagged in the database) experienced laboratory adverse events (27 are listed in the clinical summary report). Nine of these patients had elevations of ALT. Seven of them received losartan. Patients #2362, #2230 and #2207 had elevations of both ALT and AST simultaneously. Patient #2230 had the highest elevations with the maximum ALT 171 U/L and maximum AST 109 U/L. Patient #2362 transaminases returned to normal despite continued therapy. None of the patients were reported to have clinical hepatitis.

There is no difference in the mean change in pulse, weight or ECG parameters between treatment groups. ECG adverse experiences were reported in 1 placebo, 2 losartan 50/P and 7 losartan 50/100 patients. Table 50.14 lists the ECG adverse experiences reported. Two losartan patients were reported to have prolongation of the QT interval. It is unlikely that the change in QT is related to losartan since losartan does not appear to change the mean QTc.

Table 50.14 ECG Adverse Experience.

Group	Treatment	AN	Adverse Experience
Placebo		2428	Premature ventricular Contraction
LOS 50		2326	Prolonged QT interval
		2338	Sinus bradycardia
LOS 50/100		2056	Vascular disorder
		2103	AV block, first degree
		2215	AV block, first degree
			AV block, second degree
		2315	Left atrial hypertrophy
		2327	Axis disturbance
			Prolonged QT interval
	2336	Sinus bradycardia	
	2386	Sinus tachycardia	

Mean changes in laboratory parameters were unremarkable except for those listed in table 50.15. Mean uric acid appears to decrease as did total cholesterol. The decline in total cholesterol was due to a decrease in LDL cholesterol and not HDL cholesterol. As expected, plasma renin levels increased with losartan

Table 50.15. Mean Changes For Laboratory Tests

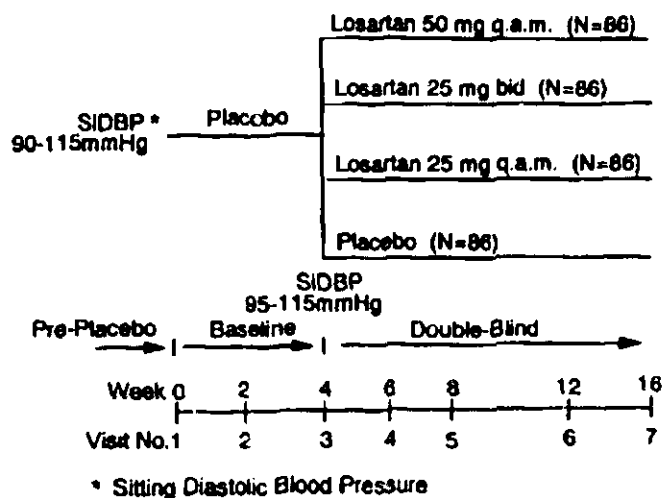
LABORATORY TEST	WEEK	TREATMENT	N	Baseline		Treatment		Change	
				Mean	S.D.	Mean	S.D.	Mean	S.D.
SERUM URIC ACID (mg/dl)	6	Placebo	102	6.34	1.43	6.46	1.61	0.12	0.82
		Losartan 50	114	6.16	1.59	5.91	1.5	-0.25	0.82
		Losartan 50/100	116	6.04	1.36	5.76	1.31	-0.29	0.85
	12	Placebo	94	6.33	1.46	6.51	1.6	0.18	0.71
		Losartan 50	111	6.15	1.6	6.07	1.68	-0.08	0.9
		Losartan 50/100	108	6.03	1.35	5.91	1.4	-0.12	0.75
TOTAL CHOLESTEROL (mg/dl)	12	Placebo	94	215.1	40	216.7	37.1	1.5	22.8
		Losartan 50	107	211.1	36.4	207.3	37.2	-3.9	21.4
		Losartan 50/100	106	212.6	38.8	204.8	34.9	-7.9	23.6
LDL CHOLESTEROL (mg/dl)	12	Placebo	90	131.3	36.9	129.2	34.4	-2	21.5
		Losartan 50	102	127.7	31.6	123.5	32	-4.2	18.7
		Losartan 50/100	95	126.3	35.5	117.9	31.9	-8.4	21.4
PLASMA RENIN ACTIVITY (mg/dl)	12	Placebo	81	1.028	0.918	1.21	1.688	0.181	1.752
		Losartan 50	99	1.3	1.114	2.889	2.884	1.589	2.341
		Losartan 50/100	96	1.473	2.253	3.724	3.242	2.251	3.69

Study 065. A Double-Blind Randomized, Parallel, Placebo-Controlled Study to Investigate the Antihypertensive Efficacy and Safety of Losartan Given Once or Twice Daily in Patients with Mild-to-Moderate Hypertension (Open Label Extension reviewed separately)

Protocol

Protocol 65 is a randomized, double-blind, placebo controlled trial in patients with mild to moderate hypertension. The primary objective was to show that losartan 50 mg once a day and losartan 25 mg twice a day decreased trough sDBP by a significantly greater amount than placebo after 12 weeks of therapy. The trial consisted of a 4 week placebo baseline period and a 12 week active treatment period as outlined in the figure 65.1. [Note: The N listed after each treatment in figure 65.1 is the projected enrollment.]

Figure 65.1 Study Design



Patients were enrolled into the baseline period (visit 1) if they had primary hypertension with a mean siDBP ≥ 90 mmHg (a patient could not have received antihypertensive drugs for at least 7 days prior to the start of the baseline period), were above the legal age to sign a consent and did not have active medical problems. The following conditions excluded patients from enrollment: pregnancy, secondary hypertension, siSBP ≥ 210 mmHg, history of CVA or TIA, MI within the past year, angina pectoris, significant AV block, sick sinus syndrome, ventricular tachyarrhythmias, unexplained syncope or a known syncopal disorder, accessory bypass tract (e.g., Wolff-Parkinson-White syndrome), current or prior history of heart failure or a known left ventricular ejection fraction $\leq 40\%$, hemodynamically significant obstructive valvular disease or hypertrophic cardiomyopathy, percutaneous coronary angioplasty or coronary artery bypass surgery within the past 6 months, concomitant use of β -blockers (except ophthalmic preparations) or any agent that may cause an alteration of blood pressure, use of phenothiazines and high-dose tricyclic anti-depressants, oral contraceptives, regular use of nonsteroidal anti-inflammatory agents (NSAIDs), renal or hepatic, hematological or metabolic dysfunction, regular use of nonsteroidal anti-inflammatory agents, obesity, abusing or previously abused alcohol or other drug substances within the past two year and absence of one kidney.

Patients whose mean siDBP was 95-115 at the end of Week 2 and Week 4 of the placebo baseline period and whose mean siDBP values at Week 2 and Week 4 did not differ by >7 mmHg were stratified by degree of hypertension (mild or moderate) and by race (black or non-black) and were randomly assigned to 1 of 4 treatment groups: placebo q.a.m., losartan 50 mg q.a.m., losartan 25 mg b.i.d. and losartan 25 mg q.a.m. Patients took double-blind therapy for 12 weeks, i.e., until Week 16. Patients had the option of continuing in an open label follow-up study. The open label study is reviewed separately in the 4 month safety update.

The procedures performed in the trial are outlined in the table 65.1.

Table 65.1. Flowchart of Study Visits For Losartan QD and B.I.D. Efficacy: Pre-Placebo - Week 16

	Pre-Placebo	Baseline		Double-Blind Period			
Visit:	1	2	3	4	5	6	7
Day:		14	28	42	56	84	112
Week:		2	4	6	8	12	16
Medical History	X						
Complete Physical Examination	X						X
Pregnancy Test			X ^l				
Sign Informed Consent	X						
Weight	X	X	X	X	X	X	X
Clinic Visits ^b		X	X	X	X	X	X
Sitting & Standing BP & HR ^c (Trough/Peak)	X ^{d,e}	T ^{f,g}	T ^{f,g}	T	T	T	T,P
Laboratory Safety Test ^{h,i}	X ^j	X ^j					X
ECG (12-lead)		X					X
Chest X-ray		X ^k					
AE Evaluation		X	X	X	X	X	X
Dispense Baseline Medications	X ^e	X					
Dispense Double-Blind Medication			X		X	X	
Discontinue Double-Blind Study Medications							X
Dispense Open-Label Medications							X

^a See Section VIII B 1 for necessity and frequency of pregnancy tests

^b Clinic Visits will occur as indicated between 6:30 and 10:30 a.m. Patients are to be in the fasted state at all clinic visits (for a minimum of 8 hours prior to each clinic visit)

^c Trough measurements are to be taken 24 hours (range 22 to 26 hours) after the last morning dose and 12 hours (10-14 hours) after the last p.m. dose

^d Mean siDBP must be 90-115 mmHg or patient cannot continue in the study

^e Patient must not have taken antihypertension medication for at least 7 full days or patient must return for another evaluation when an adequate washout period is achieved (refer to section IX B)

^f Mean siDBP must be 95-115 mmHg or patient cannot continue in study

^g Mean siDBP must be 95-115 mmHg and Week 2 and Week 4 values must differ by <7 mmHg or patient cannot continue in study

^h Fasting hematology, blood chemistry, PT, PTT and urinalysis as described in Appendix 3. At Visit 7 a trough and peak plasma sample (5 mg) will be obtained for possible additional physiological analysis

ⁱ Perform tests only if patient does not have known history or if prior tests are not available

^j Repeat labs, if abnormal at Visit #1

^k Chest x-ray will be performed if one is not available from within the previous 6-month period

NOTE: If a patient does not complete the study, all procedures scheduled for treatment Week 16 (Visit #7) were done on the day the patient discontinues treatment. All adverse experiences must be followed up until resolved or final status is ascertained

Approximately 40 sites were to be used to ensure at least 344 patients complete the study. The study was powered so that if at least 86 patients per treatment group completed the study there would be 90% (80%) probability of detecting a 4 (3.4) mmHg difference between treatment groups with respect to change in blood pressure (assuming a standard deviation of 8 mmHg or less, and a 5% level of significance for a 2-sided test). Thirty percent of the patients enrolled had to have moderate hypertension (siDBP 106-115 mmHg) and no more than 30% of the patients could be black.

Endpoints

The primary endpoint of the study is the change in trough siDBP at week 12. Secondary endpoints included response rate at week 12, the change in siDBP for losartan 25 bid versus losartan 50 once a day and trough /peak assessments.

Results

Statistical Analysis

Table 65.1a describes the statistical tests performed by the sponsor on the data.

Table 65.1a. Statistical Tests Performed in Study 065.

Parameter	Statistical Analysis
Demographics - Categorical	Fisher's Exact Test
Demographics - Continuous	Analysis of Variance (Parameter = response variable, treatment group = independent variable)
Change in BP from baseline	Least Squares analysis of means - ANCOVA for randomized block design (baseline BP = covariate, block = investigator) Pairwise Comparisons*: t-test on ranked data (error term obtained from an overall general linear model including treatment was used) multifactor analysis of covariance on Week 12 changes from baseline in trough SiDBP was done using the "all-patients-treated" approach (factors: investigator**, treatment and baseline blood pressure, race (black/non-black), age category (<65 years/>65 years) and gender)
Response Rate	cumulative logit model for the proportions of patients within each category of response (treatment group is the only independent variable, used carry forward data)
Safety	Lab (change from baseline): T-tests based on the ranked data Lab (% outside pre-defined limit): Fisher's Exact test, Kruskal-Wallis test (based upon ndit scores) Adverse Experiences: Not specified

*As stated in the protocol the primary methodology used for treatment group comparisons was parametric in nature. Due to the presence of some extreme observations, a semi non-parametric analysis was also utilized to address the robustness of the conclusions.

**Investigators with fewer than 2 patients in any treatment group were combined into "one" investigator.

Demographics

Four hundred and twenty-eight (428) patients were randomized into four treatment groups (106-108 per treatment group) at 37 centers (4 centers received drug but did not randomize patients). A list of centers can be found in the appendix. Table 65.2 lists the mean demographic characteristics of each treatment group. The patients were generally similar among the treatment groups with respect to gender (65% male overall), age (combined mean age 53.5 years), race (78% Caucasian, 16% Black, 4% Hispanic across groups) and duration of hypertension (average 10.3 year history for all patients), however, there were significantly higher percentages of Blacks in the losartan 25 q.d. treatment group compared to the losartan 25 b.i.d. group ($p \leq 0.05$). The baseline trough mean sitting diastolic blood pressures (SiDBP) were similar among the 4 treatment groups, ranging from 101.5 to 102.4 mmHg (excluding patients at center #3, these patients were excluded from the efficacy analysis because times of drug doses and times that blood pressures were measured were found to be of questionable reliability and, in most cases, could not be verified). The number of patients randomized at each center ranged from 1 - 22.

Table 65.2. Baseline Patient Demographic Characteristics

		Placebo (N=108)	Losartan 25 qd (N=108)	Losartan 50 qd (N=106)	Losartan 25 bid (N=106)	Total (N=428)
Sex	Female	38 (35%)	41 (38%)	36 (34%)	36 (34%)	151 (35%)
	Male	70 (65%)	67 (62%)	70 (66%)	70 (66%)	277 (65%)
Age (years)	< 35	4 (4%)	4 (4%)	2 (2%)	5 (5%)	15 (4%)
	35-44	18 (17%)	19 (18%)	19 (18%)	19 (18%)	75 (18%)
	45-54	30 (28%)	38 (35%)	29 (27%)	32 (30%)	129 (30%)
	55-64	34 (31%)	31 (29%)	40 (38%)	39 (37%)	144 (34%)
	65-74	21 (19%)	13 (12%)	16 (15%)	10 (9%)	60 (14%)
	> 74	1 (1%)	3 (3%)	0	1 (1%)	5 (1%)
	Mean		54.6	53	54	52.4
Range		29-75	24-79	29-74	27-78	24-79
Racial Origin	Caucasian	84 (78%)	79 (73%)	82 (77%)	89 (84%)	334 (78%)
	Oriental	1 (1%)	2 (2%)	2 (2%)	2 (2%)	7 (2%)
	Latin American	0	1 (1%)	0	0	1 (0%)
	Black	21 (19%)	22 (20%)	17 (16%)	10 (9%)	70 (16%)
	Hispanic	2 (2%)	4 (4%)	5 (5%)	4 (4%)	15 (4%)
	Vietnamese	0	0	0	1 (1%)	1 (0%)
Duration of HTN (years)	Mean	10	10.8	10.5	10	10.3
	Range	0.5-41	0.5-46	0.5-43	0.5-47	0.5-47
SiDBP (mmHg)	< 105 (Mild)	74 (70%)	78 (74%)	68 (66%)	73 (72%)	293 (70%)
	> 105 (Moderate)	32 (30%)	28 (26%)	35 (34%)	29 (28%)	124 (30%)
	Mean	101.5	101.8	102.4	102	101.9
	S.D.	5.1	5.5	6.4	5.3	5.6

These sample sizes do not include patients from investigator # 065003 which was excluded from all efficacy analyses.

Disposition

The number of patients enrolled into the baseline period is not provided in the submission. Four hundred and twenty-eight patients were randomized. 86 of 108 placebo patients, 99 of 108 losartan 25 mg patients, 94 of 106 losartan 50 mg and 96 of 106 losartan 25 mg bid patients completed 12 weeks of double-blind therapy. Two hundred and eighty-eight patients continued into the open label follow-up study. Fifty-three patients withdrew from the double-blind phase prematurely. The majority of placebo patients withdrew due to clinical adverse experience or because therapy was ineffective. Seven patients, all in losartan groups, withdrew with no reason given. Four losartan patients were lost to follow-up. Table 65.3 outlines the disposition of patients in each treatment group. A listing of patients withdrawn from therapy prematurely during the double-blind treatment period can be found in the appendix.

Table 65.3. Patient Disposition.

	Losartan			
	PBO	25 mg q.d.	50 mg q.d.	25 mg b.i.d.
	(N=108)	(N=108)	(N=106)	(N=106)
	n (%)	n (%)	n (%)	n (%)
Completed DB/ No OL	20 (18.5)	19 (17.6)	26 (24.5)	22 (20.8)
Completed DB/ Enter OL	66 (61.1)	80 (74.1)	68 (64.2)	74 (69.8)
Discontinued Double-blind Phase	22 (20.4)	9 (8.3)	12 (11.3)	10 (9.4)
Clinical AE	10 (9.3)	0	1 (0.9)	3 (2.8)
Laboratory AE	0	0	2 (1.9)	0
Clinical & Laboratory AE	0	0	0	0
Therapy Ineffective	9 (8.3)	2 (1.9)	5 (4.7)	2 (1.9)
Patient Uncooperative	0	0	0	0
Patient Withdrew	0	3 (2.8)	1 (0.9)	3 (2.8)
Protocol Deviation	3 (2.8)	2 (1.9)	1 (0.9)	2 (1.9)
Lost to Follow-up	0	2 (1.9)	2 (1.9)	0

Efficacy

Eight patients did not have any treatment period data, and could not be included in the efficacy analysis: 4 patients in the placebo group (# 1219, # 1373, # 1308 and # 1655), 1 in losartan 25 mg q.d. group (# 1685), 2 in losartan 50 mg q.d. group (# 1628 and # 1301) and 1 in losartan 25 mg b.i.d. group (# 1310). When no data were available within a day range, the last available double-blind treatment measurements were used at that time point. Patients from center #3 (Dr. Arbeit, Leonard), were excluded from the efficacy analysis since the times of drug doses and times that blood pressures were measured were found to be of questionable reliability and, in most cases, could not be verified. This investigator had 11 patients: 2 in placebo group (# 1600 and # 1603), 2 in losartan 25 mg q.d. group (# 1598 and # 1610), 3 in losartan 50 mg q.d. group (# 1599, # 1601, and # 1608) and 4 in losartan 25 mg b.i.d. group (# 1597, # 1602, # 1607 and # 1609). Thus, there were a total of 409 patients evaluable for efficacy: 102 patients in the placebo group, 105 patients in the losartan 25 mg q.d. group, 101 patients in losartan 50 mg q.d. group and 101 patients in the losartan 25 mg b.i.d. group.

Table 65.4 lists the mean change in trough siDBP at week 12 using the all patients treated analysis. The placebo subtracted mean change is -3.8 mmHg, -4.3 mmHg and -6.0 mmHg for the losartan 25 mg, losartan 50 mg and losartan 25 mg bid groups respectively. Table 65.4 lists the mean change in trough siSBP at week 12 using the all patients treated analysis.

Table 65.4. Mean Change in Trough Sitting Diastolic Blood Pressure (mmHg) At Week 12 All-Patients-Treated Approach

Treatment	N	Baseline			Treatment			Change			Adj Mean	Comparison		
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.		vs. B	vs. C	vs. D
Placebo (A)	102	101.3	97.0	5.1	99.3	98.5	9.8	-2.0	-2.5	8.4	-2.1	**	**	**
Losartan 25 qd (B)	105	101.8	100.0	5.5	96.0	93.0	8.4	-5.8	-6.0	6.7	-5.9	-	NS	*
Losartan 50 qd (C)	101	102.3	100.0	6.3	96.0	95.0	9.5	-6.3	-7.0	7.4	-6.6	-	-	NS
Losartan 25 bid (D)	101	102.0	101.0	5.3	94.0	93.0	8.8	-8.0	-8.0	7.9	-8.3	-	-	-

NS -- NOT STATISTICALLY SIGNIFICANT; * = TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, $P < 0.05$
 ** = TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, $P < 0.01$

Table 65.4a. Trough Sitting Systolic Blood Pressure (mmHg) At Week 12

Treatment	N	Baseline			Treatment			Change			Change Adj Mean	Comparison		
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.		vs. B	vs. C	vs. D
Placebo (A)	102	156.3	153.5	18.3	156.0	154.0	19.6	-0.2	0.0	15.1	0.4	**	**	**
Losartan 25 qd (B)	105	153.5	150.0	16.5	146.3	146.0	18.4	-7.2	-6.0	13.9	-7.7	-	NS	NS
Losartan 50 qd (C)	101	155.1	154.0	15.8	147.6	146.0	17.5	-7.6	-8.0	12.6	-7.9	-	-	NS
Losartan 25 bid (D)	101	150.5	149.0	15.4	141.8	139.0	17.1	-8.8	-9.0	13.0	-10.6	-	-	-

NS - NOT STATISTICALLY SIGNIFICANT; * = TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, $P \leq 0.05$

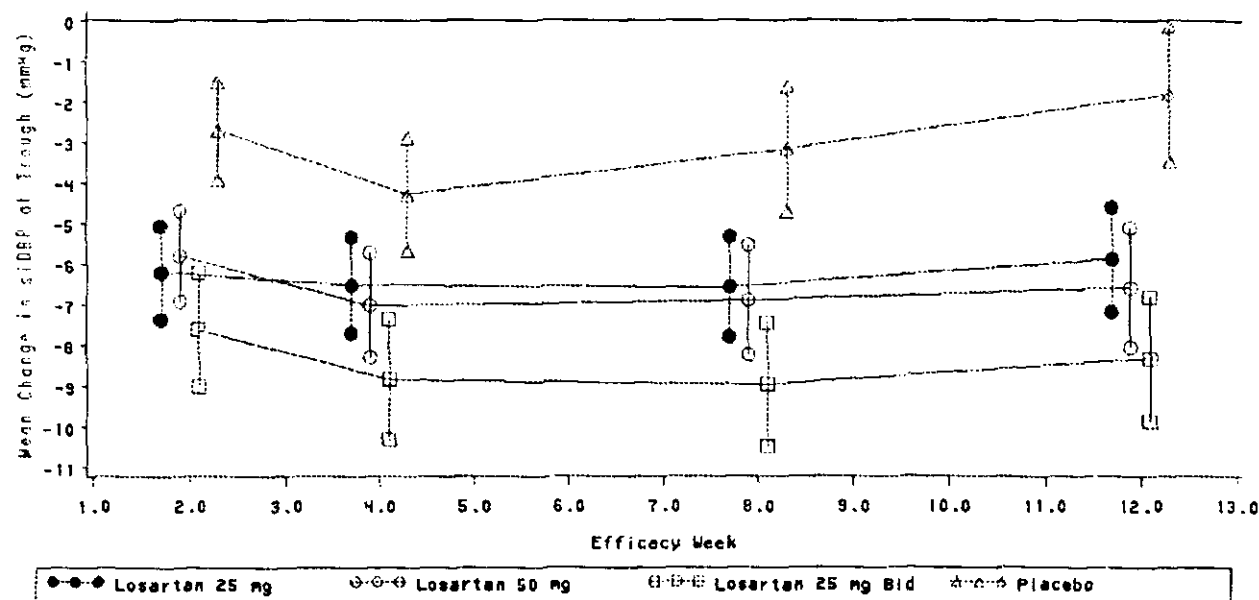
** = TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, $P \leq 0.01$

Figure 65.2 shows the mean change in trough siDBP from baseline for treatment weeks 2, 4, 8 and 12 using carry forward data (data from center #3 is included). The 95% confidence intervals are illustrated by the vertical lines at each time point for each treatment. Although there is no significant difference between losartan 25 mg bid and losartan

Figure 65.2

Study 65. Mean Change in siDBP at Trough

Carry Forward Data.



Tables 65.6 - 65.9 lists the week 12 change in siDBP (carry forward analysis) for subgroups based on race, degree of hypertension, age and gender. In all subgroups except black patients, losartan caused a decline in trough siDBP compared to placebo. The larger decline in mean siDBP (though not statistically different) with losartan 25 mg b.i.d. compared to losartan 50 mg once a day may in part be influenced by the number of black patients in the respective treatment groups (black patients were less responsive to losartan). There were more black patients in the losartan 50 mg group compared to the losartan 25 mg b.i.d. group. However, the argument against this being a factor is the observation that there is a consistently greater decline in siDBP with 25 mg b.i.d. compared to losartan 50 mg regardless of the subgroup.

Table 65.6. Mean Change In Trough Sitting Diastolic Blood Pressure (mmHg) at Week 12 By Race (All-Patients-Treated Approach)

<u>RACE</u>	<u>TREATMENT</u>	<u>N</u>	<u>BASELINE Mean</u>	<u>TREATMENT Mean</u>	<u>CHANGE Mean</u>	<u>95% Confidence Interval for Mean Change</u>
BLACK	Placebo	21	104.7	102.2	-2.5	(-6.2, 1.1)
	LOS 25 qd	21	101.9	97.9	-4.0	(-7.3, -0.7)
	LOS 50 qd	16	104.3	102.8	-1.5	(-4.7, 1.7)
	LOS 25 bid	10	103.6	100.8	-2.8	(-6.9, 1.3)
NON-BLACK	Placebo	81	100.4	98.5	-1.9	(-3.7, -0.1)
	LOS 25 qd	84	101.8	95.5	-6.3	(-7.7, -4.9)
	LOS 50 qd	85	101.9	94.7	-7.2	(-8.8, -5.7)
	LOS 25 bid	91	101.8	93.2	-8.6	(-10.2, -7.0)

Table 65.7. Mean Change in Trough Sitting Diastolic Blood Pressure (mmHg) at Week 12 by Degree of Hypertension at Baseline (All-Patients-Treated Approach)

<u>BASELINE TROUGH siDBP</u>	<u>TREATMENT</u>	<u>N</u>	<u>BASELINE Mean</u>	<u>TREATMENT Mean</u>	<u>CHANGE Mean</u>	<u>95% Confidence Interval for Mean Change</u>
MILD (≤ 105 mmHg)	Placebo	72	98.5	96.9	-1.6	(-3.5, 0.3)
	LOS 25 qd	77	98.9	93.1	-5.8	(-7.2, -4.4)
	LOS 50 qd	67	98.4	92.7	-5.6	(-7.3, -4.0)
	LOS 25 bid	72	99.1	92.0	-7.2	(-8.8, -5.5)
MODERATE (> 105 mmHg)	Placebo	30	108.2	105.1	-3.1	(-6.2, 0.0)
	LOS 25 qd	28	109.6	103.8	-5.9	(-8.7, -3.1)
	LOS 50 qd	34	110.1	102.4	-7.7	(-10.4, -4.9)
	LOS 25 bid	29	109.1	98.9	-10.2	(-13.5, -7.0)

Table 65.8. Mean Change in Trough Sitting Diastolic Blood Pressure (mmHg) at Week 12 by Age Category (All-Patients-Treated Approach)

<u>AGE CATEGORY</u>	<u>TREATMENT</u>	<u>N</u>	<u>BASELINE Mean</u>	<u>TREATMENT Mean</u>	<u>CHANGE Mean</u>	<u>95% Confidence Interval for Mean Change</u>
<65 YEARS	Placebo	80	101.4	99.1	-2.4	(-4.2, -0.6)
	LOS 25 qd	89	101.7	95.7	-6.0	(-7.4, -4.6)
	LOS 50 qd	85	102.4	96.0	-6.4	(-8.0, -4.8)
	LOS 25 bid	90	101.8	93.9	-7.9	(-9.6, -6.3)
≥ 65 YEARS	Placebo	22	100.9	100.1	-0.8	(-4.6, 3.1)
	LOS 25 qd	16	102.1	97.3	-4.8	(-8.0, -1.5)
	LOS 50 qd	16	101.7	95.9	-5.8	(-9.1, -2.5)
	LOS 25 bid	11	103.9	94.8	-9.1	(-13.7, -4.5)

Table 65.9. Mean Change In Trough Sitting Diastolic Blood Pressure (mmHg) At Week 12 By Sex (All-Patients-Treated Approach)

<u>PATIENT SEX</u>	<u>TREATMENT</u>	<u>N</u>	<u>BASELINE Mean</u>	<u>TREATMENT Mean</u>	<u>CHANGE Mean</u>	<u>95% Confidence Interval for Mean Change</u>
FEMALE	Placebo	34	100.2	97.8	-2.4	(-5.4, 0.5)
	LOS 25 qd	40	102.2	96.2	-6.0	(-8.0, -4.0)
	LOS 50 qd	33	102.2	96.1	-6.2	(-8.5, -3.8)
	LOS 25 bid	34	100.7	93.4	-7.3	(-9.9, -4.7)
MALE	Placebo	68	101.9	100.0	-1.8	(-3.8, 0.1)
	LOS 25 qd	65	101.5	95.8	-5.7	(-7.4, -4.0)
	LOS 50 qd	68	102.3	95.9	-6.4	(-8.2, -4.6)
	LOS 25 bid	67	102.6	94.2	-8.4	(-10.3, -6.5)

Table 65.10 lists the response rate for each treatment group at week 12. A positive response to therapy was defined as trough siDBP < 90 mmHg (category I) or a reduction of trough siDBP ≥ 10 mmHg in patients with trough siDBP ≥ 90 mmHg (category II). The response rate in the placebo group was significantly different from the losartan 50 mg and losartan 25 mg bid. Twenty-two percent of the placebo patients, 40% of the losartan 50 mg patients and 48% of the losartan 25 mg b.i.d. dose were responders.

Table 65.10. Categories Of Antihypertensive Response (Trough SiDBP) at Week 12 (All-Patients-Treated Approach)

TREATMENT	ANTIHYPERTENSIVE RESPONSE CATEGORY				COMPARISON		
	I	II	III	TOTAL	VS. B	VS. C	VS. D
PLACEBO (A)	12(11.8%)	10 (9.8%)	80(78.4%)	102 (100%)	NS	*	**
LOS 25 qd (B)	23(21.9%)	14(13.3%)	68(64.8%)	105 (100%)	--	NS	NS
LOS 50 qd (C)	26(25.7%)	14(13.9%)	61(60.4%)	101 (100%)	--	--	NS
LOS 25 bid (D)	33(32.7%)	15(14.9%)	53(52.5%)	101 (100%)	--	--	--

NS - NOT STATISTICALLY SIGNIFICANT

* - TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, $P < 0.05$

** - TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, $P < 0.01$

CATEGORY I - TROUGH SiDBP < 90 mmHg

CATEGORY II - TROUGH SiDBP ≥ 90 , REDUCTION ≥ 10 mmHg

CATEGORY III - NEITHER I NOR II

Response rates for subgroups based on gender and race (only black and Caucasian included) are listed in table 65.11. Caucasians and blacks were the only racial subgroups that had sufficient numbers to derive meaningful information. The response rate in black patients suggests that blacks do not respond to losartan.

Table 65.11. Trough Response Rate in Subgroups. (carry forward data)

Subgroup	losartan 25 mg	losartan 50 mg	losartan 25 mg bid	placebo
Male	37.3% (25/67)	35.7% (25/70)	45.7% (32/70)	20.0% (14/70)
Female	31.7% (13/41)	47.2% (17/36)	50.0% (18/36)	21.1% (8/38)
Caucasian	40.5% (32/79)	45.1% (37/82)	49.4% (44/89)	17.9% (15/84)
Black	18.2% (4/22)	11.8% (2/17)	20.0% (2/10)	28.6% (6/21)

Tables 65.12 and 65.13 lists the changes in peak siDBP and peak siSBP at week 12. All treatment groups had significantly greater decreases in blood pressure compared to placebo.

Table 65.12 Mean Change in Peak Sitting Diastolic Blood Pressure (mmHg) at Week 12 (All-Patients-Treated Approach).

TREATMENT	N	Baseline			Treatment			Change				Comparison		
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	Adj. Mean	vs. B	vs. C	vs. D
Placebo (A)	92	98.8	99.0	7.5	95.7	95.0	9.8	-3	-4.0	9.7	-2.8	**	**	**
LOS 25 qd (B)	95	98.2	99.0	7.7	90.5	90.0	8.9	-7.7	-8.0	8.5	-8.0	--	NS	NS
LOS 50 qd (C)	94	98.8	97.5	7.1	90.1	90.0	10.2	-8.7	-8.0	8.1	-9.0	--	--	NS
LOS 25 bid(D)	94	100.5	99.5	5.9	90.6	89.0	9.4	-9.9	-10.0	9.5	-9.3	--	--	--

NS - NOT STATISTICALLY SIGNIFICANT

** - Treatment Difference statistically significant, $p < 0.01$.

Table 65.13. Mean Change in Peak Sitting Systolic Blood Pressure (mmHg) at Week 12 (All-Patients-Treated Approach).

TREATMENT	N	Baseline			Treatment			Change				Comparison		
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	Adj. Mean	vs. B	vs. C	vs. D
Placebo (A)	92	154.2	151.0	19.8	153.1	150.0	19.7	-1.0	-2.5	15.9	0.5	**	**	**
losartan 25 qd (B)	95	151.1	149.0	18.4	141.8	139.0	17.7	-9.3	-8	16.3	-9.2	--	NS	*
losartan 50 qd (C)	94	153.1	151.0	16.6	141.9	139.0	17.8	-11.2	-11	13	-10.7	--	--	NS
losartan 25 bid(D)	94	151.3	149.0	16.0	137.7	137.5	17.0	-13.6	-12.5	15	-13.8	--	--	--

NS - NOT STATISTICALLY SIGNIFICANT

* - TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, $P < 0.05$

** - TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, $P < 0.01$

Table 65.14 lists the response rates for peak week 12 siDBP measurements. The response rate at peak for losartan treatment groups ranged from 62.2% to 53.2%. The placebo group response rate was 39.1%.

Table 65.14. Categories of Antihypertensive Response (Peak siDBP) at Week 12 (All-Patients-Treated Approach)

TREATMENT	ANTIHYPERTENSIVE RESPONSE CATEGORY				COMPARISON		
	I	II	III	TOTAL	VS. B	VS. C	VS. D
PLACEBO (A)	25(27.2%)	11(12.0%)	56(60.9%)	92 (100%)	**	*	**
LOS 25 qd (B)	47(49.5%)	13(13.7%)	35(36.8%)	95 (100%)		NS	NS
LOS 50 qd (C)	43(45.7%)	7 (7.4%)	44(46.8%)	94 (100%)			NS
LOS 25 bid (D)	48(51.1%)	11(11.7%)	35(37.2%)	94 (100%)			

NS - NOT STATISTICALLY SIGNIFICANT
 * - TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, $P \leq 0.05$
 ** - TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, $P \leq 0.01$
 I - PEAK siDBP < 90 mmHg
 II - PEAK siDBP > 90 , REDUCTION ≥ 10 mmHg
 III - NEITHER I NOR II

The trough to peak ratios at week 12 for siDBP are listed in table 65.15.

Table 65.15. Trough-to-Peak Ratios for Sitting Diastolic Blood Pressure at Week 12.

N	TREATMENT GROUP	MEAN CHANGE (mmHg)		T:P RATIO	T:P RATIO (PRO ADJUSTED)
		TROUGH	PEAK		
91	Placebo	-2.2	-3.2	69%	--
95	LOS 25 qd	-6.0	-7.7	78%	85%
93	LOS 50 qd	-7.0	-8.7	80%	87%
94	LOS 25 bid	-8.2	-9.9	83%	90%

NOTE: Only patients with both trough and peak measurements were included in this table.

An analysis which included only trough siDBP measurements collected at week 12 (not carry forward, protocol violators included) yielded results similar to the all patients treated analysis. The change in trough siDBP at week 12 based on a per protocol data analysis showed similar results as the carry forward analysis. The mean change from baseline at week 12 for trough siDBP using the per protocol data was -3.1, -6.5, -6.7 and -8.2 mmHg for placebo, losartan 25 mg qd, losartan 50 mg qd and losartan 25 bid respectively. Mean changes in trough siDBP were also generally similar for the two approaches at Week 12. The only difference between the approaches with respect to statistical significance ($p \leq 0.05$) was that losartan 50 mg q.d. was significantly different (smaller reduction) than losartan 25 mg b.i.d. using the "per-protocol" approach. In multifactor analysis of covariance, investigators who had less than two patients in any treatment group were combined for the purpose of a formal statistical test; there was no interaction observed utilizing this approach ($p=0.9102$). Except for race there were no statistically significant interactions observed between treatment and any of the other factors (age and sex). Race had a significant interaction with treatment ($p \leq 0.05$).

Safety

The percentage of patients with at least one adverse experience in the double blind period ranged from 55% to 61%. Three patients died during the study. Patient # 1330 (placebo) was a 58-year-old male hypertensive patient who had been treated for 85 days with placebo when a hydraulic lift fell on him and he died immediately. Patient # 1596 (losartan 25 bid) was a 78-year-old hypertensive male patient had a blood pressure reading of 211/143 and numbness and tingling of the right leg on Day 41 of treatment with losartan 25 mg b.i.d. He was hospitalized and diagnosed with a cerebral vascular accident secondary to malignant hypertension (Blood Pressure Measurements: 177/111, 157/110, 170/113, 176/118, 174/105 mmHg readings). Therapy was discontinued. Seven days later he had a cardiac arrest and was resuscitated. Eighteen days later he developed an arrhythmia, respiratory failure, and seizures. On Study Day 68 he had a second cardiac arrest and died. Patient # 1373 (placebo) was a 53-year-old hypertensive male patient who was hospitalized for myocardial infarction and cerebral vascular accident on Day 4 of treatment with placebo. The patient died on Day 39.

A total of 14 patients were discontinued because of clinical adverse experiences. Table 65.16. lists the adverse events associated for these patients. Of these, 10 patients were in the placebo group, 1 patient was in losartan 50 mg q.d. and 3 were in losartan 25 mg b.i.d. group.

Table 65.16. Patients Discontinued Due To Clinical Adverse Experiences

Patient #	Sex	Age	Treatment	Day Discontinued	Adverse Event	AE Start Day	AE Duration days
1145	M	61	Placebo	10	PALPITATION	5	10
					PHOTOPHOBIA	5	10
1153	F	51	Placebo	39	PAIN, BACK	14	2
					MYALGIA	27	2
					RASH	37	15
1246	M	69	Placebo	84	HEART FAILURE	81	4
1272	M	48	Placebo	33	EDEMA/SWELLING	1	34
					EDEMA/SWELLING	15	20
					STRAIN, BACK	30	4
1301	F	38	Losartan 50 mg	4	TACHYCARDIA	3	5
					HYPERGLYCEMIA	4	1
					LYMPHOCYTES DECREASED	4	1
					NEUTROPHILS INCREASED	4	1
1308	F	43	Placebo	5	DYSPNEA	4	2
1330	M	58	Placebo	85	DEATH	85	1
					TRAUMA	85	1
1373	M	53	Placebo	4	CVA	4	36
					MI	4	36
1415	F	61	Losartan 25 mg BID	16	DIZZINESS	1	28
1421	M	66	Placebo	43	DIARRHEA	22	22
					NEOPLASM, INTESTINAL, METASTATIC	43	1
1560	M	65	Placebo	52	HEMORRHAGE, RETINAL	48	5
1596	M	78	Losartan 25 mg BID	41	HEADACHE	7	4 hours
					CVA	41	28
					HYPERTENSION	41	28
1607	M	40	Losartan 25 mg BID	16	PAIN, ARM	16	1
					PAIN, CHEST	16	1
1623	M	63	Placebo	27	ARTHRALGIA	1	27

Two patients had laboratory adverse experiences that prompted withdrawal. Information pertaining to these patients are listed in table 65.17.

Table 65.17. Patients Discontinued Due To Laboratory Adverse Experiences.

PL #	Sex/ Age	Drug/ Total Daily Dosage (mg) Frequency	Rel. Day of Onset	Adverse Experience	Laboratory Value and Unit	Normal Range	Rel. Day of Discontinue.	Serious
1599	F/44	50 mg q d	84	AST Increased	73 u/L	9-34 U/L	84	No
			84	ALT Increased	56 u/L	6-34 U/L	84	No
1750	M/45	50 mg q d	90	Hyperglycemia	326/mg/dL	70-115 mg/dL	90	No

Table 65.18 lists the patients who had adverse experiences that were considered to be serious. Five of the nine patients with serious adverse events required discontinuation. Narrative summaries for these patients are provided following table 65.18.

Table 65.18. Serious Clinical Adverse Experiences

Patient	Sex	Age	Treatment Group	Rel Day of Onset	Adverse Experience(s)	Duration (Days)	Outcome
1173	F	74	Placebo	77	Phlebitis/Thrombophlebitis	16	Recovered
1330*	M	58	Placebo	85	Trauma	1	Death
1373*	M	53	Placebo	4	Myocardial Infarction	36	Not Recovered
				4	Cerebral Vascular Accident	36	Not Recovered
				39			Death
1421*	M	66	Placebo	43	Metastatic CA Bowel	1	Not recovered
1314	M	43	25 mg qd	68	Fracture Rt Patella	16	Recovered
1110	M	45	50 mg qd	34	Chest and Abdominal pain	1	Recovered
1194	M	64	25 mg bid	15	Squamous Cell Ca Forehead	13	Recovered
1596*	M	78	25 mg bid	41	Malign Hypertension	28	Not recovered
				41	CVA	28	Not recovered
			Off drug	48	Cardiac Arrest	<1	Recovered
			Off drug	66	Resp. Failure, Seizures,	3	Not recovered
			Off drug	66	Arrhythmia	3	Not recovered
	68	Cardiac Arrest	<1	Death			
1607*	M	40	25 mg bid	16	Chest Pain, Arm Pain	1	Recovered

* Discontinued the study.

Patient # 1421 - Metastatic CA Bowel (Placebo)

This 66-year-old hypertensive male patient with a history of mild to moderate diarrhea was hospitalized on Day 43 of treatment with placebo and surgically diagnosed with a malignant distal rectal tumor with metastasis to the peritoneum and liver. Therapy was discontinued.

Patient # 1173 - Phlebitis (Placebo)

This 74-year-old female hypertensive patient was hospitalized for phlebitis on Day 77 of treatment with placebo. She was medically treated and discharged on Day 88. Therapy was not interrupted.

Patient # 1330 - Trauma, Death (Placebo)

This 58-year-old male hypertensive patient had been treated for 85 days with placebo when a hydraulic lift fell on him and he died immediately. The investigator considered this event to be definitely not related to study drug.

Patient # 1373 - Myocardial Infarction, Cerebral Vascular Accident, Death (Placebo)

This 53-year-old hypertensive male patient was hospitalized for myocardial infarction and cerebral vascular accident on Day 4 of treatment with placebo. The patient died on Day 39.

Patient # 1314 - Broken Knee Cap (25 mg q.d.)

This 43-year-old hypertensive male patient was hospitalized for a broken knee cap on Day 68 of treatment with losartan 25 mg q.d. The patient had a surgical repair on Day 69 and recovered. Therapy was interrupted for surgery only. The investigator considered the event to be definitely not related to study drug.

Patient # 1110 - Chest and Abdominal Pain (50 mg q.d.)

This 45-year-old hypertensive male patient was admitted to the hospital on Day 34 of treatment with losartan 50 mg q.d. for lower abdominal pain and chest pain. His condition resolved without surgical or medical intervention and he was discharged on Day 37. Therapy was interrupted for three days.

Patient # 1607 - Chest Pain (25 mg b.i.d.)

This 40-year-old hypertensive male patient with a history of myocardial infarction was hospitalized for chest pain and pain in left arm on Day 16 of treatment with losartan 25 mg b.i.d. He was diagnosed with a possible myocardial infarction. Therapy was discontinued.

Patient # 1596 Study 065-011 - Malignant Hypertension, Cerebral Vascular Accident, Cardiac Arrest, Respiratory Failure, Seizures, Arrhythmia, Death (25 mg b.i.d.)

This 78-year-old hypertensive male patient had a blood pressure reading of 211/143 and numbness and tingling of the right leg on Day 41 of treatment with losartan 25 mg b.i.d. He was hospitalized and diagnosed with a cerebral vascular accident secondary to malignant (177/111, 157/110, 170/113, 176/118, 174/105 mmHg readings) hypertension. Therapy was discontinued. Seven days later he had a cardiac arrest and was resuscitated. Eighteen days later he developed an arrhythmia, respiratory failure, and seizures. On Study Day 68 he had a second cardiac arrest and died.

Patient # 1194 - Squamous Cell Carcinoma Forehead (25 mg b.i.d.)

This 64-year-old hypertensive male patient with a history of an excised squamous cell carcinoma of the forehead had a biopsy of the scar and was diagnosed with recurrent squamous cell carcinoma of the forehead on Day 15 of treatment with losartan 25 mg b.i.d. Therapy was not interrupted.

The number of patients in each treatment group with at least one adverse experience is listed in table 65.19. There is no difference between treatments.

Table 65.19. Adverse Experience Incidence

	PLACEBO (N=108)	LOS 25 QD (N=108)	LOS 50 QD (N=106)	LOS 25 BID (N=106)
Number (%) of Patients	n (%)	n (%)	n (%)	n (%)
With One Or More Adverse Experiences	66 (61)	60 (56)	61 (58)	60 (56.6)

Table 65.19a lists the adverse events with a reported incidence greater than 1%. This information was obtained from the CANDA by querying study 65 for adverse events during the acute period. Note that only 1 death is listed whereas three deaths occurred. Two deaths are listed as occurring in the post-acute drug treatment period. Impotence occurred only in losartan treated patients. Dizziness was not a dose related adverse event. Hemoglobinuria occurred in 3 losartan treated patients. Additional patient information is needed to determine whether hemoglobinuria is due to hemolytic anemia.

Table 65.19a. Adverse Event Incidence [Includes adverse events that have a total incidence > 1%, have potential serious clinical implications, are characteristic in ACE Inhibitors or may have clinical relevance based on the mechanism of action of losartan.]

Adverse Experience	losartan 25 mg	losartan 50 mg	losartan 25 mg bid	placebo	Total
ALT INCREASED	4	4			8
ASTHENA/FATIGUE	2	2	6	2	12
ARRHYTHMIA			1		1
AST INCREASED	2	3		1	6
BRONCHITIS	3		2		5
CONGESTION, NASAL	1		3	2	6
COUGH	5	4	3	3	15
DEATH				1	1
DIARRHEA	4	4	2	4	14
DIZZINESS	7	5	4	3	19
DYSPEPSIA	2	1	2	1	6
EDEMA/SWELLING	2	2		4	8
FEVER	1		1	3	5
GOUT		1	1	1	3
HEADACHE	17	19	18	23	77
HEART FAILURE		1		1	2
HEMOGLOBINURIA	2		1		3
HYPERGLYCEMIA		2	3		5
IMPOTENCE		3	2		5
URI	9	7	11	8	35
INSOMNIA	1	2	1	1	5
MYALGIA		1	2	2	5
NAUSEA	3	3		3	9
PAIN, CHEST	2	2	2		6
PAIN, KNEE	4	1		1	6
PARESTHESIA	2	2		1	5
PTT INCREASED	1			1	2
PERVERSION, TASTE			1		1
PHARYNGITIS	3	5		4	12
PROTEINURIA	1			2	3
PROTHROMBIN TIME INCREASED	1			1	2
RHINITIS	1	2	1	1	5
SINUS DISORDER	2	3	1	4	10
SINUSITIS	1	2	1	1	5
SWELLING, JOINT	3			2	5
URTICARIA			1	1	2

Patients had laboratory blood tests performed at baseline and week 12. Table 65.20 shows the incidence of laboratory adverse experience in all treatment groups.

Table 65.20. Laboratory Adverse Experience Summary

	Placebo (N*=104)	Losartan 25 qd (N*=105)	Losartan 50 qd (N*=103)	Losartan 25 bid (N*=104)
Number (%) of Patients With one or more Adverse Experiences	7 (6.7)	7 (6.7)	7**(6.8)	4 (3.8)

** The CANDA lists only six patients with laboratory AE

Patients # 1127 (losartan 25 mg), # 1479 (losartan 25 mg), and #1582 (losartan 25 mg bid) had hemoglobinuria. None of these patients had decreases in hemoglobin. Urine blood results are not available in the CANDA for this study. Nine patients (8 losartan, 1 placebo) had elevations of either ALT or AST. None of these patients had a simultaneous increase in both ALT or AST to double the upper limit of normal. Patients #1274 (losartan 25 mg bid) had a serum potassium of 2.7 mEq/L on day 30, 3.0 mEq/L on day 63 and 2.4 mEq/L on day 100 (baseline potassium = 3.3 mEq/L; day (-29) = 2.5 mEq/L). Patient #1744 (losartan 50 mg) had a serum potassium of 3.0 mEq/L on day 98 (baseline = 3.8 mEq/L). Patient # 1245 (losartan 25 mg) had a serum potassium of 5.6 mEq/L on day 85 (baseline = 4.4 mEq/L). Patient #1632 (losartan 50 mg) had a serum potassium of 5.5 mEq/L on day 92 (baseline = 4.1 mEq/L).

The mean changes in laboratory tests were unremarkable except for the parameters listed in table 65.21. Uric acid decreased with losartan treatment whereas potassium increased slightly. It is not clear that these changes are clinically relevant.

Table 65.21. Mean Changes from Baseline for Labs

LABORATORY TEST	UNIT	WEEK	TREATMENT	N	BASELINE		TREATMENT		CHANGE	
					Mean	S.D.	Mean	S.D.	Mean	S.D.
SERUM CREATININE	mg/dl	12	Placebo	100	1.13	0.19	1.12	0.19	-0.01	0.11
			Losartan 25 mg qd	102	1.12	0.17	1.08	0.18	-0.04	0.10 ^a
			Losartan 50 mg qd	99	1.08	0.15	1.08	0.18	0	0.11
			Losartan 25 mg bid	102	1.11	0.2	1.09	0.19	-0.02	0.1
SERUM URIC ACID ⁺	mg/dl	12	Placebo	100	5.91	1.33	5.75	1.28	-0.16	0.83
			Losartan 25 mg qd	102	5.93	1.27	5.62	1.34	-0.31	0.7
			Losartan 50 mg qd	99	5.83	1.34	5.59	1.34	-0.24	0.7
			Losartan 25 mg bid	102	5.81	1.44	5.46	1.35	-0.35	0.86 ^b
SERUM POTASSIUM ⁺	mEq/L	12	Placebo	100	4.3	0.39	4.27	0.4	-0.03	0.42
			Losartan 25 mg qd	102	4.31	0.39	4.32	0.39	0	0.39
			Losartan 50 mg qd	98	4.19	0.37	4.32	0.42	0.13	0.42 ^c
			Losartan 25 mg bid	101	4.26	0.38	4.32	0.42	0.06	0.39

⁺ These laboratory tests were statistically analyzed due to special interest.

^a Statistically significantly different from losartan 50 mg q d., p=0.003.

^b Statistically significantly different from placebo, p=0.050.

^c Statistically significantly different from placebo and losartan 25 mg q d., p=0.007 and p=0.011, respectively.

Study 021. A Double-Blind, Randomized, Parallel-Group, Placebo-Controlled Pilot Study to Investigate the Magnitude and Duration of Response and the Safety of MK-954 (50 mg Given Once or Twice Daily, or 100 mg Given Once Daily) Compared to Placebo Using Ambulatory Blood Pressure Monitoring [The open label extension portion of this study is reviewed separately.]

Protocol

This is a randomized, double-blind, placebo controlled, parallel-group study to obtain a preliminary evaluation of the magnitude and duration of the antihypertensive efficacy and safety of three different dose regimens of losartan compared to placebo. The trial consisted of a 4 week placebo baseline period at the end of which patients were randomized to either placebo, losartan 50 mg, losartan 100 mg or losartan 50 mg bid for 6 weeks of therapy. Ambulatory blood pressure monitoring (ABPM) was performed twice during the study, once at the end of the placebo washout period and again at the end of four (4) weeks of double-blind monotherapy treatment. After 4 weeks of treatment, patients with siDBP $\geq$ 85 mmHg could have ICTZ added to the double-blind treatment.

The trial enrolled only non-black patients, > 21 years of age and within 30% of ideal body weight. Mean 24 hour ambulatory monitoring blood pressure had to be $\geq$ 85 mmHg. Conventional siDBP by the mercury sphygmomanometer at screening had to be $\geq$ 90 mmHg and $\geq$ 95 mmHg at the week 2 and 4 baseline visits. The difference between the measurements taken at these 2 visits had to be no more than 7 mmHg. Table 21.1 outlines the procedures performed during the study.

Table 21.1 Clinical and Laboratory Assessments Performed During the Double-Blind Study

	Prestudy	Baseline		Double-Blind Monotherapy Treatment			Concomitant HCTZ	
		Week -3	Week -1	Week 1	Week 2	Week 4	Week 5	Week 6
Days of Treatment:		14	28	35	42	56	63	70
Procedure								
Sign informed Consent	x							
Discontinue Anti-hypertensive Medications	x							
Physical Examination Electrocardiogram (ECG)	x					x		x
Medical History	x							
Laboratory Evaluation ¹		x				x		x
Trough Sitting and Standing Blood Pressure and Heart Rate	x	x	x	x	x	x	x	x
Adverse Experience Assessment		x	x	x	x	x	x	x
Ambulatory BP Monitoring			x			x		x ²
Review Inclusion and Exclusion Criteria	x	x	x					
Body Weight and Pill Count		x	x	x	x	x	x	x
Assign Baseline Number	x							
Assign Allocation Number			x					
Dispense Medications	x		x			x		

¹ Fasting, Hematology, blood chemistry and urinalysis ² Optional

Blood pressure measurements were performed simultaneously with the ABP monitor and the mercury sphygmomanometer using a "T" tube. The purpose was to verify that the ABP monitor was measuring blood pressure consistent with the mercury sphygmomanometer (the "gold standard").

The type of statistical analysis to be performed on the data was not pre-specified in the protocol. The primary efficacy variable specified in the protocol was baseline versus week 4 ABPM mean results.

Results

Demographics

One hundred twenty-two (122) patients were randomized into four treatment groups (29-32 per treatment group) at nine treatment centers. Table 21.2 provides demographic information on the treatment groups. For the most part, demographic variables were similar among treatment groups. The number of patients on ACE inhibitor therapy prior to enrolling in this trial is provided in table 21.3. Interestingly, none of the patients were on captopril.

Table 21.2. Baseline Patient Demographic Characteristics

	Placebo (N=32)	Losartan 50 qd (N=29)	Losartan 100 qd (N=30)	Losartan 50 bid (N=31)	Total (N=122)
Sex					
Female	7 (22%)	10 (34%)	9 (30%)	13 (42%)	39 (32%)
Male	25 (78%)	19 (66%)	21 (70%)	18 (58%)	83 (68%)
Age (years)					
Mean	52.3	56.8*	51.2	54.1	53.5
S.D.	12	12.1	9.6	9	10.8
Range	28 - 76	34 - 75	34 - 73	35 - 69	28 - 76
Racial Origin					
Caucasian	30 (94%)	29 (100%)	30 (100%)	30 (97%)	119 (98%)
Oriental	0	0	0	1 (3%)	1 (1%)
Filipino	1 (3%)	0	0	0	1 (1%)
Indian	1 (3%)	0	0	0	1 (1%)
Duration of Hypertension (years)					
Mean	9.8	9.4	11.2	13.7	11.1
S.D.	10.1	7.6	7.7	10.8	9.2
Median	5.5	8	10	12	9
Range	0.08 - 46	0.25 - 28	1 - 31	0.33 - 49	0.08 - 49
SiDBP (Clinic)					
Mean	100.7	100	101.5	101.2	100.9
S.D.	4	4.6	5.1	4.8	4.6
DBP 24-Hour Mean ABPM					
N	26	28	28	30	112
Mean	94.8	94	93.8	94.4	94.2
S.D.	5.9	6.9	6	6.9	6.4

*Statistically significantly different from Los 100 qd, p<0.05. [Statistical Analysis: Categorical Variables = Fisher's Exact test, Continuous = ANOVA (treatment is independent variable)]

Table 21.3. ACE Inhibitor Use Prior to Enrollment

	Placebo (N=32)	Los 50 qd (N=29)	Los 100 qd (N=30)	Los 50 bid (N=31)
	n (%)	n (%)	n (%)	n (%)
Enalapril Maleate	2 (6.3)	6 (20.7)	4 (13.3)	5 (16.1)
Lisinopril	2 (6.3)	3 (10.3)	3 (10.0)	2 (6.5)

Disposition

Table 21.4. lists the number of patients randomized to each treatment group. Eight patients withdrew during the six week double-blind treatment period.

Table 21.4. Patient Accounting

	Placebo	Losartan 50 QD	Losartan 100 QD	Losartan 50 BID
Total Entering Monotherapy Period	32	29	30	31
Total Completing Period	30	28	29	29
Continuing Into Combination Period (sDBP > 85)	28	21	21	23
Not Continuing Into Combination Period (sDBP < 85)	2	4	7	5
Not Continuing Into Combination Period (sDBP > 85)	0	3	1	1
Total Discontinued Period	2	1*	1	2
Clinical Adverse Experience	1	1*	1	1
Protocol Deviation	0	0	0	1
Patient Withdrew	1	0	0	0
Total Entering Combination Therapy Period	28	21	21	23
Total Completing Period	28	21	19	23
Total Discontinued Period	0	0	2	0
Clinical Adverse Experience	0	0	1**	0
Protocol Deviation	0	0	1	0

* Did not adhere to protocol

* This patient (AN 81) had an adverse experience during placebo baseline that continued (without change) into double-blind. He discontinued after having Week 4 efficacy measurements obtained

**This patient (AN 88) discontinued HCTZ (on his own) after 5 days due to a loss of equilibrium (staxia). The patient continued the double-blind medication (losartan) for the remaining 7 days of the "combination" phase.

Table 21.4a lists the patients withdrawn and the reason for withdrawal.

Table 21.4a. Patients Withdrawn

Patient Number	Treatment Regimen	Reason Discontinued	Day Discontinued
11	Losartan 50 mg BID	CLINICAL AE	3
35	Placebo	CLINICAL AE	11
160	Losartan 100 mg	CLINICAL AE	20
81	Losartan 50 mg	CLINICAL AE	29
88	Losartan 100 mg	CLINICAL AE	39
46	Losartan 50 mg BID	Protocol Deviation	29
62	Losartan 100 mg	Protocol Deviation	32
99	Placebo	Patient Withdrew	8

Efficacy

According to the ABPM design specifications, the total number of readings that were to be taken during the 26-hour monitoring was 72. Less than 10% of the patients had fewer than 60 readings over 24 hours. Table 21.5 and 21.5a. displays the mean baseline, Week 4 and change in diastolic and systolic 24-hour mean ABPM by treatment group. [Adjusted means are provided in this table since baseline was included as a covariate in the model and the pairwise comparisons were based upon these adjusted means.] Ten patients were not included in the analysis for various reasons (6 placebo, 1 losartan 50 mg, 2 losartan 100 mg, 1 losartan 50 mg bid). For all losartan groups, the change in ambulatory DBP was significantly different from placebo. The losartan 50 mg b.i.d. group had a greater decline (non-significant) in ambulatory DBP than the losartan 100 mg group. Ambulatory SBP change was significantly different in all losartan groups compared to placebo.

Table 21.5. Diastolic 24-Hour Mean ABPM

Treatment	N	Baseline		Week 4		Change		Change Adj Mean	Comparison		
		Mean	S.D.	Mean	S.D.	Me/n	S.D.		vs. B	vs. C	vs. D
Placebo (A)	26	94.8	5.9	94.6	7.0	-0.2	4.8	-0.8	**	**	**
Los 50 qd (B)	28	94.0	6.9	88.8	9.9	-5.2	5.1	-5.6	--	NS	*
Los 100 qd (C)	28	93.8	6.0	87.4	6.8	-6.4	5.5	-7.1	--	--	NS
Los 50 bid (D)	30	94.4	6.9	86.0	6.9	-8.5	6.7	-9.0	--	--	--

Table 21.5a. Systolic 24-Hour Mean ABPM

Treatment	N	Baseline		Week 4		Change		Change Adj Mean	Comparison		
		Mean	S.D.	Mean	S.D.	Mean	S.D.		vs. B	vs. C	vs. D
Placebo (A)	26	147.4	13.3	147.4	12.8	0.0	7.8	-1.2	**	**	**
Los 50 qd (B)	28	150.9	15.4	141.7	17.3	-9.2	9.9	-9.4	--	NS	*
Los 100 qd (C)	28	147.7	12.2	137.9	13.5	-9.9	7.6	-10.9	--	--	NS
Los 50 bid (D)	30	148.7	12.2	135.5	12.4	-13.2	10.6	-14.2	--	--	--

NS -- Not Statistically Significant

* -- Treatment Difference Statistically Significant, $P < 0.05$

** -- Treatment Difference Statistically Significant, $P < 0.01$

Pairwise comparisons are based upon adjusted means.

The hourly mean DBP throughout the 24 hours of monitoring at baseline and week 4 is depicted in figure 21.2. The hourly mean change in DBP from baseline throughout the 24 hours of monitoring at week 4 is depicted in figure 21.3. For all losartan treatment groups, the hourly ambulatory DBP is below baseline values.

Figure 21.2. Diastolic Hourly Mean ABPM

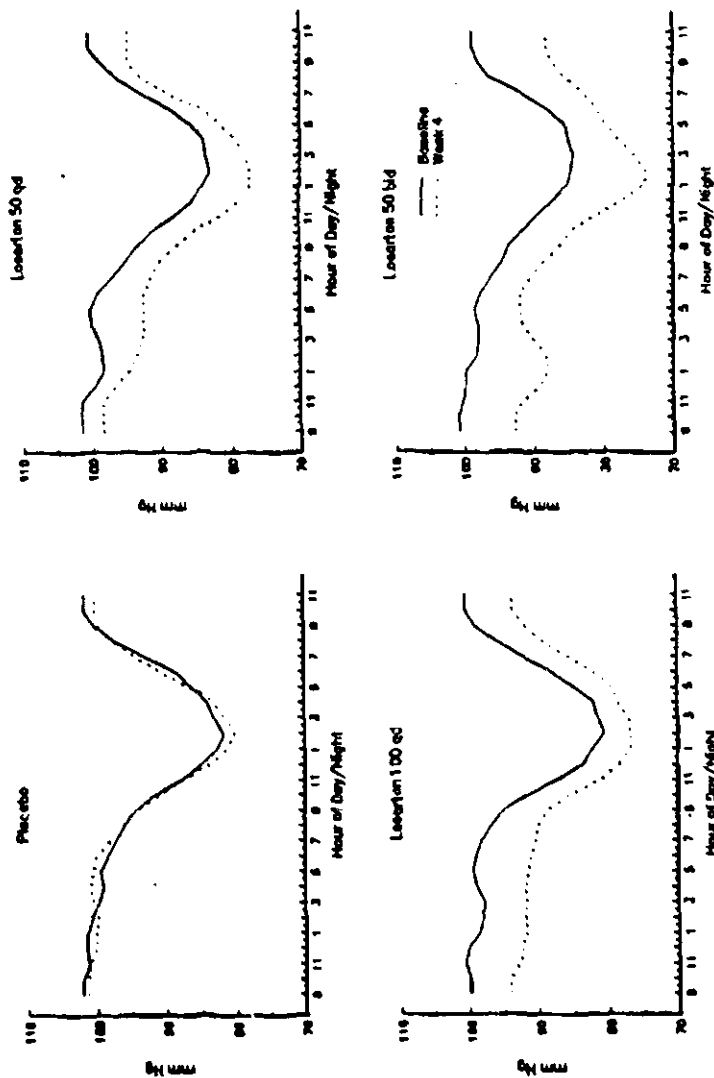


Figure 21.3. Diastolic Hourly Mean ABPM Change From Baseline

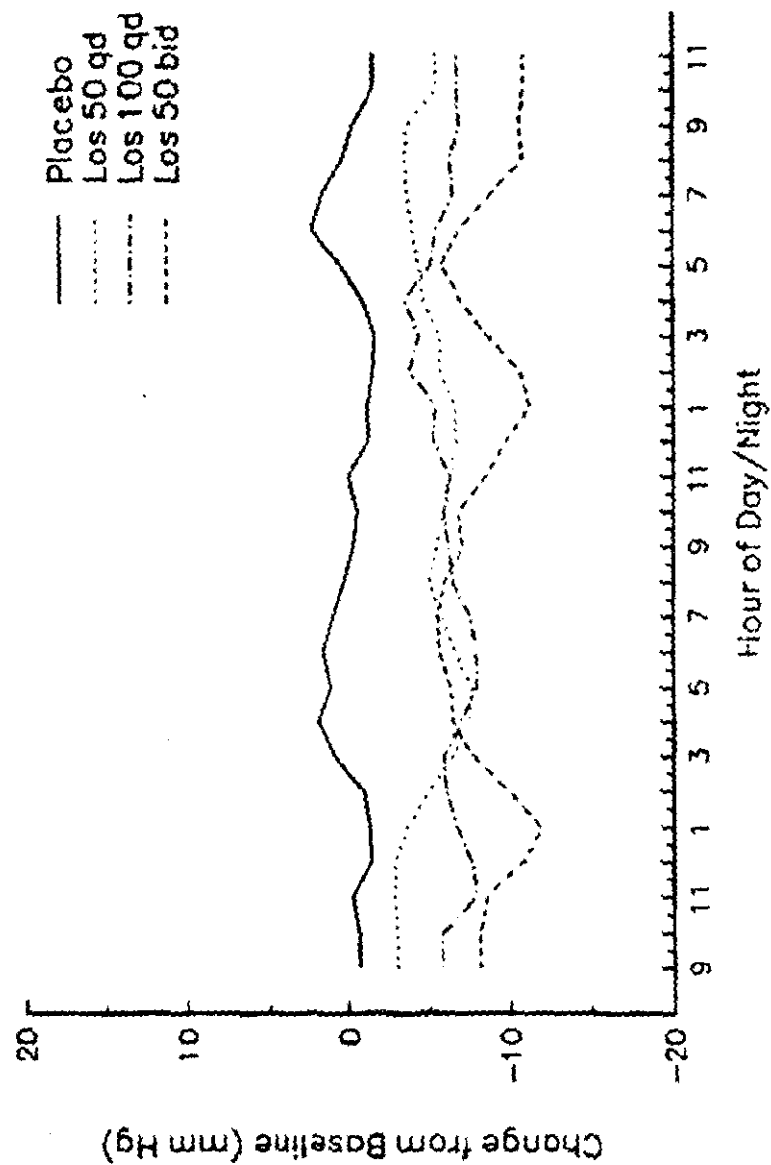


Table 21.6 and table 21.7 lists the mean change in trough siDBP and siSBP at week 4 for sphygmomanometer measurements. The results are similar to ABPM measured 24 hour means except that the changes in all groups are numerically greater with sphygmomanometer measurements and the losartan 100 mg effect on siDBP is now numerically greater than the losartan 50 mg bid effect.

Table 21.6. Mean Changes in Sitting Diastolic Blood Pressure (mmHg) at Week 4 (sphygmomanometer measurements)

Treatment	N	Baseline		Week 4		Change		Change	Comparison		
		Mean	S.D.	Mean	S.D.	Mean	S.D.		vs. B	vs. C	vs. D
Placebo (A)	30	100.3	3.6	98.2	7.5	-2.1	6.9	-2.1	*	**	**
Los 50 QD (B)	29	100.0	4.6	93.3	9.0	-6.7	7.8	-6.7	-	NS	NS
Los 100 QD (C)	28	101.1	4.8	91.5	8.8	-9.6	6.5	-9.7	-	-	NS
Los 50 BID (D)	30	101.4	4.7	92.6	8.7	-8.8	7.8	-8.6	-	-	-

NS - Not Statistically Significant, * - Treatment Difference Statistically Significant, P<0.05

** - Treatment Difference Statistically Significant, P<0.01. Pairwise comparisons are based upon adjusted means.

Table 21.7 Mean Changes in Sitting Systolic Blood Pressure (mmHg) at Week 4 (sphygmomanometer measurements)

Treatment	N	Baseline		Week 4		Change		Comparison			
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Adj Mean	vs. B	vs. C	vs. D
Placebo (A)	30	149.3	14.9	149.7	13.2	0.3	12.2	-2.3	*	**	**
Los 50 QD (B)	29	158.2	17.7	146.5	17.5	-11.7	14.2	-10.3	-	NS	NS
Los 100 QD (C)	28	149.4	12.5	138.9	15.9	-10.5	13.6	-12.9	-	-	NS
Los 50 BID (D)	30	155.5	14.8	141	14.1	-14.5	15.1	-14.4	-	-	-

NS -- Not Statistically Significant, * -- Treatment Difference Statistically Significant, P<0.05

** -- Treatment Difference Statistically Significant, P<0.01; Pairwise comparisons are based upon adjusted means.

For those patients who received HCTZ after week 4, there was an additional reduction in siDBP of 4.8 mmHg to 6.5 mmHg. This result in itself is unimpressive since this phase was essentially not blinded for the investigator.

Safety

One patient from each treatment group withdrew from monotherapy due to adverse events. One additional patient in the losartan 100 mg group withdrew after HCTZ was added. Table 21.7a lists the patients withdrawn for adverse events.

Table 21.7a. Withdrawals for Adverse Events

Patient #	Treatment	Day Withdrawn	Reason for Withdrawal
35	placebo	10	Myocardial Infarction
160	losartan 100 mg	20	tinnitus and headache
81	losartan 50 mg	completed 4 weeks	sexual dysfunction*
11	losartan 50 mg bid	3	diarrhea and nausea
88	losartan 100 mg + HCTZ, 12.5 mg	39	ataxia

* present during baseline period also

The incidence of patients experiencing adverse events was 46.9%, 37.9%, 29% and 33.3% in the placebo, losartan 50 mg, losartan 50 mg bid and losartan 100 mg groups respectively (monotherapy). Table 21.8 lists all adverse experiences with an incidence of greater than 4% in any one treatment group. Four percent was chosen as the cutoff because this would require at least 2 patients within a treatment group experience the adverse event.

Table 21.8 Most Common Clinical Adverse Experiences (Patient Incidence > 4% in Any One Treatment Group)

	Placebo (N=32)	Losartan 50 QD (N=29)	Losartan 100 QD (N=30)	Losartan 50 BID (N=31)
Monotherapy	n (%)	n (%)	n (%)	n (%)
Dyspepsia	1 (3.1)	2 (6.9)	0	0
Headache	3 (9.4)	1 (3.4)	4 (13.3)	2 (6.5)
URI	2 (6.3)	0	1 (3.3)	3 (9.7)
Pharyngitis	1 (3.1)	2 (6.9)	0	0
Congestion, Nasal	0	0	2 (6.7)	1 (3.2)
Monotherapy + Combination therapy				
Headache	4 (12.5)	1 (3.4)	5 (16.7)	6 (19.4)
Dizziness	0	2 (6.9)	1 (3.3)	1 (3.2)
URI	2 (6.3)	1 (3.4)	1 (3.3)	5 (16.1)
Pharyngitis	1 (3.1)	2 (6.9)	0	1 (3.2)
Congestion, Nasal	0	0	2 (6.7)	2 (6.5)
Asthenia/Fatigue	1 (3.1)	1 (3.4)	0	2 (6.5)
Edema	2 (6.3)	0	0	0
Pain, Chest	2 (6.3)	0	0	0
Dyspepsia	1 (3.1)	2 (6.9)	0	0
Pain, Back	0	0	2 (6.7)	0

Two losartan 50 mg bid patients (82 and 103) had mildly elevated ALT and AST. Both patients were receiving lovastatin. Mean uric acid levels tended to decrease with therapy.

Mean pulse did not differ significantly from baseline with losartan treatment.

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Clinical Pharmacology Trials						
Study #	Design/ Patient Population	Treatment Groups	N	Primary Endpoint	Other Measures	Page
001	- ol, single dose (multiple single oral doses separated by approximately 1 week) - healthy male subjects	- placebo - losartan 2.5 mg - losartan 5.0 mg - losartan 10 mg - losartan 20 mg - losartan 40 mg Total Enrolled	6 2 2 6 8 7 8	- blunting of angiotensin I pressor response	- neurohormones - losartan levels	78
002	- ol, single dosing, 8 day dosing, pc - healthy male subjects	- placebo - losartan 5.0 mg - losartan 10 mg - losartan 20 mg - losartan 40 mg Total Enrolled	6 6 6 5 6 29	- blunting of angiotensin II pressor response	- neurohormones - losartan levels	78
003	- single dose, pc, db, single center (each subject received 3 active and 1 placebo dose) - healthy male Caucasians or Hispanics	- placebo - losartan 10 mg - losartan 20 mg - losartan 40 mg - losartan 80 mg - losartan 120 mg - losartan 150 mg - losartan 200 mg - losartan 250 mg - losartan 300 mg Total Enrolled	? 7 7 15 9 15 8 8 15 7 34	- pharmacokinetics and pharmacodynamics	- urinary Na and K - baseline renin	79
004	- r, db, single center, pc, escalating single dose (each subject received 4 active and 1 placebo dose separated by 1 week) - hypertensive caucasian or hispanic males or females	- placebo - losartan 5 mg - losartan 10 mg - losartan 20 mg - losartan 40 mg - losartan 60 mg - losartan 80 mg - losartan 100 mg - losartan 120 mg Total Enrolled	18 10 8 10 8 10 8 10 8 18	- change in blood pressure	- pharmacokinetics	84
006	- ol, single dose - healthy males	- placebo - losartan 40 mg - losartan 80 mg - losartan 120 mg Total Enrolled	7 6 7 6 7	- blunting of angiotensin II pressor response	- neurohormones - losartan levels	87
007	- db, single center, pc, 7 days treatment - healthy males	- placebo - losartan 100 mg Total Enrolled	4 10 14	- compare pharmacokinetics on day 9 versus day 1	- neurohormones - urinary excretion of Na ⁺ and K ⁺	88
013	- db, pc, single dose 20 minute intravenous infusion - healthy males	- placebo - losartan 1 mg - losartan 10 mg - losartan 20 mg - losartan 40 mg Total Enrolled	9 6 6 6 6 18	- pharmacokinetics		93
015	- ol, r, 2-period co, single dose - healthy males	- losartan 100 mg	8	- change in pharmacokinetics with food	- neurohormone levels	94
017	- db, pc, r, rising single dose infusion of E-3174 - healthy males	- placebo - E-3174 .1 mg i.v. - E-3174 .5 mg i.v. - E-3174 1 mg i.v. - E-3174 5 mg i.v. - E-3174 10 mg i.v. - E-3174 20 mg i.v. - E-3174 40 mg i.v. - E-3174 80 mg i.v. Total Enrolled	17 6 7 6 6 6 6 6 6 6 19	- pharmacokinetics		96

Clinical Pharmacology Trials (continued)						
Study #	Design/ Patient Population	Treatment Groups	N	Primary Endpoint	Other Measures	Page
019	- r, db, pc, 4 period co, single dose - healthy, non-black males on sodium restricted (40 mmole/day) and furosemide	- placebo - losartan 5 mg - losartan 10 mg - losartan 25 mg - losartan 50 mg - losartan 100 mg Total Enrolled	12 4 5 7 9 8 14	- change in supine SBP	- change in supine and standing blood pressure - neurohormones	99
022	- 3 period co, single dose, losartan 100 mg tablets, capsules and losartan 30 mg i.v. - healthy male	- losartan 100 mg tablets - losartan 100 mg capsules - losartan 30 mg i.v. Total Enrolled	8 8 8 8	- bioequivalence		97
023	- r, db, pc, single dose, 2 - period co (crossover based on high and low salt diet) - healthy, non-black males	- placebo - losartan 100 mg	8 16	- renal hemodynamics and tubular function		101
024	- 2 period co cimetidine interaction study - healthy male subjects	- losartan 100 mg - losartan 100 mg + cimetidine 400 mg q6 hr. Total Enrolled	8 8 16	- pharmacokinetics		100
033	- r, db, pc, 4-period co, single dose - healthy male	- losartan 100 mg - losartan 20 mg - enalapril 10 mg - placebo Total Enrolled	8 8 8 8 8	- inhibition of the pressor response of angiotensin I and II in the dorsal hand vein		105
034	- r, db, pc, 4-period co single dose - healthy non-black males - low salt diet (40 mmol/day) + furosemide 40 mg bid and replete salt diet (100 mmol salt/day + 40mmol salt diet)	- losartan 100 mg - placebo Total Enrolled	12 12 12	- autonomic function 4 hours post dose	- 24 hour urine excretion - plasma renin activity, All, aldosterone, NE, Epi., drug concentrations	108
035	- r, db, pc, 4 period co single dose - healthy males	- placebo - losartan 20 mg - losartan 100 mg - enalapril 20 mg Total Enrolled	9 9 9 9 9	- forearm blood flow response to intraarterial infusions of angiotensin I, angiotensin II and bradykinin		112
043	- r, db, pc, ac, 6 wk Rx period - non-black hypertensives	- losartan 25 mg od - losartan 100 mg od - placebo - enalapril 20 mg od	11 14 12 14	- plasma renin - plasma angiotensin II	- losartan levels - E-3174 levels - plasma and urine aldosterone - plasma and urine NE and Epi. - supine DBP and SBP - rebound hypertension	128
060	- o, 3 period co - healthy males - losartan doses labeled with ¹⁴ C	- losartan 100 mg oral - losartan 30 mg i.v. - E-3174 20 mg i.v. Total Enrolled	6 6 6 6	- pharmacokinetics		114
067	- o, 3 period co - patients with hepatic insufficiency	- losartan 50 mg oral - losartan 10 mg i.v. - E-3174 10 mg i.v. Total Enrolled	9 9 9 9	- pharmacokinetics		115

Clinical Pharmacology Trials (continued)						
Study #	Design/ Patient Population	Treatment Groups	N	Primary Endpoint	Other Measures	Page
070	- db, pc, 2-period co, 14 day treatment period - healthy males - 30 mg warfarin on day 7 of each period	- losartan 100 mg - placebo Total Enrolled	10 10 10	- warfarin enantiomer pharmacokinetics	- change in prothrombin time	119
072	- sb, 2 period, ad, phenobarbital interaction study - healthy males - Rx included single dose of losartan then 14 day of phenobarbital followed by single dose of losartan or placebo	- losartan 100 mg - placebo	10 5	- pharmacokinetics		117
074	Refer to Biopharm Review					
075	Refer to Biopharm Review					
079	- db, r, pc, 2-period co, 15 day treatment - healthy male subjects - digoxin .5 mg i.v. on day 4 and digoxin .5 mg orally on day 11	- losartan 50 mg - placebo Total Enrolled	13 13 13	- digoxin pharmacokinetics		127
012	- ol, nc, 2 center, 7 day Rx period - hypertensives with renal insufficiency - includes hemodialysis patients	- losartan 100 mg daily		pharmacokinetic parameters (losartan and E-3174)	- plasma renin - plasma aldosterone - urine creatinine clearance - urine sodium, urea nitrogen - hemodynamics	165
018	- sb, 4 wk Rx period - female hypertensives	- losartan 50 mg	16	- change in prostaglandin excretion (PGE ₂ , prostacyclin, thromboxane A ₂)	- renin - aldosterone	132
069	- r, db, pc, single i.v. dose of E-3174 - non-black hypertensives	- placebo - E-3174 i.v.	8 12	Relationship between blood pressure changes and plasma levels of E-3174	- plasma renin - creatinine clearance	136
057	NO DATA PROVIDED					
063	- o, 2-period co, single center - elderly hypertensives (≥ 65 years)	- losartan 50 mg oral - losartan 10 mg i.v. Total Enrolled	10 10 10	- pharmacokinetics	- change in blood pressure	122

wk = week, db = double-blind, ol = open label, od = once a day, bid = twice a day, r = randomized, ac = active control, pc = placebo control, nc = no control, p = parallel, co = crossover, hx = history, HTN = hypertension, ACEI = angiotensin converting enzyme inhibitor, NE = norepinephrine, Epi = epinephrine, PRA = plasma renin activity, Rx = treatment

Study 001.

This open label trial of 8 healthy male subjects attempted to show that single doses of losartan blunt the pressor response of angiotensin I infusions. This trial was reviewed in the original IND application. Patients received multiple intravenous infusions of angiotensin I until a dose that increased supine systolic blood pressure by 20 - 30 mmHg was determined. Single doses of placebo and losartan were administered and angiotensin I infusions were repeatedly administered over time. The change in blood pressure was measured with each infusion. Each patient was to receive a single dose of placebo and 3 single doses of either losartan 2.5 mg, 5 mg, 10 mg, 20 mg or 40 mg (oral solution lot # 88 RM 018). Each dose was separated by 1 week. There were some deviations from the protocol by the investigator that do not impact the outcome of the trial. The following results were obtained.

- 1) Losartan doses of 10 mg or greater blunted the angiotensin I pressor response.
- 2) Pre-angiotensin I challenge systolic blood pressure increased after losartan dosing. It is unclear whether this is due to a losartan agonist effect.
- 3) Immunoreactive angiotensin II increased with losartan treatment.

Study 002.

This was an open label trial in 29 healthy male subjects (24 Caucasians, 3 blacks, 1 Asian, 1 Arab) that attempted to show that losartan (multiple doses) blunts the pressor response of angiotensin II infusions. The amount of angiotensin II infusion required to increase systolic blood pressure by 20 - 30 mmHg was determined during the week prior to treatment. Subjects received a single dose of either placebo or losartan (5 mg, 10 mg, 20 mg, 40 mg). This was followed by multiple infusions of angiotensin II on day 1, 4 and 8 [pre-dose, 6, 12 (except day 4) and 24 hours post-dose] of treatment during which blood pressure changes were measured. The following results were obtained.

- 1) Losartan blunted the pressor response of angiotensin II predominantly at 6 and 12 hours with some effect apparent at 24 hours.
- 2) Plasma renin and immunoreactive angiotensin II increased post losartan dosing (table 2.1. and table 2.2.)

Table 2.1. PLASMA RENIN ACTIVITY (ng/ml/h)

Dose (mg)		Time Relative to Dosing			
		Day 1		Day 8	
		0 hrs	6 hrs	0 hrs	6 hrs
Placebo	N	6	6	6	6
	MEAN	0.79	1.09	0.96	1.16
	STDERR	0.28	0.23	0.19	0.25
5	N	6	6	6	6
	MEAN	0.99	2.00	1.29	2.57
	STDERR	0.37	0.59	0.33	0.62
10	N	6	6	6	6
	MEAN	1.18	3.31	1.75	3.80
	STDERR	0.24	0.88	0.36	0.95
20	N	5	5	5	5
	MEAN	1.00	4.24	2.02	6.78
	STDERR	0.16	0.91	0.47	2.06
40	N	6	6	6	6
	MEAN	0.77	4.18	2.30	8.93
	STDERR	0.12	1.17	0.29	1.00

Table 2.2. Immunoreactive-ANGIOTENSIN II (pg/ml)

Dose (mg)		Time Relative to Dosing			
		Day 1		Day 8	
		0 hrs	6 hrs	0 hrs	6 hrs
Placebo	N	6	6	6	6
	MEAN	4.08	6.72	4.73	6.63
	STDERR	1.07	1.53	1.11	1.42
5	N	6	6	6	6
	MEAN	6.45	13.95	7.47	18.02
	STDERR	2.33	5.09	2.19	5.15
10	N	6	6	6	6
	MEAN	9.30	18.98	9.36	18.90
	STDERR	1.77	5.01	1.77	5.01
20	N	5	5	5	5
	MEAN	5.62	20.82	11.44	35.24
	STDERR	0.78	4.10	2.59	9.80
40	N	6	6	6	6
	MEAN	4.38	21.47	13.55	49.50
	STDERR	0.73	4.84	1.88	7.05

- 3) Aldosterone and epinephrine remained unchanged compared to placebo.
- 4) No serious adverse events were reported.
- 5) Losartan levels were essentially non-detectable for doses less than 40 mg. For losartan 40 mg, levels were detectable at 3 and 6 hours post dose. E-3174 levels were detectable up to 12 hours post-dose. (see table 2.3)

Table 2.3. Losartan and E-3174 Concentrations

	losartan concentrations (ng/ml)							E-3174 concentrations (ng/ml)						
	Hour	losartan 20 mg			losartan 40 mg			Hour	losartan 20 mg			losartan 40 mg		
		Mean	S.D.	Range	Mean	S.D.	Range		Mean	S.D.	Range	Mean	S.D.	Range
Day 1	0	0	0	bql	0	0	bql	0	0	0	bql	0	0	bql
	3	22.4	13.2	bql - 35.2	31.2	8.1	22.1 - 45.3	3	68.3	23.7	31.9 - 91.7	181	88.3	75.5 - 292.1
	6	5.1	11.5	bql - 25.6	6	14.6	bql - 35.8	6	93	63.6	37.7 - 195.5	151.3	60.7	86.1 - 249.5
	12	0	0	bql	0	0	bql	12	22.8	16.5	bql - 38.3	56	10.9	42 - 70.1
	24*	0	0	bql	0	0	bql	24*	0	0	bql	0	0	bql
Day 4	72*	0	0	bql	0	0	bql	72*	0	0	bql	0	0	bql
	75	13	17.7	bql - 32.5	38.9	14.9	24.1 - 64.3	75	90.2	63.7	36.1 - 200.8	182.7	84.6	86.1 - 320.7
	78	0	0	bql	0	0	bql	78	73.9	22.4	44.8 - 95.1	131.3	34.6	85.9 - 167
	84	0	0	bql	0	0	bql	84	18.9	17.3	bql - 32.5	48.2	11.2	37.4 - 64.6
Day 8	168*	0	0	bql	0	0	bql	168*	0	0	bql	3.5	8.7	bql - 21.2
	171	0	0	bql	29.2	19.9	bql - 55.5	171	94.2	32.6	56.5 - 137.8	186	97.1	92.3 - 326.5
	174	0	0	bql	5.3	12.9	bql - 31.6	174	81.4	18.8	65.3 - 111.8	160.3	54.3	118.1 - 237
	180	0	0	bql	0	0	bql	180	27.3	15.9	bql - 39.9	56.3	25	33.7 - 96.6
Day 9	192	0	0	bql	0	0	bql	192	0	0	bql	0	0	bql
	198	0	0	bql	0	0	bql	198	0	0	bql	0	0	bql
	204	0	0	bql	0	0	bql	204	0	0	bql	0	0	bql

bql = below quantifiable limit, * = pre-dose (trough)

Study 003.

Protocol

The study was conducted in a single center employing a double-blind, placebo-controlled design. The study enrolled healthy male subjects. Each subject received four single-dose treatments of study drug (three active, one placebo) in rising dose order with respect to active drug and placebo inserted into the sequence according to a random allocation schedule. A one-week washout period was maintained between treatments, resulting in a per subject study duration of five weeks. There were four treatment groups with Group 1 receiving single doses of 10 mg, 20 mg, and 40 mg; Group 2 receiving doses of 40 mg, 80 mg, and 120 mg; Group 3 receiving 120 mg, 150 mg, and 200 mg; and Group 4 receiving 200 mg, 250 mg, and 300 mg. Prior to the start of the active treatment periods, each subject received a single dose of placebo (open-label) and blood pressure and ECG recording were measured for a 24 hour period. These measurements were treated as baseline values.

Table 3.1 outlines the clinical procedures and laboratory measurements performed during the study.

Table 3.1. Procedures

EVALUATION	Days	PLACEBO PHASE***									TREATMENT GROUP 1-4							Post
		-9	-8	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	
	Screen										7	8	9	10	11	12	13	
											14	15	16	17	18	19	20	
											21	22	23	24	25	26	27	
Medical History	X																	
Physical Exam	X																	
12-Lead ECG	X		X	X								X	X					
BP Measure	X		X	X								X	X					
Vital Signs	X		X	X								X	X					
Lab Tests	X											X	X					
Drug Screens	X	X									X							
Plasma Samples												X	X					
Urine Samples												X	X					
Drug Administration			P									X						

P = Placebo only

*** = Placebo phase occurs one week prior to the start of each treatment group, respectively. BP and vital signs measured only through 24 hours post dose.

12-Lead ECG: Prior to each dose administration and at 3, 6, 12, and 24 hours post dose.

BP and Vital Signs: 1, 0.75, 0.5, 0.25 hours, and immediately prior to each dose administration and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, 23, 24, 28, 32 and 36 hours post dose.

Clinical Labs: Prior to each dose administration and prior to discharge from clinic after plasma samples and BP measurements completed.

Losartan PK profile: At 0 (pre-dose), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 30 hours post-dose.

Urine collection intervals: Pre-dose, 0-2, 2-4, 4-12, 12-24 and 24-36 hours post-dose.

Effect of Losartan dose on urinary excretion of sodium (Na), potassium (K) and creatinine (Cr) was explored. Excretion per hour was calculated for each parameter and displayed for each subject by collection interval and by total excreted over 24 hours. Glomerular filtration rate (GFR) was estimated from total Cr excreted in 24 hours divided by plasma creatinine concentration post-dose.

Descriptive pharmacokinetic parameters were determined based on the plasma concentration-time data. Pharmacokinetic parameters and their methods of estimation are presented in table 3.1a.

Table 3.1a. Pharmacokinetic Parameters Definitions

Parameter	Definition
C _{max}	observed maximum plasma concentration
T _{max}	time C _{max} is observed
AUC	area under the plasma concentration-time curve from time zero to infinity. The AUC from time zero to the last quantifiable concentration time point was calculated by the linear trapezoidal rule. The residual area was estimated from the calculated concentration (linear regression) at the last quantifiable concentration time divided by λ . If the calculated concentration was not available (i.e. subject failed the criteria for half-life determination), the observed concentration was used.
Half-life ($t_{1/2}$)	the 'apparent' disposition or terminal $t_{1/2}$. It is calculated as $\ln 2/\lambda$, where λ is the absolute value of the terminal slope from linear regression of natural logarithm of plasma concentrations versus time. The number of concentration-time points used for regression analysis was based on the goodness of fit and on the coefficient of determination (r^2) which had to be equal to or exceeding 0.90. If these criteria were not met and a terminal slope was required in a subsequent calculation (i.e. estimating AUC), then the mean of the terminal slopes from other doses of the same subject was used as the best estimate.

Data are expressed as arithmetic mean $\pm$ standard deviation (S.D.) unless otherwise indicated. The harmonic mean was calculated for $t_{1/2}$ along with a pseudo S.D. based on the jackknife variance technique.^[3] The median and range were calculated for T_{max}. When calculating mean and S.D., bql (below quantifiable limit for the assay) was treated as zero. If all values were bql, the mean concentration was reported as zero. The bql for Losartan was 20 ng/mL and for E-3174 the bql was 17 ng/mL.

Results

The study was conducted with a total of 34 enrolled subjects. All subjects were male caucasian. The subjects ranged in age from 19 to 47 years with a median age of 32.5 years. Five subjects discontinued the study prematurely. Table 3.2 lists the reasons for discontinuation.

Table 3.2. Patients Discontinued Prematurely

Subject #	Last Treatment	Reason Discontinued
#17	open label placebo	Adverse Event - cellulitis
#30	open label placebo	Positive hepatitis A IgM
#10	not provided	protocol violation - erroneous report of alcohol use
#5	20 mg	adverse event - persistent headache (negative rechallenge)
#115	200 mg	adverse event - severe orthostatic hypotension 8 hours post dosing

Table 3.3 lists the pharmacokinetic results for losartan and E-3174. The harmonic mean elimination half-life for losartan ranged between .9 and 1.6 hours. Increases in mean C_{max} were slightly greater than expected for the percentage increase in dose. AUC increased dose proportionally. The harmonic mean elimination half-life for E-3174 ranged between 3.9 and 5.5 hours (excluding the 10 mg dose group - only one patient's values could be measured). As with losartan, increases in mean C_{max} were slightly greater than expected for the percentage increase in dose. AUC increased dose proportionally.

Table 3.3. Pharmacokinetic Parameters

Dose (mg)		Losartan					E-3174				
		C _{max} (ng/mL)	T _{max} (hr)	AUC (ng-hr/mL)	λ(n) (hr ⁻¹)	t _{1/2} ^b (hr)	C _{max} (ng/mL)	T _{max} (hr)	AUC (ng-hr/mL)	λ(n) (hr ⁻¹)	t _{1/2} ^b (hr)
10	Mean	21.1	1.00	94.1	0.4418	1.6	30.3	6.00	434.3	0.0393	17.6
	S.D.	15.9	(0.25-1.50)	NA	NA	NA	15.8	(4.0-8.0)	178.0	NA	NA
	n	7	5	2	2	2	7	6	6	1	1
20	Mean	71.6	0.50	337.8	0.7437	0.9	66.4	4.00	777.9	0.1266	5.5
	S.D.	35.2	(0.5-2.0)	17.9	0.5327	0.7	35.4	(3.0-6.0)	122.8	0.0182	0.8
	n	7	7	7	4	4	7	6	6	6	6
40 ^c	Mean	214.8	0.75	391.5	0.4539	1.5	186.7	4.00	1723.8	0.1607	4.3
	S.D.	123.4	(0.5-1.5)	225.1	0.2062	0.7	80.9	(3.0-4.0)	509.2	0.0460	1.3
	n	15	15	15	14	14	15	14	14	14	14
80	Mean	537.5	0.75	932.7	0.5262	1.3	480.6	3.00	3639.3	0.1669	4.1
	S.D.	226.1	(0.5-1.5)	519.2	0.2269	0.6	181.5	(2.0-4.0)	1451.7	0.0390	1.0
	n	8	8	8	7	7	8	8	8	8	8
120 ^c	Mean	866.5	1.00	1277.7	0.6111	1.2	907.7	2.00	5333.7	0.1781	3.9
	S.D.	371.3	(0.5-1.5)	572.7	0.2974	0.6	206.2	(1.5-3.0)	1664.1	0.0715	1.6
	n	15	15	15	15	15	15	15	15	15	15
150	Mean	1141.1	1.00	1678.0	0.4029	1.7	1241.6	1.75	6806.9	0.1610	4.3
	S.D.	364.3	(0.5-2.0)	296.6	0.1194	0.5	236.2	(1.5-3.0)	1735.2	0.0672	1.9
	n	8	8	8	8	8	8	8	8	8	8
200 ^c	Mean	2177.3	0.75	2371.6	0.4636	1.5	1718.5	1.50	8118.6	0.1454	4.8
	S.D.	826.8	(0.5-1.5)	704.1	0.2471	0.8	452.5	(1.0-3.0)	2110.3	0.0445	1.5
	n	15	15	15	15	15	15	15	15	15	15
250	Mean	2118.7	1.00	2567.3	0.5410	1.3	2039.9	2.00	9057.8	0.1693	4.1
	S.D.	1442.6	(0.5-2.0)	1062.1	0.3758	1.1	639.3	(1.5-2.0)	2910.9	0.0647	1.6
	n	7	7	7	7	7	7	7	7	7	7
300	Mean	2870.3	0.50	3492.4	0.5471	1.3	2327.1	2.00	10546.6	0.1426	4.8
	S.D.	1659.8	(0.5-1.0)	1593.8	0.3696	0.9	669.5	(1.5-3.0)	3219.1	0.0233	0.8
	n	7	7	7	7	7	7	7	7	7	7

a = Median and range.

b = Harmonic mean and pseudo standard deviation based on the jackknife variance.

c = Mean and S.D. of all subjects in two groups for this dose.

NA. Not applicable.

Figures 3.1 and 3.2 show the concentration versus time plots for losartan (Dul' 753) and the metabolite E-3174.

Figure 3.1.

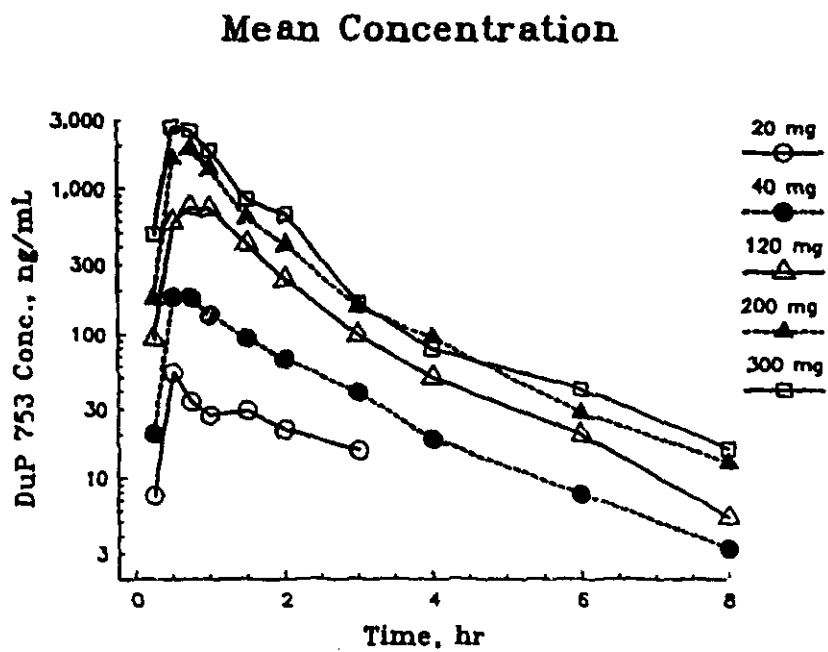


Figure 3.2.

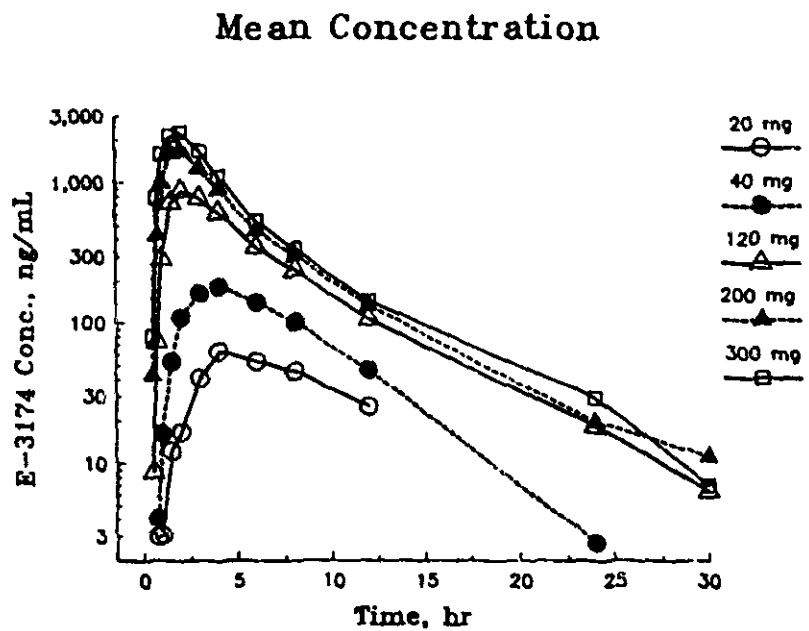


Figure 3.3 and 3.4 show the individual C_{max} values for losartan and E-3174 concentrations at each dose.

Figure 3.3.

FIGURE 3
Cmax for DuP 753 vs. DuP 753 Dose

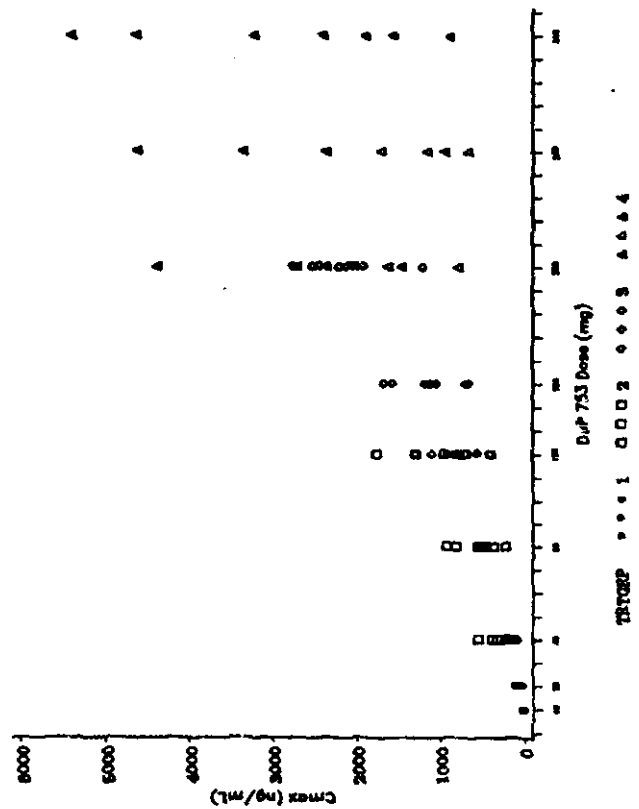
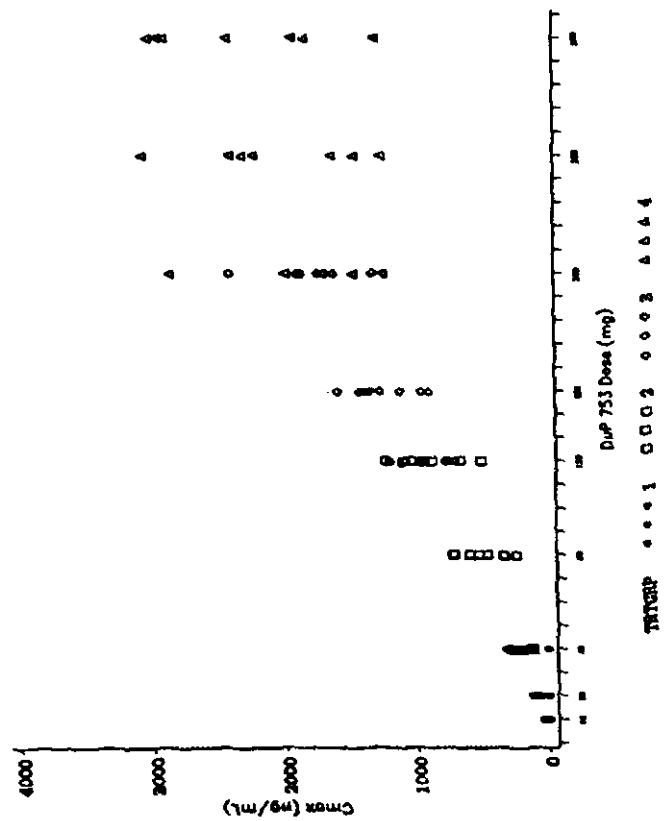


Figure 3.4.

FIGURE 4
Cmax for E-3174 vs. DuP 753 Dose



For the most part, adverse events were unremarkable. Subject #2 had three instances of maculopapular rash on the palms; one instance occurred 3 days after dosing while the other 2 occurred 6 days after dosing. One subject (#15, Group 2) had a laboratory adverse experience. Hematuria was reported after the 0 mg dose which was mild.

There was no significant change in sodium excretion, potassium excretion or in creatinine clearance.

Study 004.

Protocol

This was a single center, randomized, double-blind, placebo controlled trial in 18 hypertensive patients. To be enrolled, patients had to have a supine DBP 95 - 115 mmHg on three consecutive screening visits. None of the screening DBP could be > 5 mmHg from the mean of the three screening measurements. There were two treatment groups with Group 1 receiving single doses of 5 mg, 20 mg, 60 mg and 100 mg and Group 2 receiving doses of 10 mg, 40 mg, 80 mg, and 120 mg. Group 1 and Group 2 patients were staggered in enrollment by three days so that preliminary safety and tolerance data on the lower doses were available before giving the next higher dose.

Table 4.1 summarizes the dosing sequence of the active phase of the study for Group 1 and Group 2, respectively:

Table 4.1. Treatment Allocations (dose expressed in mg)

Group 1

Dosing Sequence	Period				
	P1	P2	P3	P4	P5
S1	PLACEBO	5	20	60	100
S2	5	PLACEBO	20	60	100
S3	5	20	PLACEBO	60	100
S4	5	20	60	PLACEBO	100
S5	5	20	60	100	PLACEBO

Group 2

Dosing Sequence	Period				
	P1	P2	P3	P4	P5
S1	PLACEBO	10	40	80	120
S2	10	PLACEBO	40	80	120
S3	10	40	PLACEBO	80	120
S4	10	40	80	PLACEBO	120
S5	10	40	80	120	PLACEBO

Prior to the active phase, each patient received a single dose of placebo and their blood pressure and ECG recording was obtained for a 24 hour period. Patients advanced to the next higher dose if the previous dose was tolerated. Table 4.2 outlines the clinical procedures and laboratory measurements performed during the study.

Table 4.2. Procedures

12-Lead ECG: Prior to each dose administration and at 3, 6, 12 and 24 hours post-dose.
Vital Signs: At -60, -45, -30, -15 and 0 minutes and at 15, 30, 45, 60, 90 minutes post-dose and at 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, 23, 24, 28, 32, 36 and 48 hours post-dose.
Clinical Labs: Prior to each dose administration and at approximately 24 hours post-dose
DuP 753 PK Profile: Pre-dose, and at 30 minutes, 1, 2, 4, 8, 12, 24, 36 and 48 hours post-dose.
Urine Collection Intervals: Pre-dose and each void for 24 hours post-dose

Results

Eighteen patients enrolled in the active treatment periods. An additional patient had been enrolled in the placebo phase of the study, but this patient was discontinued prior to the start of the active treatment periods. Group 1 consisted of 5 males (4 Hispanic, 1 Caucasian) and 5 females (all Hispanic) and Group 2 consisted of 8 males (5 Hispanic, 3 Caucasian). The patients ranged in age from 32 to 65 years with a median age of 51.5 years. The demographic data is summarized in table 4.3.

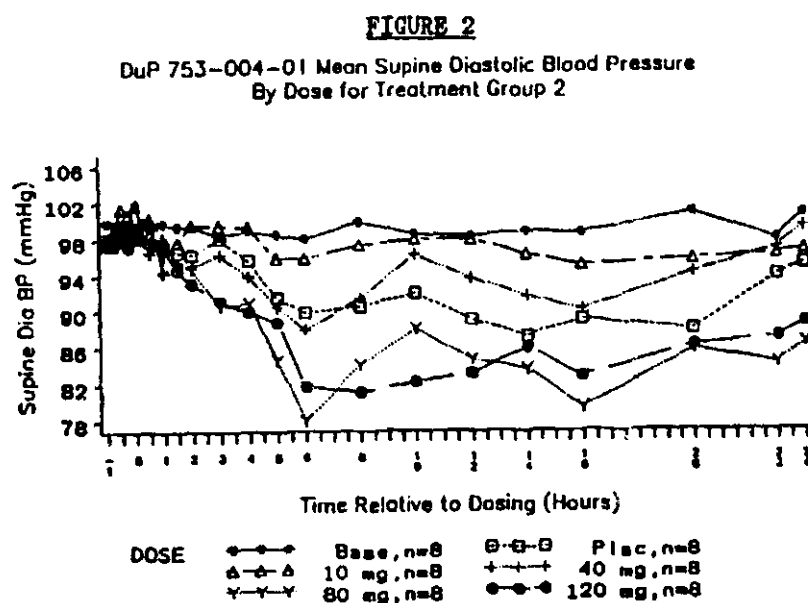
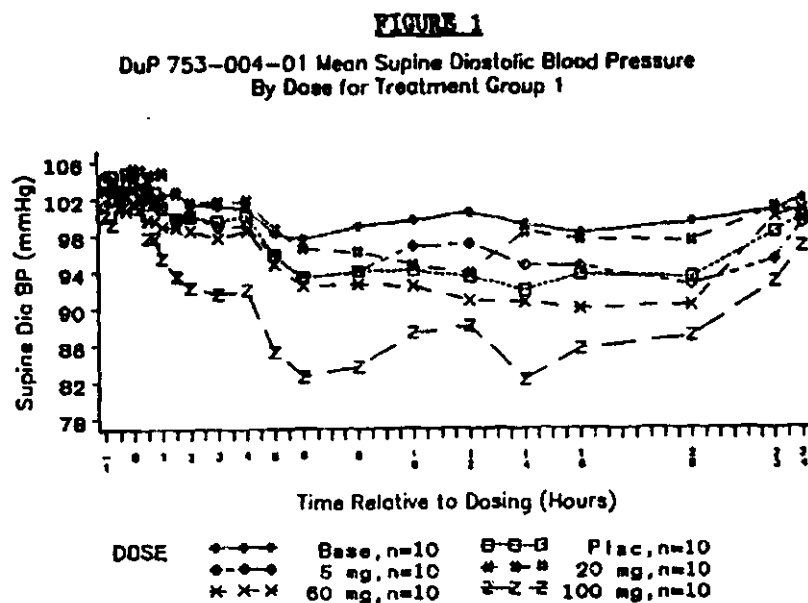
Table 4.3. Demographic Data

	Mean (S.D.)	Median (Min-Max)
Group 1 (n=10)		
Age (Yrs)	49.4 (6.3)	48.6 (37-58)
Weight (kg)	74.0 (13.3)	78.5 (61-99)
Hypertension (Yrs)	9.8 (8.2)	7.7 (1-30)
Group 2 (n=8)		
Age (Yrs)	56.6 (11.2)	61.2 (32-65)
Weight (kg)	85.8 (9.5)	85.7 (69-98)
Hypertension (Yrs)	9.2 (5.1)	8.2 (3-16)

Several models were used to test whether there was a sequence effect that could influence blood pressure outcome. The effect of sequence on pre-dose mean blood pressures was significant for supine DBP and standing SBP in group 2 patients.

The effect of sequence on the change in placebo response was significant for supine and standing DBP and supine SBP. Thus, there appears to be some sequence effect. Since lower doses are given in the early sequences in the escalating dose design, a sequence effect would influence the higher doses more than the lower with placebo somewhere in between. However, keeping in mind the limitations of this design, it is worthwhile to review the effect of dose on blood pressure over time. Figures 4.1 and 4.2 show the change in mean supine DBP over time. There appears to be a larger decrease in DBP with increases in dose.

Figures 4.1 and 4.2. Mean Supine DBP



The effect of dose on SBP are less distinguishable but still tend to be greater with higher doses.

Table 4.4 lists the pharmacokinetic parameters for losartan by dose. The mean (harmonic) elimination half life is approximately 1 hour. There is a linear relationship between C_{max} and dose but the relationship is not proportional. There is a linear relationship between AUC and dose that is proportional (e.g. a doubling of dose results in a doubling of the AUC).

Table 4.4. Pharmacokinetic Parameters for Losartan

Dose (mg)		C _{max} (ng/mL)	T _{max} (hr)	AUC (ng·hr/mL)	Cl _o (L/min)	λ(n) (hr ⁻¹)	t _{1/2} (hr)
5	Mean	12.5	0.75	NA	NA	NA	NA
	S.D.	17.1	(0.5-2.0)	NA	NA	NA	NA
	n	10	4	NA	NA	NA	NA
10	Mean	36.7	0.5	116.3	1.594	NA	NA
	S.D.	24.1	(0.5-1.0)	41.6	0.576	NA	NA
	n	8	7	5	5	NA	NA
20	Mean	124.5	0.5	381.2	1.229	0.500	1.4
	S.D.	63.8	(0.5-2.0)	245.8	0.786	0.273	0.9
	n	10	10	7	7	5	5
40	Mean	206.5	0.5	403.4	1.792	0.498	1.4
	S.D.	130.3	(0.5-1.0)	143.0	0.472	0.244	0.8
	n	8	8	8	8	6	6
60	Mean	521.1	0.5	876.8	1.287	0.677	1.0
	S.D.	225.1	(0.5-1.0)	280.4	0.563	0.411	0.7
	n	10	10	10	10	9	9
80	Mean	471.8	1.0	882.4	1.609	0.558	1.2
	S.D.	257.8	(0.5-1.0)	212.0	0.476	0.205	0.5
	n	8	8	8	8	8	3
100	Mean	863.0	0.75	1533.9	1.367	0.664	1.0
	S.D.	466.8	(0.5-2.0)	789.4	0.729	0.311	0.5
	n	10	10	10	10	10	10
120	Mean	811.0	0.75	1409.1	1.490	0.684	1.0
	S.D.	298.3	(0.5-1.0)	322.1	0.363	0.253	0.4
	n	8	8	8	8	8	8

a Median and Range, b Harmonic mean and pseudo standard deviation based on jackknife variance.
c Not available.

Table 4.5 list the pharmacokinetic parameters for E-3174. C_{max} increases linearly with dose but not proportionally. AUC increases linearly with dose.

Table 4.5. Pharmacokinetic Parameters for E-3174

Dose (mg)		C _{max} (ng/mL)	T _{max} (hr)	AUC (ng·hr/mL)	Cl _o (L/min)	λ(n) (hr ⁻¹)	t _{1/2} (hr)
5	Mean	7.2	8.0	288.4	NA	NA	NA
	S.D.	11.8	(4.0-12.0)	107.4	NA	NA	NA
	n	10	3	2	NA	NA	NA
10	Mean	39.5	8.0	526.1	NA	NA	NA
	S.D.	12.0	(8.0)	123.1	NA	NA	NA
	n	8	8	7	NA	NA	NA
20	Mean	89.9	4.0	955.7	0.125	5.5	5.5
	S.D.	44.6	(4.0-8.0)	413.5	0.056	2.8	2.8
	n	10	10	10	6	6	6
40	Mean	198.6	4.0	2113.4	0.132	5.2	5.2
	S.D.	50.0	(4.0)	698.0	0.027	1.1	1.1
	n	8	8	8	7	7	7
60	Mean	486.5	4.0	3563.0	0.200	3.5	3.5
	S.D.	234.2	(1.0-8.0)	1075.9	0.060	1.0	1.0
	n	10	10	10	8	8	8
80	Mean	585.7	4.0	4536.1	0.176	3.9	3.9
	S.D.	237.7	(2.0-4.0)	1360.1	0.047	1.2	1.2
	n	8	8	8	8	8	8
100	Mean	839.0	2.0	5056.6	0.209	3.3	3.3
	S.D.	352.3	(1.0-4.0)	1170.0	0.070	1.1	1.1
	n	10	10	10	10	10	10
120	Mean	1036.7	2.0	6774.4	0.189	4.1	4.1
	S.D.	374.8	(2.0-4.0)	2116.5	0.034	0.8	0.8
	n	8	8	8	8	8	8

a Median and Range, b Harmonic mean and pseudo standard deviation based on jackknife variance.
c Not available.

T_{max} results were not dose dependent for plasma losartan. For plasma E-3174, T_{max} decreased with increasing dose.

There were no serious adverse events reported. The most common laboratory AE was hematuria with 7 occurrences in three patients.

Twenty-four hour urinary excretion of Na, K, and Cr, and of glomerular filtration (creatinine clearance) rate were measured. There was no significant treatment effect.

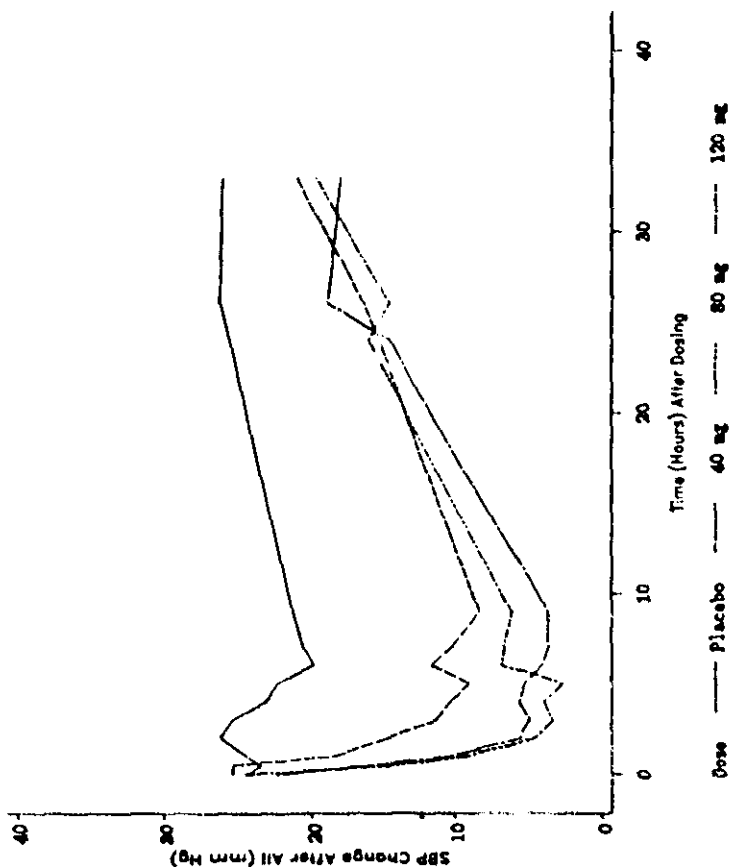
Study 006.

This was an open label trial that attempted to evaluate the ability of losartan 40 mg, 80 mg and 120 mg to suppress the pressor response of infusions of angiotensin II. The methodology is similar to that previously described in study 001 and 002. Subjects received a single dose of placebo, losartan 40 mg, losartan 80 mg and losartan 120 mg. After each dose, infusions of angiotensin II that increased the SBP by 20 - 30 mmHg on no therapy was administered on numerous occasions post dosing. Seven healthy males (5 caucasian, 2 arab) enrolled. The mean age was 24 years. One subject withdrew prematurely due to abdominal cramps.

In study 001, there was data to suggest that the SBP increased post dosing compared to baseline (measured prior to angiotensin I infusion). The concern was that this may suggest losartan has agonist activity (similar to saralasin). In this study, at 30 and 60 minutes post dosing, there was no evidence of an increase in SBP prior to angiotensin II infusion.

Figure 6.1 shows the mean responses to angiotensin II challenges. The suppression of the angiotensin II pressor effect persists for up to 30 hours. A similar response was seen with DBP. Heart rate generally decreases with angiotensin II infusion. After losartan, the decline in heart rate after angiotensin II infusion was less pronounced.

Figure 6.1. Mean Change in SBP in Response to Angiotensin II.



Repeated measures analysis of variance showed that plasma renin activity, ir-angiotensin II, and aldosterone levels were significantly affected by dose ($p < 0.05$). Mean plasma renin, ir-angiotensin II and aldosterone are listed in tables 6.1 - 6.3.

Table 6.1. Plasma renin (ng/ml/h) after Losartan administration

TIME	PLACEBO	Losartan DOSE (mg)		
		40	80	120
PRE-DOSE	0.82	0.73	0.61	0.88
4 hours	1.28	3.23	4.15	10.82
9 hours	1.13	3.50	4.78	10.80
24 hours	1.19	2.09	2.41	3.10
33 hours	0.77	1.83	1.55	1.89

Post-tests showed that plasma renin levels after the 80 mg and 120 mg doses were larger than levels after placebo ($p < 0.05$), and that plasma renin levels after the 120 mg dose were larger than the 40 mg and 80 mg doses ($p < 0.05$). There was no significant difference between plasma renin levels after the 40 mg and 80 mg doses.

Post-tests least square difference (LSD) showed that ir-angiotensin II levels after the 120 mg dose were statistically significantly larger than levels observed after the other doses of Losartan or placebo ($p < 0.05$).

Table 6.2. Plasma ir-angiotensin II (pm) after Losartan administration

TIME	PLACEBO	Losartan DOSE (mg)		
		40	80	120
PRE-DOSE	6.00	7.23	3.43	4.38
4 hours	8.52	22.78	31.13	46.02
9 hours	12.10	21.42	19.02	50.00
24 hours	9.44	12.48	15.93	13.77
33 hours	11.53	10.75	8.73	9.24

Table 6.3. Plasma aldosterone (pg/ml) after Losartan administration

DOSE (MG)	PLACEBO	Losartan DOSE (mg)		
		40	80	120
TIME				
PRE-DOSE	71.83	52.67	68.33	83.83
4 hours	45.00	21.20	21.83	26.00
9 hours	46.00	25.33	26.83	26.00
24 hours	48.83	46.50	48.50	47.67
33 hours	47.17	41.83	41.33	29.67

For aldosterone, LSD showed that plasma concentrations after all doses of Losartan were significantly lower than concentrations after placebo ($p < 0.05$). Also, levels after 120 mg of Losartan were larger than levels after 40 mg of Losartan ($p < 0.05$).

Patient #1 experienced syncope after losartan 120 mg which was attributed to a vasovagal reaction. Scant information on this patient was provided in the study report.

Study 007.

Investigator: Thorir D. Bjornsson, M.D.

Jefferson Medical College

Protocol

This is a double-blind, parallel, placebo-controlled, three-phase study in fourteen healthy male volunteers between the ages of 18 and 40 years and within 20% of ideal body weight. The primary objectives of the study were as follows: (1) To determine whether the pharmacokinetics of losartan change with multiple dosing. (2) To determine the safety, tolerability, and hemodynamic effects in normotensive volunteers. (3) To investigate the effects of losartan on renin, angiotensin II, and aldosterone. For 3 days prior to the initiation of study drug, all subjects received a diet with 135 - 165 mEq of sodium and 70 - 90 mEq of potassium. The study was divided into 3 phases. During phase 1, subjects received a single dose of placebo (day 0). During phase 2, subjects received a single dose of either losartan 100 mg or placebo on day 1. During phase 3, subjects received 7 days of losartan 100 mg or placebo on days 3 through 9. Procedures performed during the study are outlined in table 7.1.

Table 7.1. Study Flow Chart

Procedure	Pre-study	Days -3, -2, -1	Phase 1	Phase 2		Phase 3								Post-Study		
			Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10			
Physical Examination	X															X
ECG	X		X	X					X			X				X
Laboratory Safety	X			X		X		X	X	X	X	X	X	X	X	X
Diet*		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dosing with Placebo Q.D.			X													
Dosing with losartan or Placebo Q.D.				X		X	X	X	X	X	X	X	X			
Blood Pressure/Heart Rate Monitoring			X**	X**		X	X	X	X	X	X	X	X**	X		
Plasma Collection for Drug Concentration				X	X			X+		X+	X+	X	X			
Urine Collection for Drug Concentration				X								X				
RAAS Profile a			X	X								X				
Norepinephrine/Epinephrine			X	X								X				
24-Hour Urine			X	X								X				
Overnight Stay at CRU		X	X	X								X	X			

*Diet - 135-165 mEq Na⁺, 70-90 mEq K⁺ to be started Day-3. a = -1, 6, 24 hours (supine 60 minutes prior to sample) and 6.5 hours (upright 30 minutes prior to sample)

**Frequent monitoring for 24 hours postdose.

+ Trough Drug

The angiotensin II assay utilized in this study was highly specific for angiotensin II octapeptide, combining HPLC separation of a plasma extract with radioimmunoassay of defined fractions utilizing an antibody with low crossover activity of angiotensin I.

Results

Fourteen male volunteers ranging in age from 18 to 31 years were enrolled in the study. Table 7.2 lists the demographic characteristics of the volunteers who entered and completed the study.

Table 7.2. Subject Characteristics

Subject	Race	Age (Years)	Weight (lb.)	Height (in.)
1	Caucasian	24	137	66
2	Caucasian	25	183	69.5
3	Caucasian	22	214	70
4	Caucasian	21	175.5	72
5	Caucasian	22	175	70
6	Caucasian	24	158	72
7	Negro	18	137	69
8	Caucasian	28	147.5	69.5
9	Caucasian	31	168	66
10	Caucasian	25	134.5	65
11	Caucasian	24	149.5	71
12	Caucasian	27	151.5	67
13	Caucasian	23	165	69
14	Caucasian	26	157.5	76
Mean		24.3	160.9	69.4
S.D.		3.15	21.6	2.89

Pharmacokinetic variables were evaluated for both losartan and E-3174. E-3174 is the active metabolite of MK-954. For losartan, the respective AUC_{24} and AUC_{∞} values were corrected for renal clearance prior to statistical evaluation. Table 7.3 lists mean pharmacokinetic data for day 1 and day 9. The mean C_{max} was 38% greater at day 9 compared to day 1. Renal clearance of losartan accounted for less than 4% of the dose. Table 7.4 lists the pharmacokinetic parameters of the active metabolite E-3174.

Table 7.3. Mean Changes From Day 1 on Day 9 In Pharmacokinetic Variables for losartan (N=10) Difference Analyses

Variable	Day 1	Day 9	Difference (Day 9-Day 1)	P-Value
C _{max} (ng/ml)	315.5 ± 126.4	436.9 ± 311.6	121.4 ± 304.4	0.24
T _{max} (Hours)	1.5 ± 0.9	0.9 ± 0.5	(-) 0.6 ± 0.9	0.066
Elimination Rate (Hours ⁻¹)	0.352 ± 0.127	0.312 ± 0.111	(-) 0.040 ± 0.104	0.26
t _{1/2} (hours)	2.0 ± .7	2.2 ± .8		
Renal Clearance	74.3 ± 17.7	91.9 ± 24.2	17.7 ± 20.9	0.020
Urine % Dose	3.42 ± 1.08(c)	3.60 ± 1.67(c)	0.18 ± 1.19(c)	0.67

(c) N=9; Data excluded for Subject #1 due to possible incomplete urine collection on Day 9.

Table 7.4. Mean Changes From Day 1 on Day 9 In Pharmacokinetic Variables for E-3174 (N=10) Difference Analyses

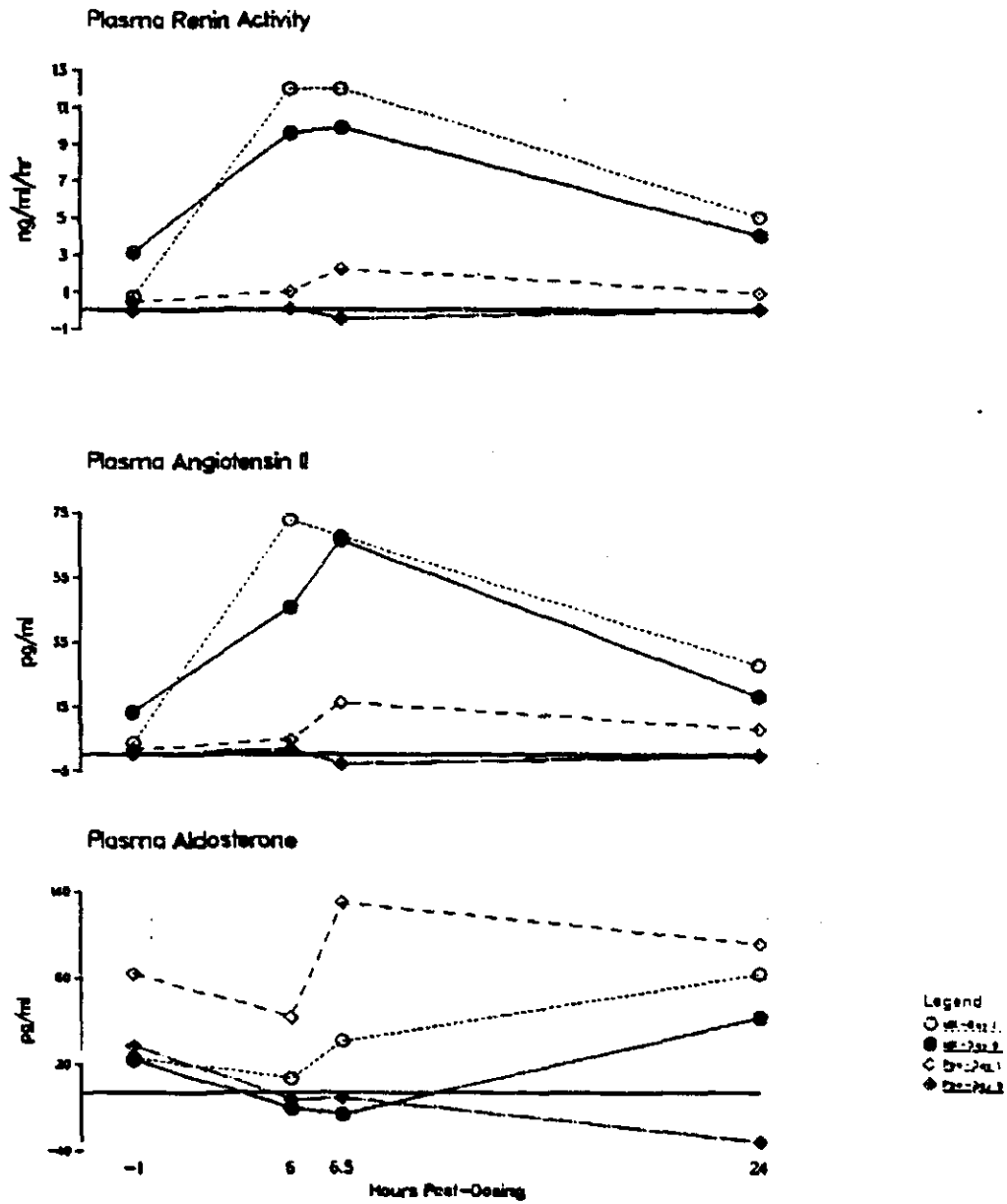
Variable	Day 1	Day 9	Difference (Day 9-Day 1)	P-Value
C _{max} (ng/ml)	568.4 ± 205.4	547.2 ± 179.2	(-)21.2 ± 131.7	0.62
T _{max} (Hours)	3.4 ± 0.9	2.7 ± 0.9	(-)0.7 ± 1.4	0.11
Elimination Rate (Hours ⁻¹)	0.077 ± 0.015	0.077 ± 0.014	(-)0.0004 ± 0.0189	0.95
t _{1/2} (hours)	9.0 ± 1.7	9.1 ± 1.6		
Renal Clearance (ml/min)	25.1 ± 5.0	26.6 ± 5.9	1.5 ± 7.1	0.51
Urine % Dose	5.7 ± 1.8(a)	5.8 ± 2.1(a)	0.1 ± 1.3(a)	0.84

(a) N=9; Data excluded for Subject #1 due to possible incomplete urine collection on Day 9.

The clinical summary report only includes the AUC corrected for clearance and expressed as the geometric mean of the ratio of day 9/day 1. The actual numerical values for AUC are not provided.

As illustrated in figure 7.1, plasma renin and angiotensin II levels increase with losartan treatment. Plasma aldosterone does not appear much different between treatments.

Figure 7.1. Renin, angiotensin II and aldosterone activity.



Urine excretion of sodium and potassium was not affected by losartan in subjects on a restricted sodium and potassium diet.

Adverse Experience

Table 7.5 lists the patients who experienced adverse events during the clinical trial.

Table 7.5. Clinical Adverse Experiences

Patient #	Day	Symptoms	Treatment	Intensity	Serious	Duration
1	-1	Headache	Placebo Run-In	Mild	No	3 hours
	1	Orthostatic BP	100 mg	Mild	No	6 hours
	off drug	Orthostatic BP	off drug	Moderate	No	30 min
	3	Orthostatic BP	100 mg	Mild	No	30 min
	10	Diarrhea	off drug	Mild	No	1 day
2	1	Esophageal Spasm	100 mg	Moderate	No	1.8 hours
	3	Orthostatic BP	100 mg	Moderate	No	8.7 hours
	10	Esophageal Spasm	off drug	Moderate	No	70 min
3	-1	Vasovagal Reaction	Placebo Run-In	Mild	No	1 day
	9	Vasovagal Reaction	100 mg	Mild	No	1 day
	15	Upper Respiratory	off drug	Mild	No	5 days
			Infection			
4	15	URI	off drug	Moderate	No	5 days
5	-1	Abdominal Cramps	Placebo Run-In	Mild	No	55 min
	1	Orthostatic BP	100 mg	Moderate	No	11 hours
	2	Listlessness	off drug	Mild	No	1.3 hours
	7	Change in Bowel Habit	100 mg	Mild	No	5 days
	16	Staph. Infection	off drug	Mild	No	10 days
	24	Head Trauma	off drug	Mild	No	2 days
12	6	Eyelid Disorder	100 mg	Mild	No	200 min
13	1	Orthostatic BP	100 mg	Moderate	No	30 min
	3	Palmar Inflammation	100 mg	Mild	No	68 days

Subject AN 013 had several peripheral smears which showed evidence of hemolysis, and an increase of serum creatinine level (within the normal range), both related to study drug. The hemolysis was noted during the study, while the rise in serum creatinine was noted poststudy. Events on this subject, who also had a dermatological reaction are summarized as follows. On October 3, 1990 (Day 8 of study), subject #13 reported that his palms were peeling. Upon examination he was noted to have had mild palmar desquamation with mild inflammation. There were no findings on the soles of his feet, and he reported no other symptoms. The subject had first noted the peeling Day 3 of the study (2 days after the initiation of dosing). He denied any change in soap, detergent or activities of daily living that might have accounted for his findings. He was evaluated by _____ who felt that his physical findings were consistent with a resolving inflammatory process.

On October 5, 1990, his peripheral smear, prepared from a heparinized specimen, revealed schistocytes and crenated red blood cells. His hemoglobin and hematocrit were 14.2 g/dl and 41.4%, respectively. At the time of his prestudy evaluation, on September 22, 1990, his hemoglobin was 16.3 with a hematocrit of 49.3. His hemoglobin and hematocrit continued to decrease and were 13.9 and 38.9 at the time of his poststudy physical exam, these were the lowest levels noted throughout his course.

On October 5, 1990, the subject was referred to _____ for further evaluation. After a thorough exam, including evaluation of a fresh peripheral smear, _____ concluded that the subject had experienced a transient hemolytic episode. A haptoglobin done at this time was within normal limits. An LDH was also normal at all timepoints. At the time of this visit, blood was sent for a serum creatinine and it was noted that the creatinine was elevated from a baseline of 1.2 mg/dl to a value of 1.5 thus suggesting that this episode might also be associated with mild alteration in renal function. Table 7.6 lists relevant laboratory values.

On October 18, 1990, the subject had an ESR of 2, a negative RPR, a negative Monospot, negative titers for cytomegalovirus, Lyme disease, and herpes simplex viruses type 1 and 2. His titers to Epstein-Barr virus on the same day revealed a negative IgM titer and a positive IgG titer suggesting a history of exposure to this virus at an unknown time in the past.

By October 20, 1990, the subject's hemoglobin had returned to 14.6 with a hematocrit of 44.0. His serum creatinine had also returned to baseline. All other laboratory safety screens including liver function tests, electrolytes, blood glucose, blood urea nitrogen, and urinalysis remained stable throughout his course. Follow-up with _____ on December 4, 1990,

revealed complete resolution of his physical and laboratory findings. At this time he was discharged from the study. Pertinent laboratory results for subject #13 are listed in table 7.6.

Table 7.6. Laboratory Values for Patient 013

Date	Phase	Hgb.	Hct.	Creatinine	Comments
8/23/90	Prestudy	15.9	46.6	1.2	
9/20/90	Prestudy	15.3	45.5		
9/22/90	Prestudy	16.3	49.3	1.4	
9/25/90	Run-In Placebo				
9/26/90	Single Dose-DuP	14.8	42.5	1.2	
9/27/90	Multiple Dose-DuP				
9/28/90	Multiple Dose-DuP	15	44.1	1.3	
10/1/90		14.2	39.1	1.2	
10/3/90	Day 8 - AE				
10/5/90	Day 10	14.2	41.4	1.3	
10/9/90	Poststudy	13.9	38.9	1.4	
10/16/90	Dr. Martinez			1.5	
10/18/90				1.2	Hgb/Hct Hemolysis
10/20/90		14.6	44		

10/18/90: Monospot-Negative; CMV - Negative; HSV 1 & 2 - Negative; EBV - Positive IgG; Lyme - Negative; ESR-2

Study 013.

Protocol

This was a double-blind, randomized, rising-dose, placebo-controlled study in two alternating panels of 9 healthy male subjects per panel to evaluate the safety and tolerability of IV losartan infused over a 20-minute period. On each study day, 6 subjects in each panel received losartan and 3 received placebo, according to a randomized allocation schedule. Panel I (also referred to as Panel A) received 1, 10 and 40 mg of losartan or placebo and Panel II (also referred to as Panel B) received 5 and 20 mg of losartan or placebo. Panel II was to receive a maximal dose of 80 mg. However, adverse events and preliminary data suggesting changes in vital signs at 40 mg resulted in a decision to stop dose advancement at this dose.

Subjects reported to the clinic on the morning of each study day after an overnight fast. Predosing blood and urine samples were collected from each subject. Subjects then received the designated IV losartan or placebo infusion over a 20-minute period, according to a randomized allocation schedule. At specified doses, blood was to be collected for measurement of losartan concentration at the following time intervals: 0, 5, 10, 15, 20, 25, 30, 45, 60, 80, 100 and 120 minutes, 3, 4, 5, 6, 8, 10, 12, 16, 24, 30 and 36 hours post-initiation of infusion of losartan.

Urine samples for losartan concentration were collected at the following time intervals: 0-6, 6-12, 12-24, 24-36 and 36-48 hours postinitiation of infusion of losartan. Dose escalation occurred after a 7-day washout.

Results

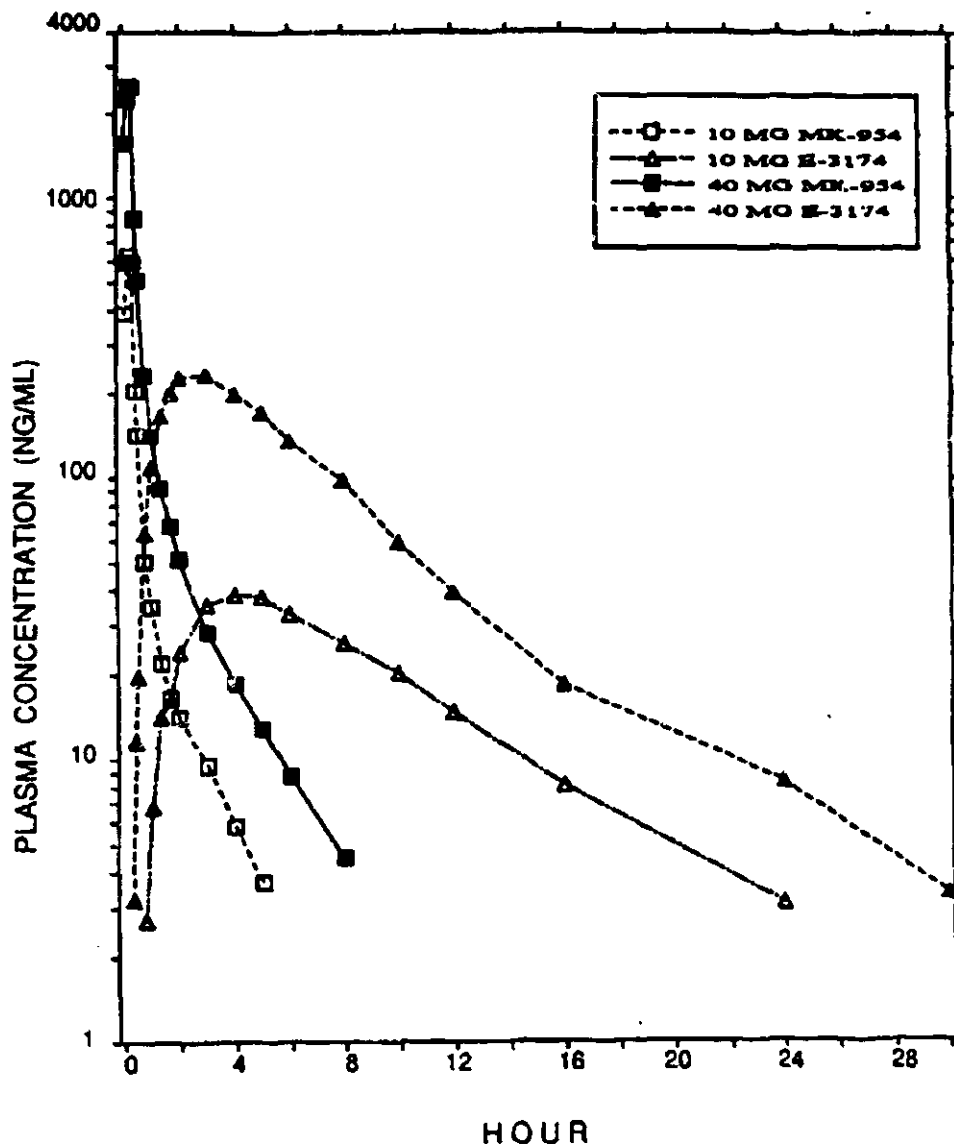
Eighteen healthy male (15 caucasian, 2 black, 1 hispanic) subjects were enrolled. The mean age of subjects was 23.8 years (range: 19 - 40). Table 13.1 lists the mean pharmacokinetic parameters for losartan and E-3174. Figure 13.1 plots the concentration versus time curve for losartan and E-3174.

Table 13.1. Losartan (MK-954) Intravenous Safety Study. Summary of Pharmacokinetic Analysis

	Losartan				E-3174			
	10 mg		40 mg		10 mg		40 mg	
	mean	s.d.	mean	s.d.	mean	s.d.	mean	s.d.
C ₂₀ (ng/mL)	594	+/- 131	2501	+/- 564				
C _{max} (ng/mL)					40	+/- 14	241	+/- 63
T _{max} (hr)					4	+/- 0.9	2.6	+/- 0.9
AUC _(0-∞) (ng*hr/mL)	307	+/- 56	1187	+/- 254	433	+/- 122	1786	+/- 369
t _{1/2} (hr)	2.1	+/- 0.7	2.2	+/- 0.7	6.2	+/- 2.3	6.7	+/- 1.6
V _{dss} (L)	33	+/- 11	26	+/- 10				
Cl (mL/min)	563	+/- 93	585	+/- 102				
Cl _r (mL/min)	87	+/- 26	80	+/- 31	25	+/- 12	25	+/- 6
% Dose	15	+/- 2	16	+/- 4	5	+/- 1	7	+/- 1

*Values are mean (SD) except for t_{1/2} (harmonic mean [pseudo standard deviation])
 C₂₀ = Concentration at end of infusion, Cl = Systemic clearance, Cl_r = Renal clearance
 % dose = Percent of dose found in urine (0-48 hours)

Figure 13.1. Mean Plasma Concentrations of Losartan and L-158,641 (E-3174) Following 10 mg and 40 mg Losartan (n=6)



Blood pressures were measured frequently after dosing. There was no evidence of agonist activity (exemplified by no increase in blood pressure immediately after infusion). The maximum effect on DBP seemed to occur at 5 - 8 hours post dosing. Since these were non-hypertensive subjects, it is not clear if this can be extrapolated to the hypertensive population.

The original protocol planned for subjects to receive up to 80 mg of losartan. However, dosing was stopped after the 40 mg dose because five of six subjects receiving 40 mg experienced adverse events and heart rates increased after 40 mg. The adverse events included dizziness, headache and tachycardia.

Study 015.

At an early stage of the losartan program, preliminary data from the Japanese development program showed a significant delay in absorption of losartan and reduction in the apparent bioavailability of losartan formed when the dose was given with a standard Japanese meal (see table 15.1). In addition to the apparent reduction in bioavailability, the biochemical response to losartan, as measured by the 6-hour postdose increase in plasma renin activity (PRA) and immunoreactive angiotensin II, was also attenuated (see table 15.2).

Table 15.1 Losartan and L-158,641 Pharmacokinetic Parameters in Food* Interaction Study

Losartan 100 mg	C _{max} (ng/mL)	T _{max} (hr)	AUC (ng·hr/mL)	t½ (hr)
Losartan Fasted	801 ± 331	0.7 ± 0.3	1069 ± 373	1.5 ± 0.4
	282 ± 98	2.8 ± 1.2	855 ± 239	1.6 ± 0.2
E-3174 Fasted	1211 ± 271	2.0 ± 0.6	3957 ± 1192	4.2 ± 0.5
	775 ± 157	4.5 ± 1.2	5116 ± 702	4.2 ± 0.4
Mean ± S.D., n=6				

*The meal consisted of rice, miso soup (soybean soup), fried vegetables, boiled beans and grilled dried fish (710 Kcal, 36 g protein, 2.1 g salt).

Table 15.2. Influence of Feeding on RAAS Response to Losartan 100 mg

		Pre-dose	6 hr	Post-dose
PRA	Fasted	1.0 ± 0.1	18.5 ± 3.5	4.5 ± 3.0
	Fed	1.1 ± 0.1	6.0 ± 3.0	1.0 ± 0.2
All	Fasted	2.0 ± 0.5	9.0 ± 3.5	3.0 ± 1.0
	Fed	1.0 ± 0.5	2.8 ± 0.8	1.0 ± 0.5

This study was performed to verify the data in the Japanese trial. It is an open label, 2 period crossover study in healthy male subjects designed to evaluate the effect of food on the absorption of a single 100 mg losartan tablet as compared to administration in the fasting state. The natural log transformed area under the plasma concentration curve (ln AUC), natural log transformed maximum plasma concentration (ln C_{max}), the maximum plasma concentration (C_{max}), and the time of maximum plasma concentration (T_{max}), were used to evaluate the equivalence of losartan administered in the fed and fasted states. Plasma renin activity (PRA) and plasma angiotensin II (A II) levels were collected at -1 Hour predose and 2, 4, 6, 8, 12, and 24 hours postdose.

Results

For losartan, there were statistically significant (p<.05) and/or graphical indications of carryover effects for the ln AUC, ln C_{max}, and C_{max} variables. Therefore, separate first period and second period analyses were performed comparing the fed and fasted states using a two-sample Student t-test. For the eight subjects in this study, this analysis compared the four subjects who were fasting in the first period with the four who were fed (see Table 3) and, for the second period, the converse comparison was made. Ninety percent confidence intervals for the ratio of geometric means were computed.

Eight healthy male volunteers between the ages of 19 and 29 were initially deemed acceptable for participation in the study. One subject (AN 004) discontinued from the study after the first period due to a scheduling conflict. A second subject (AN 005) discontinued due to a deviation from the protocol (proteinuria present prior to the first dose of losartan and increased SGOT, SGPT and LDH) during Period I. Two replacement subjects entered the study and completed the study after the 6 original subjects. The average age was 23.9 years. Four black and 6 caucasians entered the study.

The data from the 8 subjects who completed the study are included in the bioequivalence and pharmacodynamic analysis. Table 15.3 and 15.3a lists the pharmacokinetic parameters for losartan. The AUC for losartan decreases approximately 20%. C_{max} decreases by approximately 52%. There is a decrease in C_{max} and AUC for E-3174 as listed in table 15.3b and 15.3c.

Table 15.3. Equivalence Analyses: Losartan Summary of Ratio Analyses

Variable	Geometric Means		Fed/Fasted		ANOVA P-Values				
	Fed	Fasted	Geometric Means	90% C.I.	For Ratio	Carryover	Treatments	Periods	MSE
AUC (ng·hr/mL)	662.1	808.9	.82	(.71, .94)		.19	.024*	.97	.0178
1st Period Only ^(*)	596.2	900.6	.66	(.47, .93)		-	.054 ^Δ	-	.0593
2nd Period Only ^(*)	735.2	726.7	1.02	(.75, 1.36)		-	.94	-	.0444
C _{max} (ng/mL)	232.5	483.8	.48	(.32, .72)		.025*	.011*	.70	.1646
1st Period Only ^(*)	169.9	611.4	.28	(.16, .48)		-	.0035*	-	.1522
2nd Period Only ^(*)	318.2	382.8	.83	(.48, 1.42)		-	.52	-	.1491

Δ = .05 < p ≤ .10; * = p ≤ .05; ** = p ≤ .01

Table 15.3a. Equivalence Analyses: Losartan
Summary of Difference Analyses

Variable	Arithmetic Means		Fed Minus Fasted	90% C.I. for Difference	ANOVA P-Values			
	Fed	Fasted	Arithmetic Means		Carryover	Treatments	Periods	MSE
C _{max} (ng/mL)	267.3	514.0	-246.7	(-420.6, -72.8)	.021*	.033*	.67	32,026.4
1st Period Only ^(a)	184.8	635.6	-450.8	(-673.7, -227.9)	-	.0077**	-	26,306.6
2nd Period Only ^(a)	349.7	392.5	-42.8	(-251.7, +166.1)	-	.70	-	23,118.4
T _{max} (Hours)	2.95	1.29	+1.66	(+0.46, +2.86)	.20	.035*	.97	1,5167

Δ = .05 < p ≤ .10; * = p ≤ .05; ** = p ≤ .01

MSE = Mean Squared Error (6 d.f.) (a) = Evaluated using two-sample pooled variance student t-test with N=4 per fed or fasted treatment group.

Table 15.3b. Equivalence Analyses: E-3174
Summary of Ratio Analyses (N=8)

Variable	Geometric Means		Fed/Fasted	90% C.I. For Ratio	Crossover ANOVA P-Values			
	Fed	Fasted	Ratio		Carryover	Treatments	Periods	MSE
AUC (ng•hr/mL)	2,637.7	3,042.3	0.87	(0.76, 0.99)	.28	.078Δ	.99	.0181
C _{max} (ng/mL)	373.9	489.2	0.76	(0.58, 1.00)	.93	.094Δ	.97	.0731

Δ = .05 < p ≤ .10

MSE = Mean Squared Error (6 d.f.)

Table 15.3c. Equivalence Analyses: E-3174
Summary of Difference Analyses (N=8)

Variable	Arithmetic Means		Fed Minus Fasted	90% C.I. for Difference	Crossover ANOVA P-Values			
	Fed	Fasted	Arithmetic Means		Carryover	Treatments	Periods	MSE
C _{max} (ng/mL)	414.6	502.3	-87.7	(-193.5, +18.1)	.84	.15	.96	11,845.2
T _{max} (Hours)	4.75	3.07	+1.68	(+0.26, + 3.10)	.23	.060Δ	.68	2,1303

Δ = .05 < p ≤ .10

MSE = Mean Squared Error (6 d.f.)

Study 017.

This was a randomized, double blind, placebo controlled, rising single dose study to evaluate the pharmacokinetics of intravenous doses of E-3174 infused over 20 minutes. The study subjects were divided into 2 panels of eight. Panel 1 received single i.v. doses of placebo and/or E-3174 .1 mg, 1 mg, 10 mg or 40 mg. Panel 2 received placebo and/or E-3174 .5 mg, 5 mg, 20 or 80 mg. Each subject received 4 infusions.

Results

Nineteen healthy males (14 caucasians, 2 blacks, 1 asian, 1 mulatto, 1 hispanic) were enrolled in the study. The mean age of subjects was 24.2 years. Three subjects (#5, #9, #14) discontinued prematurely and were replaced. Patient #9 was discontinued due to elevated SGPT. This subject did not receive E-3174. The reason for discontinuation of the other subjects is not provided. Patient #5 did not experience any adverse events. Patient #14 experienced headache after E-3174 5 mg on day 16, pharyngitis on day 18 and an elevated WBC on day 21. No additional doses of E-3174 were received by this patient.

Table 17.1 lists the pharmacokinetic parameters for E-3174 10, 40 and 80 mg. There appears to be a dose proportional increase in AUC and C_{max}. The harmonic mean elimination half-life was similar for all doses. Approximately half of the E-3174 was eliminated in the urine.

Table 17.1. Pharmacokinetic Parameters of E-3174.

	10 mg	40 mg	80 mg
$C_{20 \text{ min}}$ (ng/mL)	1818 + 132	7814 + 1129	14,305 + 2676
AUC_{∞} (ng·hr/mL)	2897 ± 407	12,808 ± 2688	24,310 ± 4147
$t_{1/2}$ (hr ⁰)	6.9 + 5.0	6.5 + 1.2	6.6 + 1.2
$V_{d_{ss}}$ (L)	16.4 + 5.6	10.3 + 2.4	9.8 + 1.3
CL (mL/min)	53.0 + 7.4	48.8 + 9.5	51.4 + 11.9
CL _{renal} (mL/min)	27.5 + 6.1	23.8 + 4.7	27.9 + 5.4
% Dose in urine	52.6 ± 2.7	49.2 ± 6.6	54.9 ± 9.7

*Harmonic mean and pseudo standard deviation.

There were no serious adverse events attributable to E-3174 therapy.

Study 022.

This was a 3 period, crossover study in healthy males to assess the following:

1. the bioequivalence of 100 mg losartan tablets as compared to 100 mg losartan capsules;
2. the absolute bioavailability of oral losartan;
3. the plasma concentration profile of the metabolite E-3174 following administration of 100 mg losartan tablet as compared to 100 mg losartan capsule;
4. the plasma concentration profile of the metabolite E-3174 following administration of losartan, 100 mg orally and 30 mg intravenously.

The primary hypotheses of this study was that the geometric mean ratio of $AUC_{0-\infty}$ for losartan of 100 mg losartan tablets as compared to 100 mg losartan capsules will be between 0.8 and 1.25. The formulations used in this study are outlined in table 22.1.

Table 22.1. Formulations Used in Study 022

Dose	Batch #	Formulation #
Losartan Capsule (100 mg)	C-W737	0954DFC001D003
Losartan Tablet (100 mg)	C-W738	0954FCT004D001
Losartan Solution (30 mg)	C-W739	0954HSS001A001

Results

Eight healthy male subjects (6 caucasian, 1 black, 1 other) were enrolled in and completed the trial. The mean age of subjects was 26 years.

Table 22.2 lists the losartan and E-3174 AUC and C_{max} data for the tablet and capsule. The estimated bioequivalence AUC ratio of tablets relative to capsules based upon back transformation of the natural log transformed data was 0.93 with a corresponding 90% confidence interval of (0.68, 1.25). The estimated 90% interval (back transformed from natural log data) for the tablet relative to the capsule C_{max} ratio was (0.53, 1.38) with a geometric mean estimate of the ratio as 0.86. Since the confidence intervals of the geometric mean ratios for losartan are outside of the .80 - 1.25 interval, the tablet and capsule can not be considered to be bioequivalent. The geometric mean ratios for E-3174 are within the interval .80 - 1.25.

Table 22.2. AUC and C_{max} for Tablet and Capsule

Compound	Variable	Geometric Means		Tablet/Capsule Geometric Mean Ratio	90% C.I. for ratio	Crossover ANOVA p-values			
		Tablet	Capsule			Carryover	Treatment	Period	M.S.E.
Losartan	AUC (ng·hr/ml)	660.3	711.9	0.93	(.68, 1.25)	0.59	0.64	0.35	0.0937
	C _{max} (ng/ml)	430.4	502.6	0.86	(.53, 1.38)	0.2	0.54	0.63	0.2769
E-3174	AUC (ng·hr/ml)	3,501.2	3,423.3	1.03	(.95, 1.10)	0.29	0.55	0.77	0.0053
	C _{max} (ng/ml)	572.7	537.3	1.07	(.92, 1.23)	0.23	0.41	0.29	0.0217

Each individuals AUC and C_{max} ratio is plotted in figures 1 and 2.

Figure 22.1. Individual AUC Ratios (Tablet/Capsule) and 90% Confidence Interval About Geometric Mean Ratio (●)

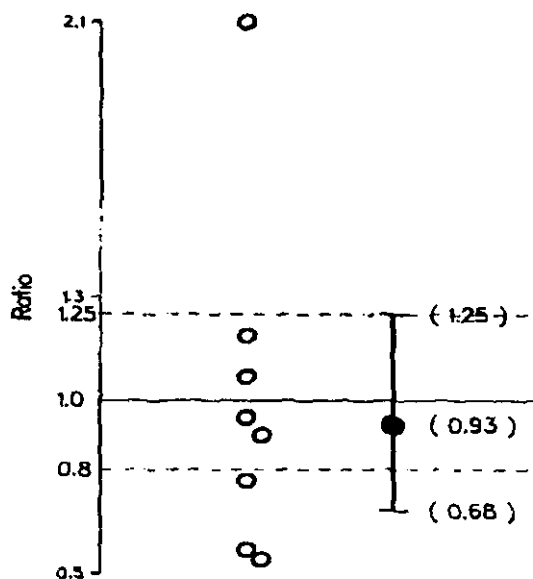


Figure 22.2. Individual C_{max} Ratios (Tablet/Capsule) and 90% Confidence Interval About Geometric Mean Ratio (●)

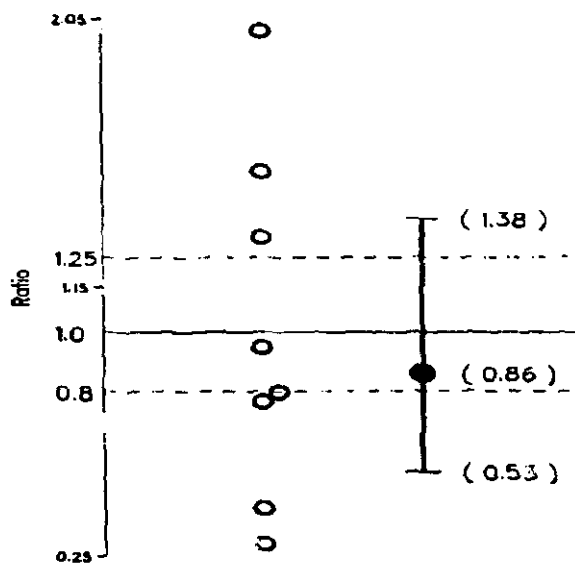


Table 22.3 lists the pharmacokinetic parameters for the tablet and i.v. formulation. The absolute bioavailability of losartan tablet is 23%.

Table 22.3 Summary of Pharmacokinetics of Losartan and E-3174 Following Oral (100 mg Tablet) and Intravenous (30 mg) Losartan

Parameter ¹	Losartan		E-3174	
	Oral Tablet	i.v.	Oral Tablet	i.v.
C_{max} (ng ^l)	31.7	—	584 (119.5)	112.5 (21.8)
T_{max} (hr)	3	—	5.1 (1.0)	3.8 (0.5)
AUC_{∞} (r)	375.8	925.6 (349.7)	3561 (686)	1066 (198)
K (hr ⁻¹)	0.36 (0.09)	0.31 (0.11)	0.084 (0.012)	0.090 (0.021)
$t_{1/2}$ (hr)	1.9 (0.5)	2.3 (0.9)	8.3 (1.2)	7.7 (1.8)
V_{dss} (L)	—	40.2 (13.0)	—	—
Cl (ml/min)	—	618 (247)	—	—
Clr (ml/min)	90 (42)	76 (39)	22.5 (6.1)	24.2 (4.6)
Urinary Recovery				
(% dose)	3.7 (1.3)	11.6 (2.5)	5.0 (1.7)	5.3 (1.5)
F^2	0.23 (0.17, 0.30)			

1 Values are mean (SD). C_{max} and AUC values for losartan and E-3174 were normalized to nominal doses of 100 mg (oral) and 30 mg (i.v.) based on actual doses given.

$t_{1/2}$ is harmonic mean and pseudo SD.

2 Geometric mean (90% Confidence Interval)

Study 019.

The aim of this study was to obtain information on the dose-response relationship with losartan in subjects whose renin system had been stimulated by sodium depletion. This study was a double-blind, randomized, placebo-controlled, four period, crossover study. Three separate dose panels were employed. Each panel was designed to allow 4 subjects to receive three different doses of losartan (5, 10, 25, 50 or 100 mg) and one dose of placebo. The time elapsed between each study period was 7 to 10 days. During the three days prior to each study day, subjects were maintained on a 40 mmol/day sodium diet and received oral furosemide 40 mg b.i.d. Subjects were normotensive as defined by a resting supine blood pressure less than 145/90 mmHg and a lack of a history of hypertension. Additional inclusion criteria included: heart rate of 45 to 100 beats/minute and body weight within 10% of ideal body weight for height and build. Furthermore, only non-black subjects were eligible to enter this study. Table 19.1 and 19.1a outline the testing performed in the trial.

Table 19.1. Procedures

Approx. Time:	8:00		9:00		10:00		11:00		12:00		13:00		14:00		15:00		16:00		17:00		18:00		19:00		
	Hour: -24	-1	-½	0	½	1	1 ½	2	2 ½	3	3 ½	4	4 ½	5	5 ½	6	6 ½	7	7 ½	8	8 ½	9	9 ½	10	24
Empty Bladder		X																							
Body Weight		X																							
Insert Venous Cannula			X																						
BP & HR (Supine and Standing)		X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Comparison of Semiautomated BP Device with Mercury Column				X												X									
RAAS Hormones & NE, Epinephrine & [Drug]				X	X	X	X				X				X			X					X	X	
Hematology & Biochemistry																									X
Urine Collections		X*	X																						X
Urinalysis		X																							X
Standard Meal							X						X									X			
Test Drug Administration				X*																					
ECG		X																							

* Following Hour 0 evaluations: † For purposes of acclimating subjects to procedure. NE = norepinephrine

* 24-hour urine collection for determination of Na⁺ (to establish compliance with the restricted sodium/furosemide regimens)

Table 19.1a. Labs

Hematology	Biochemistry	Urinalysis	RAAS Hormones
Hemoglobin	Sodium	Protein	Plasma Renin Activity
Hematocrit	Potassium	Glucose	Plasma Renin Concentrations
WBC	Chloride	Uric Acid	Angiotensin Peptides
Platelet Count	Bicarbonate	Ketones	Aldosterone
Ferritin	Urea	Blood	Angiotensin Converting Enzyme
	Calcium		
	Alkaline Phosphatase		
	AST		
	ALT		
	Glucose		
	Globulin		

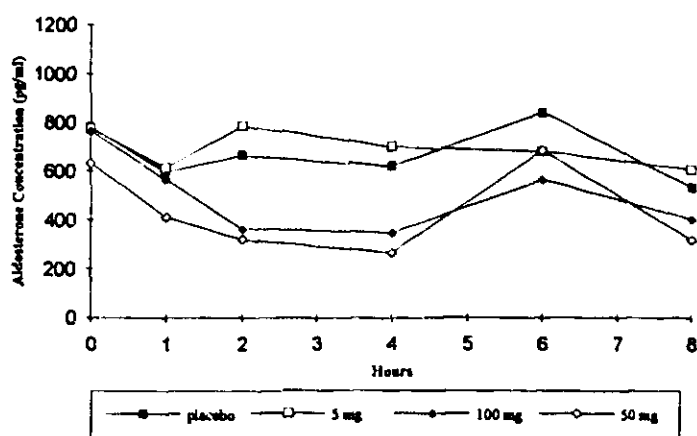
Results

Fourteen subjects entered the study. Subjects were healthy white males between the ages of 22 and 34. The median age was 24. Eleven subjects completed all four period. Subject #1 developed a sore throat after the third period and withdrew. Subject #101 from the study after the second period due to alcohol consumption. Subject #12 withdrew from the study after the second period and was replaced by patient #112.

Plots of blood pressure versus time in the clinical summary report are uninterpretable because the different treatment groups can not be differentiated.

Plasma renin increased with losartan therapy. Plasma aldosterone levels were difficult to interpret from the graph provided. Figure 19.1 was produced from data in appendix 13. Plasma aldosterone levels versus time over the first 8 hours post-dosing are plotted. During the first 6 hours post dosing, losartan 50 mg and 100 mg tend to have lower aldosterone levels compared to placebo and 5 mg. The difference is less impressive by 8 hours.

Figure 19.1. Aldosterone Levels



Angiotensin converting enzyme activity appeared to be unchanged with losartan therapy.

Not unexpectedly, orthostatic hypotension and vasovagal reactions were common in patients treated with losartan (especially 100 mg). Subject #112 had an elevation of serum creatinine (baseline = 93 µmol/L; post-100 mg = 190 µmol/L) and blood urea nitrogen (baseline = 5.8 mmol/L; post-100 mg = 10.1 mmol/L). These results suggest possible renal insufficiency related to losartan. Subject #6 had an elevation of SGPT to 74 IU/L (normal = 11 - 55 IU/L) without a significant increase in SGOT.

Study 024.

This was a 2 period crossover study to evaluate the effect of cimetidine on the pharmacokinetics of losartan. Patients received a single dose of losartan 100 mg alone and on day 6 of a 7 day course of cimetidine 400 mg every 6 hours. Eight healthy, caucasian males completed the study. The average age of subjects was 27.5 years. Table 2.1 lists the mean pharmacokinetic parameters for losartan and E-3174. The elimination half-life is the expressed as the harmonic mean. Cimetidine was associated with an 30% increase in losartan C_{max} and 23% increase in losartan AUC. There was no increase in E-3174 C_{max} or AUC.

Table 2.1. Geometric Mean Pharmacokinetic Parameters

Pharmacokinetics:	Losartan		E-3174	
	-Cimetidine	+Cimetidine	-Cimetidine	+Cimetidine
C _{max} , ng/ml.	614 + 366	836 + 921	504 + 253	499 + 218
C _{max} Range	262.5 - 1391.3	166.3 - 3047.1	259.5 - 900.7	259.1 - 784.7
T _{max} , hr	0.7 + 0.2	1.2 + 1.2	2.6 + 0.8	2.8 + 1.1
AUC _∞ , ng·hr/ml.	849 + 383	1047 + 647	3359 + 1329	3430 + 1553
AUC _∞ Range, ng·hr/mL	512.4 - 1712.7	533.2 - 2583.5	2112.1 - 5326.6	1701.2 - 6055.3
t _{1/2} , hr@	1.7 + 0.6	1.7 + 0.5	8.7 + 3.6	8.1 + 2.1
λ, hr ⁻¹	0.40 + 0.13	0.42 + 0.12	0.080 + 0.031	0.085 + 0.021

@Harmonic mean and pseudo standard deviation.

Study 023.**Protocol**

This was a randomized, double blind, placebo controlled, 2-period crossover, single center trial designed to study the effect of losartan on renal hemodynamics and mineral excretion in healthy, non black male subjects on high and low sodium diets. Sixteen patients received losartan 100 mg and eight patients received placebo during both treatment periods. Subjects were also randomized to receive a High-Salt (HS) [200 mmol/day] or Low-Salt (LS) [50 mmol/day] diet in the first period and the opposite diet in the second period.

Subjects were maintained on a low salt or high salt diet on days 1 - 6 (period I) and 12 - 17 (period II). Losartan 100 mg or placebo were administered as single doses on days 6 and 17. Patient did not cross over therapies. Diets were crossed over. Twenty-four-hour urine collections were obtained on days 2, 3, 4 and 5, as well as days 13, 14, 15, and 16. Sodium balance was assessed by measuring the 24-hour urinary sodium excretion. In order to receive therapy, subjects on a low sodium diet had to have a mean 24 hour urinary sodium excretion no greater than 70 mmol/day on days 4 and 5 or 15 and 16. Subjects on high sodium diets had to have a mean 24 hour urinary sodium excretion no less than 180 mmol/day on days 4 and 5 or 15 and 16 (individual daily urinary sodium excretion rate must have been > 165 mmol/day).

Studies which assessed the effects of the oral administration of 100 mg losartan and PBO on renal hemodynamic and tubular functions were performed at the day of drug administration.

Table 23.1 lists the procedures performed during the study.

Table 23.1. Procedures

Study Day	-14 to -1	Period I						Washout Period					Period II					
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Clinical Evaluations																		
Hx/PE/ECG	X																	X
BP/PULSE	X						X											X
Height/Weight	X						X											
Laboratory Evaluations																		
Blood hematology	X						X											X
Blood Chemistry*	X						X											X
24 hr. Urine Chem.	X	X		X		X	X					X		X		X	X	X
Timed Urine Chem.							X											X
Renal Function Studies																		
Inulin							X											X
PAH							X											X
Lithium							X											X
Creatinine Clearance	X						X											X
PRA and AII							X	X									X	X
Pregnancy Test**							X											X

Hematology tests included: Hgb, Hct, WBC, Diff, Platelet. Blood Chemistry tests included: Aldosterone, Calcium, Chloride, Amino Acids, Creatinine, Glucose, Bicarbonate, Magnesium, Osmolality, Phosphorus, Potassium, Sodium, Uric Acid. 24-Hour Urine Chemistries included: Creatinine, Potassium, Sodium, Uric Acid, Chloride, Glucose, Phosphorus

**Timed Urine Collections included: Aldosterone, Calcium, Chloride, Creatinine, Glucose, Magnesium, Osmolality, pH, Phosphorus, Potassium, Sodium, Uric Acid, Bicarbonate, Amino Acids, Ammonium, Titrateable Acids and fractional clearances of Amino Acids. Urine was collected at 30 minute intervals for 6 hours after dosing. PRA and AII results were sent directly to MSDRL. PRA and AII were measured on Day 6 at -3 hours, 0 hours, 4 hours and 6 hours.

* Samples were collected every 30 minutes during renal function studies

** A pregnancy test had to be done and negative results had to be obtained 72 hours prior to administration of study medication.

Results

Twenty four healthy male volunteers, between the ages of 20 and 35, were entered into this study. Sixteen were randomized to losartan and 8 were randomized to PBO. Twenty two (91.7%) of the 24 subjects were caucasian. No black patients were enrolled. One placebo patient dropped out due to an arrhythmia. No other information is provided.

Because data collection was for the first six hours post-dosing, it is not clear how the results can be applied to long term therapy in assessing the effect of losartan on renal hemodynamics or excretion of electrolytes. The clinical summary report and appendices do not include the data from the 24 hour urine collections. The only data presented is for the six hours post dose. The extensive amount of information collected in this trial is outside the realm of this review to describe in its entirety. Only selected information is presented. Most of this will be presented in graphical form without emphasis on the p values. Many tables providing analysis with p values can be found in the sponsor's clinical summary report.

In figure 23.1 and 23.2, plasma renin and plasma angiotensin II activity increased after losartan therapy. The effect was more pronounced in patients on a low salt diet.

Figure 23.1. Plasma Renin Activity

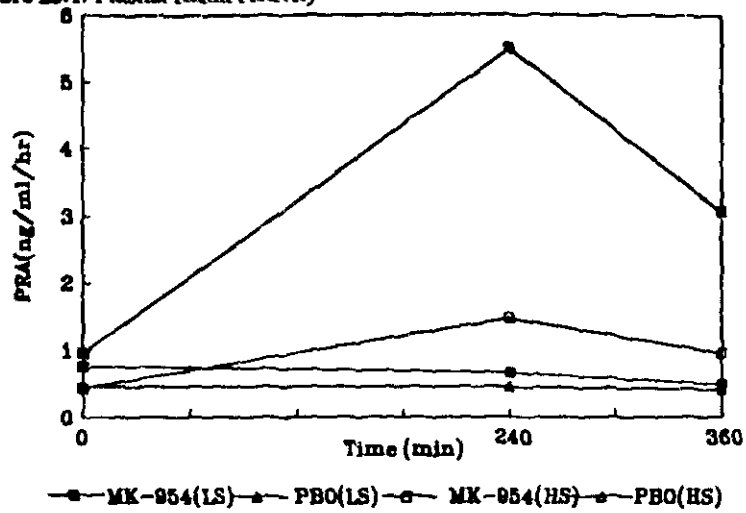
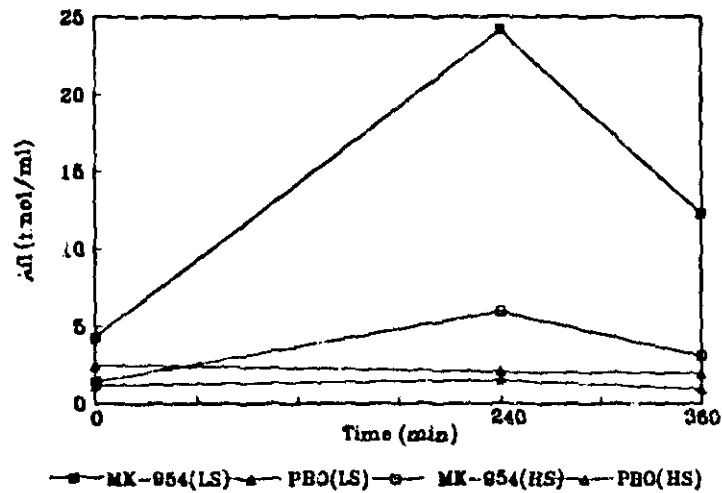


Figure 23.2. Angiotensin II Levels



As might be expected, baseline aldosterone levels were elevated with the low salt diet. Placebo and losartan had a similar effect on aldosterone levels regardless of diet.

Figure 23.3. Aldosterone Levels

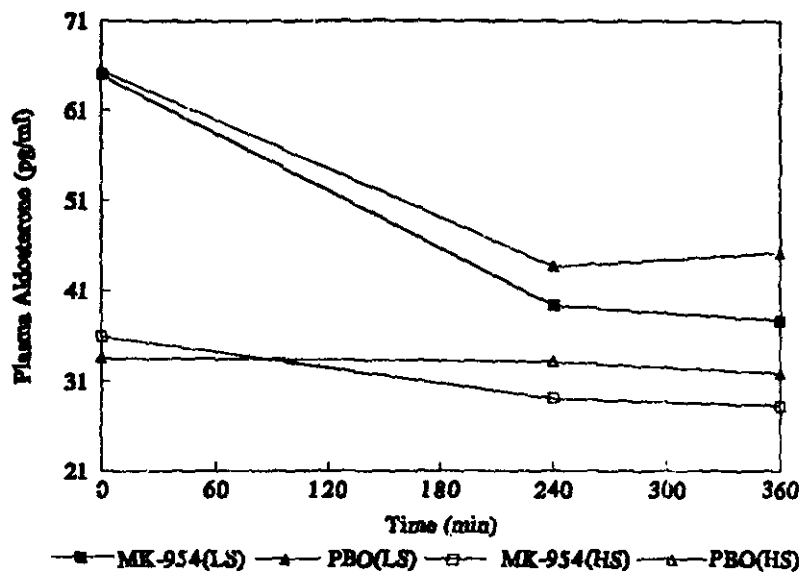
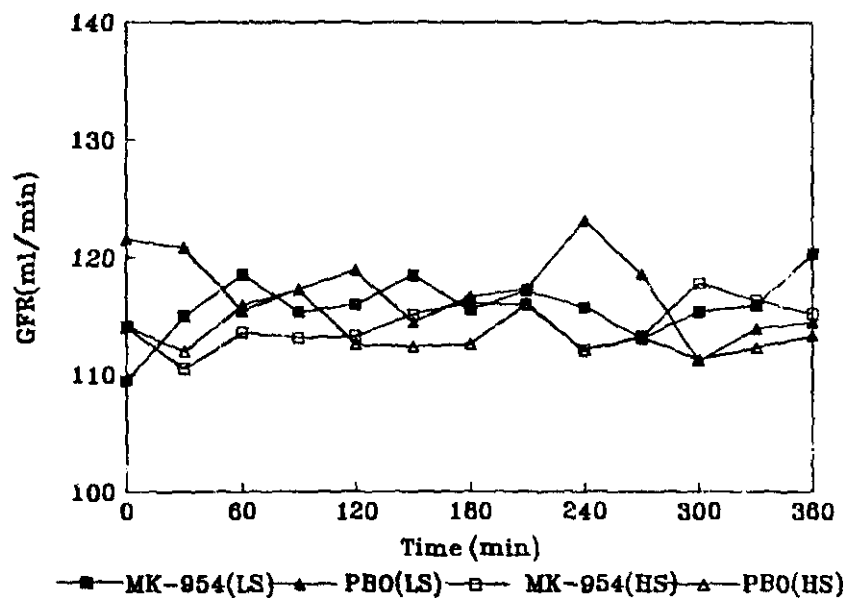


Figure 23.4 illustrates that there does not appear to be any trends in the change of GFR (presumably measured by inulin clearance) during the first 6 hours post treatment.

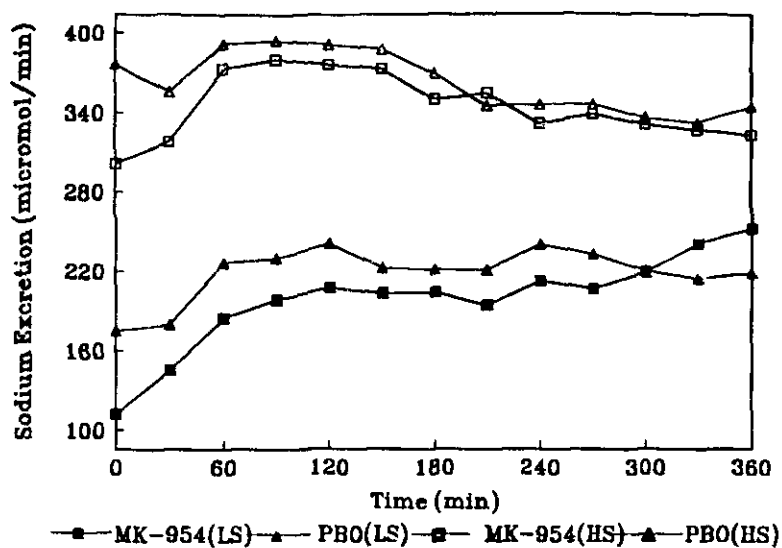
Figure 23.4. GFR Results



Effective renal plasma flow and filtration fraction do not appear to be affected much with losartan therapy.

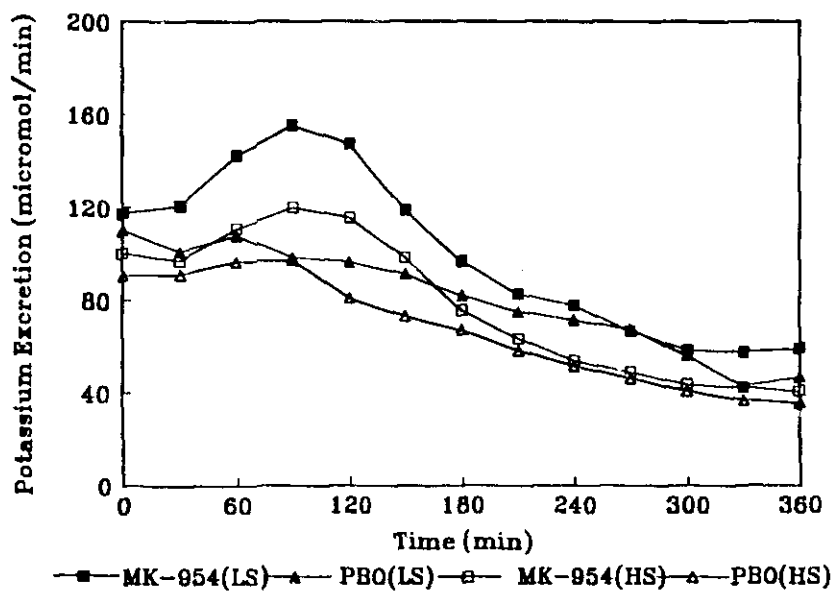
As illustrated in figure 23.5, sodium excretion was greater in subjects on high salt diets. Losartan does not change sodium excretion in the first 6 hours after dosing.

Figure 23.5. Urinary Sodium Excretion



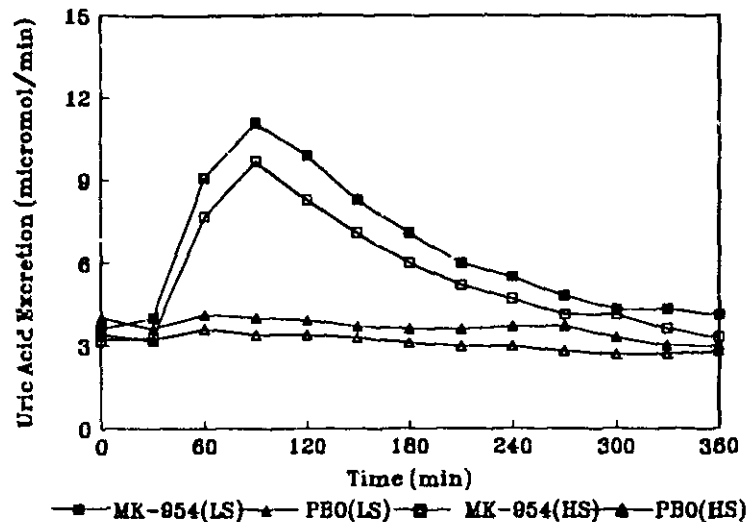
There may be an acute increase in urinary excretion of potassium with losartan as illustrated in figure 23.6. The effect, if present, is short lived.

Figure 23.6. Urinary Potassium Excretion



The urinary excretion of uric acid increases acutely with losartan regardless of salt intake but is short lived.

Figure 23.7. Urinary Uric Acid Excretion

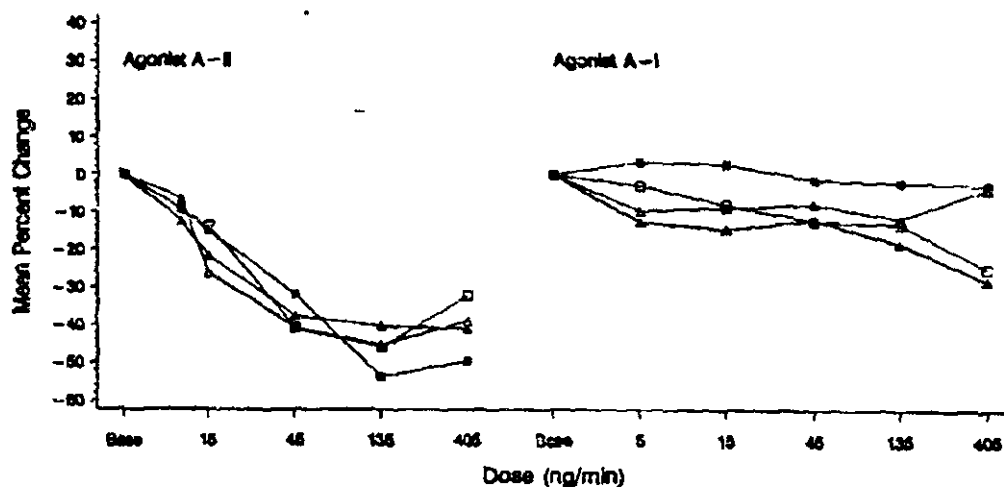


Study 033.

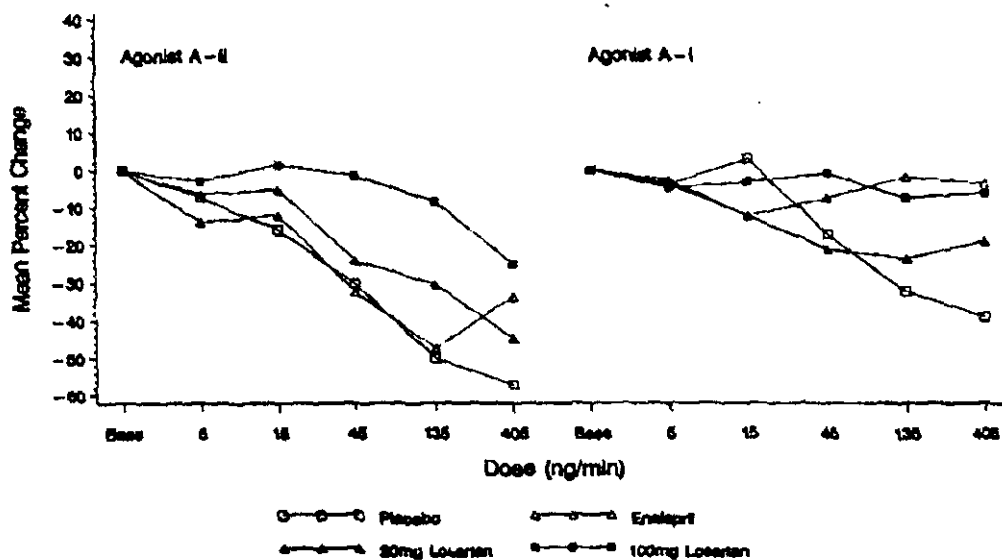
Angiotensin I and II have a vasoconstrictor effect on the dorsal hand vein of humans. This study attempted to show that losartan and enalapril could inhibit the pressor response to angiotensin I and losartan but not enalapril inhibited the pressor response to angiotensin II by measuring dorsal hand vein diameters. This study is a randomized, double-blind, placebo controlled 4 - period crossover study in which healthy male subjects received single doses of losartan 20 mg, losartan 100 mg, placebo and enalapril 10 mg. Five different doses of angiotensin I and II were infused over 4 minutes in 2 cycles at 1.0 and 3.5 hours after dosing of randomized therapy. A cycle started with saline baseline infusion, followed by angiotensin II infusion with stepwise increasing infusion rates, then a second saline baseline infusion followed by the angiotensin I infusion with stepwise increasing infusion rates.

Eight caucasian male subjects ranging in age from 23 to 31 years were enrolled in the study. Figure 33.1 shows the mean percent change in dorsal hand vein diameter from baseline. At 2 hours post dose (first cycle), there is little distinction between treatments. At 4 hours post dose, losartan attenuated the response to angiotensin II infusion. At the higher doses of angiotensin I infusion, enalapril and losartan 100 mg attenuated the pressor response.

Figure 33.1. Dorsal Hand Vein Response to Angiotensin II (Left Side) and Angiotensin I (Right Side)
Two Hours Post-Dose



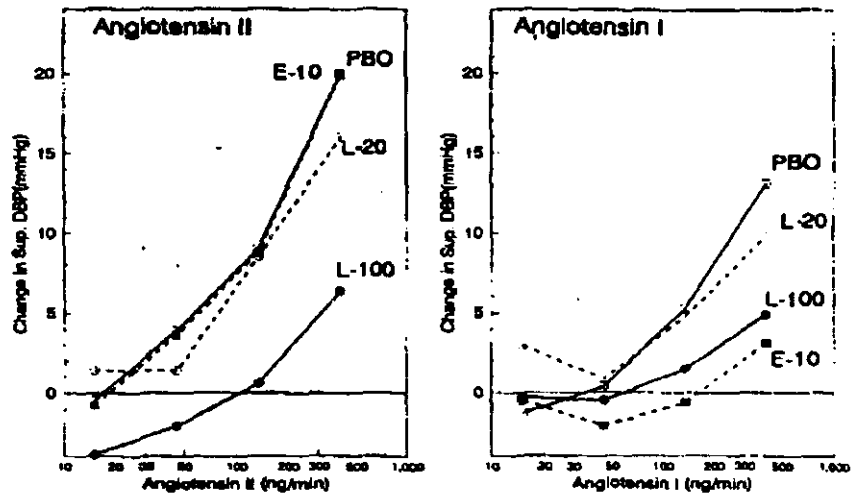
Four Hours Post-Dose



Figures 33.2 and 33.3 plot the change in DBP and SBP with each dose of angiotensin I and II. In general, losartan 100 mg and enalapril attenuated the increase in blood pressure with angiotensin I infusion. Enalapril and losartan 20 mg did not block the increase in blood pressure associated with angiotensin II infusion. Losartan 100 mg attenuated the increase in blood pressure associated with angiotensin II infusion.

Figure 33.2. Diastolic Pressor Responses to Angiotensin II

Two Hours Post-Dose



Four Hours Post-Dose

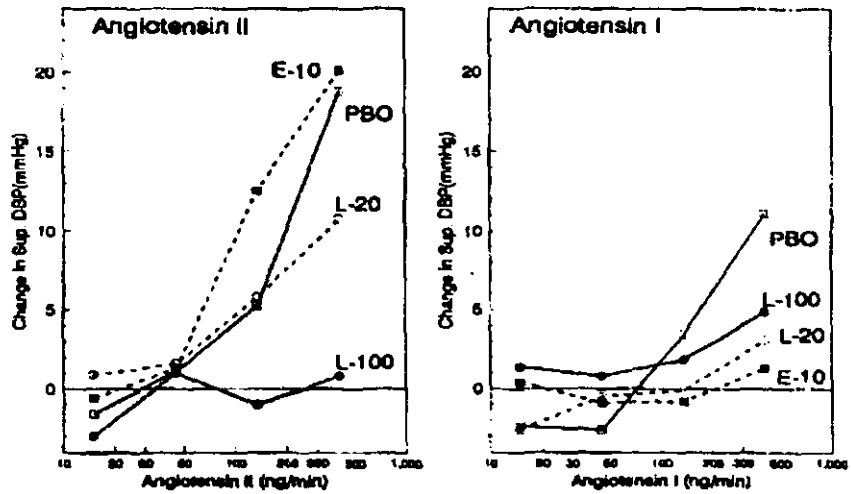
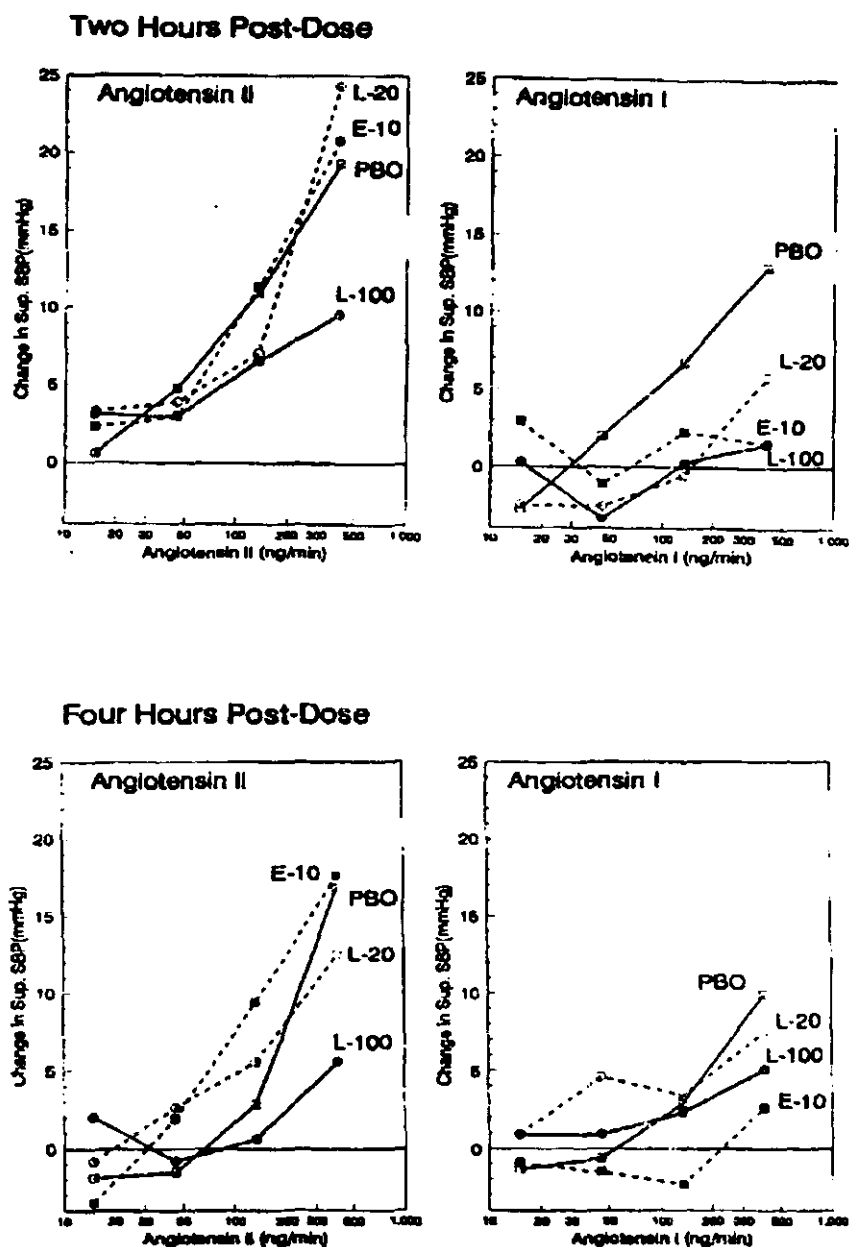


Figure 33.3. Systolic Pressor Responses to Angiotensin II

**Study 034.**

The purpose of this study was to evaluate the effect of losartan on the autonomic nervous system in subjects who were sodium deficient and sodium replete. This was a double-blind, randomized, placebo-controlled, four-period, crossover study in which a single oral dose of placebo or losartan (100 mg) was administered to healthy, non-black male subjects under sodium-depleted and sodium-replete conditions. Sodium depletion was produced by starting subjects on a 40 nmol/day sodium diet plus furosemide 40 mg twice a day for three days prior to dosing. Sodium repletion was produced by giving a subject a 40 nmol/day diet plus Slow Sodium® tablets (100 mmol/day) for three days prior to dosing. Each subject received a single dose of losartan and a dose of placebo on each sodium supplementation regimen. Approximately 14 days elapsed between dosing. The study was performed at a single center.

Prof. John L. Reid
 University Department of Medicine & Therapeutics
 Gardiner Institute, Western Infirmary
 Glasgow, Scotland

The procedures performed in the study are outlined in table 34.1.

Table 34.1. Flowchart of Clinical and Laboratory Procedures

Approximate Time:		8.00					9.00					10.00															
Time Postdose: (Hours)	Pre-study	-24	-2	-1	-5	-2.5	Pre-dose	0.25	0.5	0.75	1	1.5	2	3	4	5	6	7	8	9	10	24	48	Post-study			
PE	X																							X			
Weight	X	X																						X			
ECG	X																							X			
Urine Electrolytes & Creatinine	X						X					X	X	X	X	X	X	X	X	X	X	X	X				
Urine Aldosterone & Osmolality							X					X	X	X	X	X	X	X	X	X	X	X	X				
Urinalysis	X						X																	X			
Insert Venous Cannula			X																								
Hematology	X	X																						X			
Biochemistry	X	X					X								X							X	X	X			
PRA, All, Plasma Drug Conc							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
BP & HR: Supine	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
BP & HR: Erect	X						X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Comparison of Semiautomatic BP Device with Hg Manometer							X									X											
Test Drug Administration							X ⁴																				
Meal			X																	X							
Autonomic Function Tests															X	X											
Urine Void Collection	X		X ¹	-----			X ²	-----			X ²	X ²	-----			X ²	X ²	-----			X ²	X ²	X ³				
Fluid Replacement			X ⁵	X ⁵			X ⁵																				

1 = 24-hour collection, 2 = 2-hour collection, 3 = 14-hour collection, 4 = Following all predose evaluations, 5 = 15 ml/kg of fluid will be given in 3 equal portions.

The tests outlined in table 34.2 were initiated beginning 4 hours after study drug administration. Descriptions of the testing procedures can be found in the clinical summary report of the sponsor.

Table 34.2. Test of Autonomic Function

Test	Rationale	Measure
Standing-to-Lying Test	Bradycardia following this maneuver is due to activation of the parasympathetic system	Heart rate change. Standing-to-lying ratio was calculated as the ratio of the mean erect heart rate* period to the shortest heart rate period in the first 10 beats after starting to lie down.
Forearm Isometric Exercises	This maneuver assessed the sympathetic nervous system	Blood pressure and heart rate change.
Valsalva's Maneuver	Blood pressure overshoot is sympathetically mediated and bradycardia following the maneuver is vagally mediated	Heart rate change. Difference between pre- and post-Valsalva blood pressures and the ratio of the longest heart rate period after the maneuver to the shortest during the maneuver
Diving Reflex	The profound bradycardia induced by the test is due to parasympathetic stimulation.	Heart rate change. Difference between the heart rate before the test and the minimum heart rate during the test
Cold Pressor Test	Sympathetic efferent integrity was assessed	Blood pressure and heart rate change. Maximum difference between inspiratory and expiratory heart rate in the final cycle of respiration. Plasma NE before and after dosing.
Heart Rate Variation With Deep Breathing	The variation in heart rate (an increase in inspiration and a decrease in expiration) is due to changes in vagal tone	Heart rate change. Maximum difference between inspiratory and expiratory heart rate in the final cycle of respiration

* Mean erect heart rate period is defined as the average time interval between heart beats before lying down.

The study enrolled twelve caucasian males between the ages of 18 and 38. Twenty-four hour sodium excretion prior to dosing was not available for two to four subjects depending on the diet and dosing regimen. No explanation for the missing data was provided. For both sodium-depleted regimens, the predose urinary sodium values were less than 100 mmol/24 hours in all subjects for which data were available with the exception of AN 1 and AN 6 (118 mmol/24 hours and 128 mmol/24 hours prior to losartan treatment, respectively). Data were not received for AN 1 and AN 4 prior to placebo administration or for AN 2, AN 7 and AN 8 prior to losartan administration. For the sodium-replete diet regimen, the urinary sodium values recorded were greater than 100 mmol/24 hours for all subjects for which data were available with the exception of 2 subjects prior to placebo dosing (AN 10: 11 mmol/24 hours; AN 12: 21 mmol/24 hours) and 2 subjects prior to losartan dosing (AN 10: 6 mmol/24 hours; AN 11: 56 mmol/24 hours). No data were available for AN 1, AN 2, AN 3 and AN 5 prior to placebo dosing or for AN 4 prior to losartan dosing. AN 8 in the sodium replete/placebo group did not have a postdose value.

All subjects completed each dosing period. Table 34.3 lists the results from the autonomic tests performed. Overall, reflexes following losartan administration, whether in the sodium-replete or sodium-deplete state, were not different from the reflexes following placebo with one exception. In the sodium-deplete state (but not the sodium-replete state), the Valsalva

ratio in the losartan group was significantly ($p \leq 0.050$) lower than that of the placebo group (2.0 vs. 2.2). In view of the many multiple comparisons, the lone significant result is unlikely to represent a true difference between treatments.

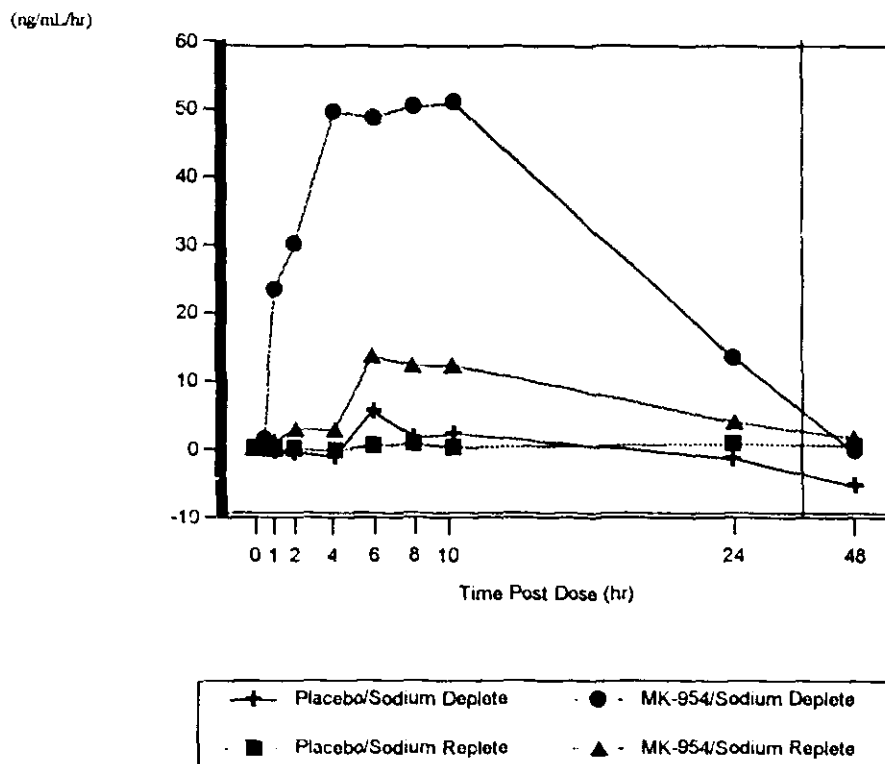
Table 34.3. Summary Of Autonomic Nervous System Tests

Test	Placebo/Deplete		Placebo/Replete		MK-954/Deplete		MK-954/Replete	
	N	Mean (SEM)	N	Mean (SEM)	N	Mean (SEM)	N	Mean (SEM)
Hand Grip SBP (mmHg)	12	19.8(2.9)	12	20.9(3.1)	12	19.7(2.8)	12	24.8(4.6)
Hand Grip DBP (mmHg)	12	15.3(1.7)	12	17.4(2.4)	12	16.8(3.0)	12	15.4(3.1)
Hand Grip HR (bpm)	12	5.7(1.6)	12	13.3(2.6)	12	9.2(1.9)	12	11.2(2.6)
Cold Pressor SBP (mmHg)	12	21.8(4.3)	12	27.9(4.1)	12	24.3(3.1)	11	27.9(3.8)
Cold Pressor DBP (mmHg)	12	15.0(2.6)	12	19.3(3.7)	12	20.8(3.5)	11	24.2(4.5)
Cold Pressor HR (bpm)	12	10.3(1.8)	12	11.9(2.5)	12	9.1(3.9)	11	9.5(2.1)
Valsalva Maneuver (ratio)	12	2.2(0.1)	12	2.3(0.1)	12	2.0(0.2) ⁺	12	2.2(0.1)
Diving Reflex (msec)	12	300.0(41.8)	12	485.0(125)	12	408.4(75.0)	12	504.6(61.6)
Deep Breathing (%)	12	26.2(2.5)	12	35.3(4.8)	12	25.2(2.3)	12	30.8(3.3)
Supine to Erect (ratio)	12	1.2(0.1)	12	1.1(0.0)	12	1.0(0.0)	12	1.1(0.0)

⁺ Significant difference between MK-954 and placebo within sodium deplete diet, $p \leq 0.05$.
There were no significant differences between MK-954 and placebo within sodium replete diet, $p > 0.05$.
There were no significant differences between treatments across diet regimens, $p > 0.05$.

Plasma renin activity was measured at baseline and at 0.5, 1, 2, 4, 6, 8, 10 and 24 hours postdose. All but the 0.5- and 1-hour evaluations postdose were analyzed. Clinically meaningful increases in baseline PRA were observed in both sodium-depleted treatment groups (losartan 11.6 ng/mL/hr, placebo 8.1 ng/mL/hr) compared to the sodium-replete groups (losartan 1.3 ng/mL/hr, placebo 1.8 ng/mL/hr) indicating an activation of the renin-angiotensin system in the sodium-depleted group. Figure 34.1 shows the change in renin activity with each treatment. Losartan caused an increase in renin activity regardless of treatment. The effect is most pronounced in the sodium deplete group.

Change From Baseline in Plasma Renin Activity (ng/mL/hr)



There was no difference in creatinine clearance between treatments. Urine potassium and sodium excretion are plotted in figures 34.2 and 34.3. There is no difference between treatments in sodium and potassium excretion.

Figure 34.2. Urine Potassium (mmol/L)
(mmol/L)

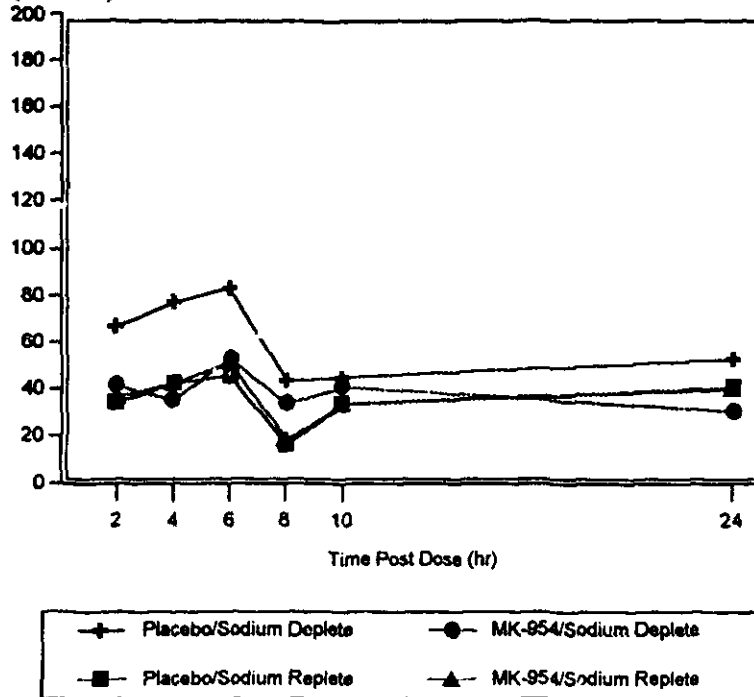
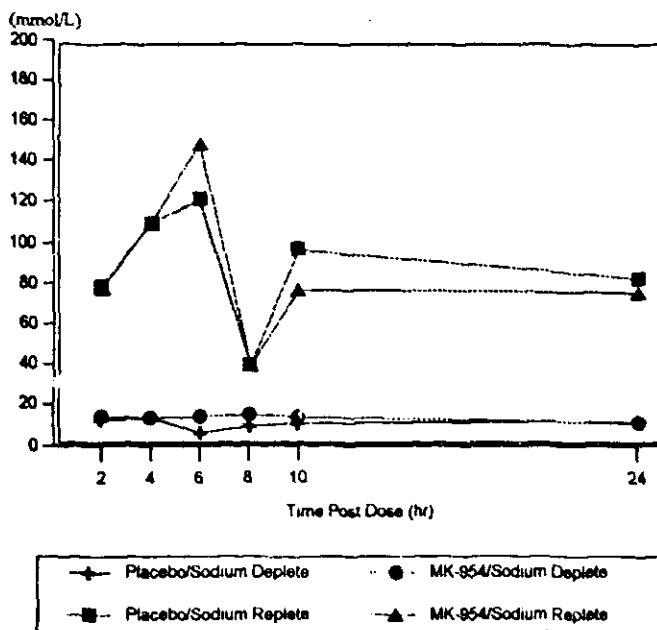


Figure 34.3. Mean Urinary Sodium (mmol/L)
(mmol/L)



Twenty-four hour urinary aldosterone collections were provided for 3 to 6 subjects depending on the diet/treatment regimen.

Of the 12 subjects who entered and completed the study, 7 (58%) subjects had at least one adverse experience after treatment with study drug. Overall, these 7 subjects had 13 adverse experiences that were considered by the investigator to be drug related. All but 2 of these events occurred on the sodium-depleted diet. The most frequent adverse events on the sodium-depleted regimen involved postural hypotension (7 subjects, 58%, including orthostatic effects and hypotension). Other

adverse events included nausea (3 subjects, 25%), vomiting (2 subjects, 17%), headache (1 subject, 8%) and paresthesia (1 subject, 8%). In the sodium-depleted regimen, the percentage of subjects experiencing at least one AE was significantly greater after losartan administration (58%) compared to placebo (8%). This difference was due primarily to the occurrence of orthostatic-related events (defined as adverse experiences involving lightheadedness and postural hypertension in the sodium-depleted/losartan-treated group).

Two subjects (AN 1 and AN 2) experienced laboratory adverse events which were probably related to test therapy according to the investigator. In both cases, elevations in serum urea and serum creatinine occurred at 8 hours after the losartan 100 mg dose on the sodium-depleted diet regimen. No increases were noted with losartan treatment or the sodium-replete diet regimen for these subjects.

Serum urea for AN 1 increased from a predose value of 6.2 mmol/L to 9.2 mmol/L at 8 hours postdose (normal range 2.5 to 7.5 mmol/L). At 24 hours postdose, serum urea was still elevated (8.8 mmol/L), but returned to within normal range at 48 hours postdose (5.3 mmol/L). For AN 2, serum urea increased from 6.7 mmol/L (predose) to 8.9 mmol/L at 8 hours postdose. The serum urea was still elevated at 24 hours (8.8 mmol/L), but returned to normal at 48 hours postdose (5.8 mmol/L).

Serum creatinine for AN 1 increased from a predose value of 81 μ mol/L to 214 μ mol/L (normal range 60 to 110 μ mol/L), but returned to normal at 24 hours (99 μ mol/L). For AN 2, serum creatinine increased from 95 μ mol/L predose to 193 μ mol/L at 8 hours postdose. The value was normal at 24 hours (101 μ mol/L).

Study 035.

This study was a double blind, placebo controlled, single dose, 4-period crossover study. Healthy male subjects received single oral doses of placebo, enalapril 10 mg, losartan 20 mg and losartan 100 mg. Each dose was separated by a 7 day washout period. Approximately 5 - 7 hours after each dose, subjects received sequential 6 minute intraarterial infusions of saline, angiotensin I (16, 64, 256, 1024 pmol/min.), angiotensin II (16, 64, 256, 1024 pmol/min.) and bradykinin (10, 30, 100 pmol/min.). For the last 3 minutes of each 6-minute intra-arterial infusion of saline or one infusion rate of one agonist, blood flow was measured. Forearm blood flow was measured using a mercury-in-Silastic strain gauge as previously established by the investigator. Briefly, on each study day, at the appropriate time, inflatable cuffs were placed on each wrist and each arm (above the elbow) and connected to calibrated air pumps for inflation to appropriate, timed, preset pressures (200 mmHg at the wrists; 40 mmHg at arm). Strain gauges were applied to each arm and adjusted until the blood flow signal was similar for each arm. It was anticipated that the infusion rate for angiotensin I and angiotensin II would be increased until forearm blood flow decreased to 50% or until the maximum infusion rate was achieved. For bradykinin, the infusion rate was increased until forearm blood flow had increased approximately 3-fold (150 to 300%), or the maximal rate had been achieved.

During each of the four treatment periods, forearm blood flow rates (ml/min) were measured in both the infused arm and the other, noninfused, arm during both saline and agonist administration. These flow rates were designated as follows:

$F_{Ag,Inf}$ = Flow rate during agonist in the infused arm,

$F_{Sal,Inf}$ = Flow rate during saline in the infused arm,

$F_{Ag,Nif}$ = Flow rate during agonist in the control (noninfused) arm, and

$F_{Sal,Nif}$ = Flow rate during saline in the control (noninfused) arm.

The agonist/saline ratio of flow rates for each arm are:

$$R_{Inf} = F_{Ag,Inf} / F_{Sal,Inf} \text{ and}$$

$$R_{Nif} = F_{Ag,Nif} / F_{Sal,Nif}$$

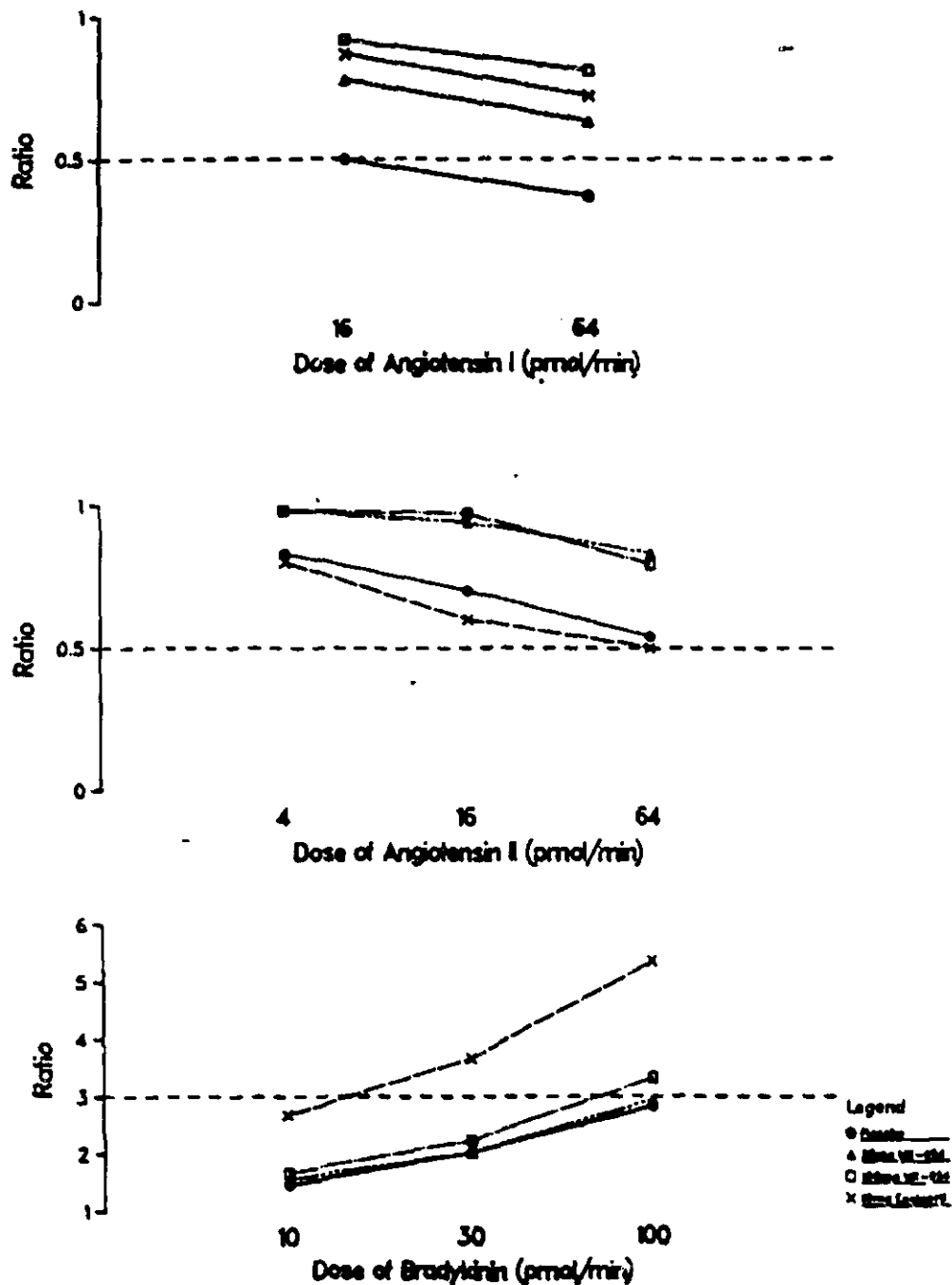
The primary hypothesis of the trial was that during angiotensin II administration, the geometric mean ratio of R_{Inf}/R_{Nif} following MK-954 100 mg to the R_{Inf}/R_{Nif} following placebo will be ≥ 1.8 , i.e., during at least one infusion rate of angiotensin II, the blood flow following MK-954 will be 1.8 times that following placebo (or enalapril).

Secondary hypothesis stated that during angiotensin I administration, the geometric mean ratio of R_{Inf}/R_{Nif} following MK-954 100 mg to the R_{Inf}/R_{Nif} following placebo will be > 1.8 . This will also be the response following 10 mg enalapril. During bradykinin administration, the geometric mean ratio of R_{Inf}/R_{Nif} following enalapril 10 mg to the R_{Inf}/R_{Nif} following placebo will be ≥ 1.5 , i.e., at least 50% enhancement of the response.

Nine healthy male, caucasian volunteers ranging in age from 22 to 47 years of age were enrolled in the study. Complete data from only five patients is included in the analysis. Selective data from four patients is included. As a consequence, it is difficult to determine whether there is some investigator/sponsor bias in the the data presentation. If the results from this trial are to be included in labeling, a complete audit of the data is warranted.

Figure 35.1 plots the geometric mean ratios for some of the doses agonist infused. During angiotensin I infusion, the enalapril and losartan treatments should blunt the pressor effect compared to placebo. This is suggested from the plot. During angiotensin II infusion, losartan but not enalapril should blunt the pressor effect compared to placebo. This is suggested from the plot. During bradykinin infusion, enalapril should enhance the vasodilatory response compared to losartan and placebo. This is suggested from the plot.

Figure 35.1. Within Treatment Geometric Mean Ratios of Forearm Blood Flow



The interpretations of these graphs are further supported by the comparison of the ratios in tables 35.1 - 3.

Table 35.1. Treatment Comparison of Ratios during Angiotensin I Infusion.

Treatment		vs Placebo		vs Enalapril		100 mg losartan vs 20 mg losartan	
		16	64	16	64	16	64
20 mg losartan	Ratio	1.56	1.72	0.90	0.87		
	95% C.I.	(1.42, 1.70)	(1.42, 2.08)	(0.81, 0.99)	0.72, 1.05		
	P-Value	< 0.001	< 0.001	0.23	13		
100 mg losartan	Ratio	1.84	2.20	1.06	1.17	1.18	1.28
	95% C.I.	(1.67, 2.02)	(1.80, 2.70)	(0.96, 1.17)	(0.91, 1.36)	(1.07, 1.30)	(1.05, 1.56)
	P-Value	< 0.001	< 0.001	.24	.26	0.022	0.15
10 mg Enalapril	Ratio	1.74	1.97				
	95% C.I.	(1.58, 1.91)	(1.63, 2.38)				
	P-Value	< 0.001	< 0.001				

Table 35.2. Treatment Comparison of Ratios during Angiotensin II Infusion.

Treatment		vs Placebo			vs Enalapril			vs 20 mg losartan		
		4	16	64	4	16	64	4	16	64
20 mg losartan	Ratio	1.18	1.34	1.55	1.23	1.57	1.65			
	95% C.I.	(1.00, 1.38)	(1.08, 1.65)	(1.23, 1.94)	(1.04, 1.43)	(1.28, 1.93)	(1.30, 2.08)			
	P-Value	.042	.010	.0021	.014	.0002	.0023			
100 mg losartan	Ratio	1.19	1.38	1.47	1.23	1.62	1.56	1.00	1.03	0.95
	95% C.I.	(1.00, 1.41)	(1.10, 1.73)	(1.17, 1.85)	(1.04, 1.46)	(1.30, 2.02)	(1.21, 1.98)	(0.85, 1.20)	(0.83, 1.29)	(0.76, 1.20)
	P-Value	.051	.0080	.0039	.019	.0003	.0043	.92	.78	.67
10 mg Enalapril	Ratio	0.96	0.86	0.94						
	95% C.I.	(0.82, 1.13)	(0.69, 1.05)	(0.74, 1.19)						
	P-Value	.61	.13	.65						

Table 35.3. Treatment Comparison of Ratios during Bradykinin Infusion.

Treatment		vs Placebo			vs Enalapril			100 mg MK-954 vs 20 mg MK-954		
		10	30	100	10	30	100	10	30	100
20 mg Losartan	Ratio	1.07	1.00	1.04	0.58	0.55	0.55			
	95% C.I.	(0.86, 1.33)	(0.82, 1.20)	(0.81, 1.32)	(0.49, 0.73)	(0.45, 0.67)	(0.43, 0.70)			
	P-Value	.51	.95	.74	< 0.001	< 0.001	< 0.001			
100 mg Losartan	Ratio	1.14	1.10	1.17	0.62	0.61	0.67	1.07	1.10	1.13
	95% C.I.	(0.91, 1.43)	(0.90, 1.33)	(0.91, 1.51)	(0.49, 0.78)	(0.49, 0.74)	(0.48, 0.80)	(0.85, 1.34)	(0.90, 1.35)	(0.87, 1.46)
	P-Value	.23	.33	.20	.0003	< 0.001	.0009	.58	.34	.36
10 mg Enalapril	Ratio	1.84	1.81	1.89						
	95% C.I.	(1.49, 2.26)	(1.50, 2.18)	(1.50, 2.39)						
	P-Value	< 0.001	< 0.01	< 0.001						

Ratios of R_{inf}/R_{Nd} between treatments, 95% confidence interval, and test that the ratio between the treatments is different from 1.0.

Study 060.

This was an open, three-period crossover study in 6 healthy male subjects. ^{14}C -losartan (MK-954) was administered in a randomized manner in the first and third periods as a single 100 mg oral dose (100 μ Ci) and as a single 30 mg intravenous dose (100 μ Ci). At least 7 days separated periods 1 and 2 and 2 and 3, providing a total of at least 14 days between the two radioactive treatments. During the second treatment period, E-3174 (without radioisotope) was administered as a single 20 mg intravenous dose. Blood samples were collected up to 48 hours after dosing. Urine samples were collected up to 96 hours after dosing. Feces were collected over the 168-hour period following each radioisotope (Periods 1 and 3) drug administration.

Six healthy male volunteers (5 caucasians, 1 black) between the age range of 22 and 30 years entered and completed the study. Following the completion of this study (#060), subject AN 0012 was identified from Study #075 who, based upon analysis of his plasma following three separate administrations of losartan 50 mg, had barely detectable E-3174 in plasma. To further investigate the metabolism of losartan in this subject, this protocol was amended (Amendments 060-01/02) to enroll this subject as subject number 007 and to specifically investigate his metabolism of losartan, using radiolabelled drug and to incorporate metabolic phenotyping using specified probe drugs. The data from the six subjects (AN 001-006) who completed the study were included in the pharmacokinetic analyses. Data from patient AN 007 was not included in the summary of this study.

Table 60.1 lists the pharmacokinetic parameters measured after each treatment. The mean (harmonic) elimination half life is approximately 3 hours for losartan and 6 - 8 hours for E-3174. The absolute bioavailability of the oral solution is approximately 39%.

Table 60.1. Pharmacokinetics Parameters (mean±S.D.) of Losartan and E-3174

	Intravenous E-3174 20 mg	Intravenous Losartan 30 mg (100 µCi)		Oral Losartan (Solution) 100 mg (100 µCi)	
	E-3174	Losartan	E-3174	Losartan	E-3174
C _{20min} , ng/mL	3720.7 ± 342.2	1452.8 ± 636.4	-	-	-
C _{max} , ng/mL	-	-	148.9 ± 78.9	659.1 ± 244.0	652.6 ± 259.1
T _{max} , hr	-	-	4.0 ± 2.1	0.46 ± 0.29	2.33 ± 0.52
AUC _{0-∞} , ng/mL·hr	5969.27 ± 709.03	851.18 ± 234.54	1331.96 ± 490.24	1091.35 ± 397.46	4072.54 ± 1252.91
λ, hr ⁻¹	0.1105 ± 0.0228	0.2181 ± 0.0531	0.1304 ± 0.0501	0.2418 ± 0.0502	0.0881 ± 0.0092
t _{1/2} , hr ^a	6.27 ± 1.36	3.18 ± 0.78	5.32 ± 2.1	2.87 ± 0.57	7.87 ± 0.82
V _{ds} , L	10.33 ± 1.09	46.59 ± 20.50	-	-	-
CL, mL/min	46.93 ± 5.79	558.71 ± 188.01	-	-	-
CL _T , mL/min	25.88 ± 5.59	64.39 ± 25.96	25.25 ± 7.00	64.63 ± 17.28	27.00 ± 6.10
Recovered in Urine (mg)	9.129±1.414	3.020±0.836	1.911±0.616	4.297±1.878	6.516±2.186
% Dose ^c	55.07 ± 8.95	11.50 ± 3.49	7.59 ± 2.30	4.77 ± 2.08	7.63 ± 2.58
F, % ^b	-	-	-	38.90 ± 14.67	-

^a Harmonic mean and pseudo standard deviation.

^b Oral Bioavailability, geometric mean was 36.47% with 90% confidence interval limits of 26.11% to 50.94%.

^c % dose recovered in the urine as losartan.

Radioactivity in plasma, urine and feces was determined after the administration of 100 mg (100 µCi) of oral losartan (solution) and 30 mg (100 µCi) of intravenous losartan as listed in Table 60.2. Plasma radioactivity following I.V. and oral administration was primarily accounted for by losartan and E-3174. Metabolic profiling of urine was determined after the 100 mg (100 µCi) of oral losartan (solution) and 30 mg (100 µCi) of I.V. losartan. Metabolic profiling in the feces was a qualitative assessment using specimens following I.V. administration from subjects 001 and 002; therefore only these individual data are presented. The three major metabolites identified in the urine were L-158,795, L-158,796, E-3174 and L-158,783 was considered a minor metabolite.

Table 60.2. Total Radioactivity and Metabolic Profiling (% dose)

	I.V. Losartan 30 mg (100 µCi)		Oral Losartan 100 mg (100 µCi) ^a	
	Urine	Feces	Urine	Feces
Total Radioactivity	43.3 ± 8.4	49.5 ± 13.3	35.2 ± 6.2	57.7 ± 7.9
Metabolic Profile		AN001	AN002	
Losartan	11.4 ± 4.0	12.8	7.77	4.91 ± 2.27
L-158,795	9.35 ± 1.73	8.20	8.38	9.09 ± 1.79
E-3174	6.44 ± 2.45	6.92	13.38	6.41 ± 2.22
L-158,796	8.24 ± 1.76	7.3	9.44	7.64 ± 1.80
L-158,783	0.267 ± 0.109	0.794	1.31	-

^a 30 mg radioactive losartan + 70 mg of non-radioactive losartan

Study 067.

This was a randomized, open, three-period crossover pharmacokinetic study in 9 patients with Class A or B hepatic insufficiency. Patients received 3 different treatments in a randomized sequence. Each treatment was separated by a 7-day washout. The 3 treatments were a single oral 50 mg tablet of losartan, a single 10 mg I.V. dose of losartan and a single 10 mg I.V. dose of E-3174.

Subjects had a clinical diagnosis of hepatic insufficiency due to alcoholic liver disease, met the Child-Pugh Classification as having Class A (5-6) or B (7-9) liver disease, had a serum creatinine and BUN within 150% of normal range values and had a creatinine clearance ≥ 65 ml/min/1.73m². Table 67.1 lists the criteria used in the Child-Pugh classification. Each variable is given a point score of 1 to 3 and then totaled giving a class of severity.

Table 67.1. Pugh's Modification of Child's Classification of the Severity of Liver Disease

Points Score for Increasing Abnormality	1	2	3
Encephalopathy (grade)	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Bilirubin (mg/100 mL)	1-2	2-3	>3
Albumin (g/l)	>35	28-35	<28
Prothrombin time (seconds over control)	1-4	4-6	>6
Bilirubin in PBC (mg/100 mL) ¹	1-4	4-10	>10

¹The Bilirubin classification criteria differs for patients with primary biliary cirrhosis. PBC = Primary Biliary Cirrhosis

Nine patients with hepatic insufficiency between the ages of 42 and 63 entered and completed the study. All patients had a Child-Pugh score greater than 5, ranging from 5-9. Table 67.2 gives the demographic characteristics of the patients who entered and completed the study. All subjects had elevations in the prothrombin time at some point in the study. Other lab abnormalities related to liver dysfunction varied between patients. For example, only 3 of 9 had abnormal total bilirubin.

Table 67.2. Patient Characteristics

Patient	Age Years	Sex	Race	Weight (lbs)	Child-Pugh Score	CrCl ml/min
1	59	M	Caucasian	171.5	5	89.3
2	57	F	Caucasian	172.5	5	83.85
3	48	M	Caucasian	191.0	7	195
4	53	M	Caucasian	200.0	7	106
5	63	M	Caucasian	115.5	8	65
6	60	M	Caucasian	151.0	7	92.6
7	55	M	Caucasian	181.0	7	110.8
8	61	M	Caucasian	250.0	5	116.4
9	42	M	Caucasian	201.0	9	113.9
Mean	55.3			181.5	-	108.09
Range	42 to 63			115.5 to 250	5-9	65 to 195

Data from these patients was compared to data from other pharmacokinetic trials (study 74 and 75) that enrolled healthy males. In general, the AUC, C_{max} and absolute bioavailability of losartan was increased compared to healthy male subjects. Total clearance and volume of distribution was decreased. The terminal elimination half-life and time to maximum concentration was unchanged. For E-3174, the volume of distribution and systemic clearance were decreased slightly. The area under the curve was increased by approximately 50%. The C_{max} increased by approximately 20%. The elimination rate constant was essentially unchanged. Tables 67.3 - 67.4 list the pharmacokinetic parameters for losartan and E-3174.

Table 67.4. Pharmacokinetic Parameters for Oral Losartan

	STUDY	N	Mean	Median	95% CI for the mean
AUC (ng•hr/mL) for losartan					
	Study 67	9	2187.84	2267.56	(1320.85, 3004.82)
	Study 74	12	475.56	474.17	(348.78, 602.35)
	Study 75	17	402.80	377.77	(351.13, 454.47)
Volume of Distribution (Liters) of Losartan					
	Study 67	9	19.65	16.31	(12.14, 27.15)
	Study 60	6	46.59	43.12	(25.07, 68.10)
	Study 74	12	28.36	23.02	(19.72, 37.01)
C_{max} (ng/mL) of Losartan					
	Study 67	9	1171.77	1186.10	(658.98, 1684.56)
	Study 74	12	296.38	242.30	(158.48, 434.28)
	Study 75	17	209.24	168.70	(157.89, 260.58)
Systemic Clearance (mL/min) of Losartan					
	Study 67	9	285.04	301.55	(210.13, 359.96)
	Study 60	6	558.71	500.59	(361.40, 756.01)
	Study 74	12	635.95	644.32	(567.71, 704.19)
AUC (ng•hr/mL) for E-3174 Following Oral Losartan					
	Study 67	9	3131.19	3254.55	(2193.75, 4068.62)
	Study 74	12	1915.25	1811.52	(1573.53, 2256.96)
	Study 75	17	1778.33	1808.31	(1555.03, 2001.63)
C_{max} for E-3174 (ng/mL) Following Oral Losartan					
	Study 67	9	296.21	264.80	(212.54, 379.88)
	Study 74	12	249.40	245.00	(202.60, 296.20)
	Study 75	17	225.42	211.40	(165.41, 285.43)
Systemic Clearance (mL/min) of E-3174 Following IV E-3174					
	Study 067	9	33.18	26.32	(23.06, 43.30)
	Study 060	6	46.93	47.64	(40.85, 53.01)

Table 67.5. Bioavailability of Losartan

STUDY	N	Mean	Geometric Mean	Median	95% CI for the mean	95% CI for the Geometric mean
67	9	64.76	61.31	56.31	(48.02, 81.50)	(45.61, 82.41)
74	12	35.80	32.65	35.26	(25.93, 45.66)	(25.27, 42.17)

Diastolic blood pressure on average did not appear to decline precipitously. The maximum mean decrease from baseline in supine DBP was -5.0 mmHg. The greatest individual decline in supine DBP was -13 mmHg. Although the blood pressure data in this study did not suggest that on average there is dramatic decline secondary to the increased C_{max}, consideration should be given to starting with a lower initial dose in patients with hepatic insufficiency and titrating carefully based on effect.

Study 72.

This was a single blind, single dose, 2 period study in 15 healthy males subjects. The trial consisted of 2 treatment periods. In period one, all subjects received a single dose of losartan on Day 1. After a 48 hour washout, period two commenced, consisting of a 16-day course of either phenobarbital or placebo and a single dose of losartan between doses 14 and 15 of phenobarbital/placebo. Ten subjects received 14 days of phenobarbital followed by a single dose of losartan and five subjects received 14 days of placebo and a single dose of losartan. Table 72.1 lists the pharmacokinetic parameters measured in the study. Phenobarbital administration caused the AUC of losartan and E-3174 (L-158,641) to decrease by approximately 20%.

Table 72.1. Pharmacokinetic Parameters

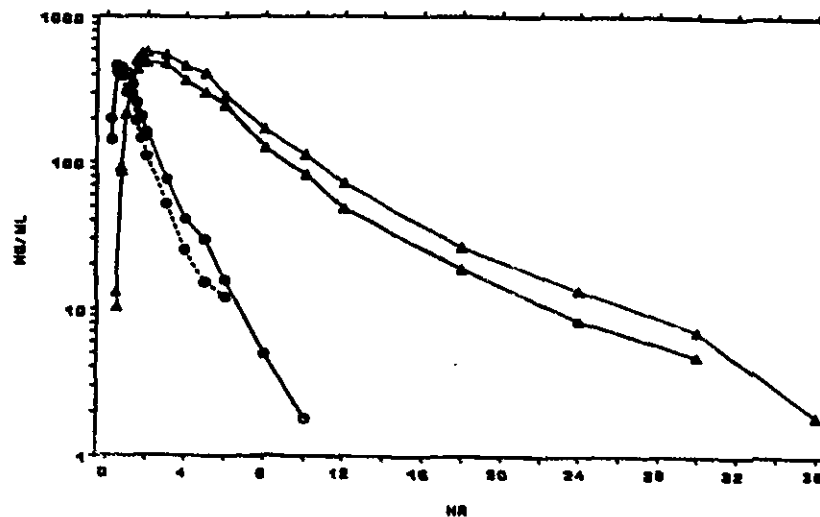
		Period I - 100 mg of MK-954 Given Prior to Phenobarbital or Placebo Administration		Period II - 100 mg of MK-954 Taken on Day 15 of Phenobarbital or Placebo Administration	
		MK-954	L-158,641	MK-954	L-158,641
Phenobarbital Treatment Group (n=10), 100 mg Once a Day for 16 Days					
C _{max} , ng/mL		588.4 ± 300.1	646.3 ± 136.8	586.9 ± 268.8	583.8 ± 132.9
T _{max} , hr		0.88 ± 0.29	2.23 ± 0.70	0.88 ± 0.46	2.38 ± 1.14
AUC, ng·hr/mL		854.31 ± 193.97	3784.92 ± 468.61	673.84 ± 124.98	3022.17 ± 361.38
λ, hr ⁻¹		0.4041 ± 0.1298	0.1012 ± 0.0391	0.4049 ± 0.1100	0.1102 ± 0.0482
t _{1/2} , hr ^a		1.72 ± 0.55	6.85 ± 2.76	1.71 ± 0.45	6.29 ± 2.88
CL _r , mL/min		69.55 ± 4.96	22.70 ± 2.08	68.50 ± 6.29	22.19 ± 3.11
Urinary Recovery	mg	3.725 ± 0.931	5.105 ± 0.504	2.825 ± 0.634	3.964 ± 0.429
	% Dose	3.75 ± 0.94	5.42 ± 0.54	2.84 ± 0.64	4.21 ± 0.45
Placebo Treatment Group (n=5), Placebo Once a Day for 16 Days ^b					
C _{max} , ng/mL		381.5 ± 140.7	470.9 ± 119.3	355.8 ± 83.8	444.4 ± 172.2
T _{max} , hr		1.31 ± 0.13	3.50 ± 0.58	1.25 ± 0.41	3.50 ± 1.29
AUC, ng·hr/mL		684.10 ± 206.49	3048.38 ± 909.43	697.93 ± 189.38	3179.42 ± 1098.9
λ, hr ⁻¹		0.4098 ± 0.0622	0.0958 ± 0.0438	0.3172 ± 0.083	0.0656 ± 0.0248
t _{1/2} , hr ^a		1.69 ± 0.25	7.23 ± 3.13	2.18 ± 0.59	10.56 ± 4.02
CL _r , mL/min		78.87 ± 8.26	26.37 ± 2.19	77.13 ± 5.64	24.77 ± 1.09
Urinary Recovery	mg	3.440 ± 1.125	4.816 ± 1.654	3.291 ± 0.929	4.655 ± 1.798
	% Dose	3.46 ± 1.13	5.11 ± 1.76	3.31 ± 0.93	4.94 ± 1.91
^a Harmonic mean and pseudo standard deviation.					
^b C _{max} , T _{max} , AUC, λ, t _{1/2} , CL _r and urinary recovery: n=4, data for subject #5 excluded.					

Patient #5 had had low levels of the metabolite and therefore this subject was considered to be an outlier. To further investigate the metabolism of losartan in this subject, the protocol was amended (Amendments 072-01/02). The results of the amendments did not make the in-house cutoff date (1/14/93) for the clinical study report and are not included in the sponsor's summary. This patient's data was not included in the calculations of the pharmacokinetic parameters.

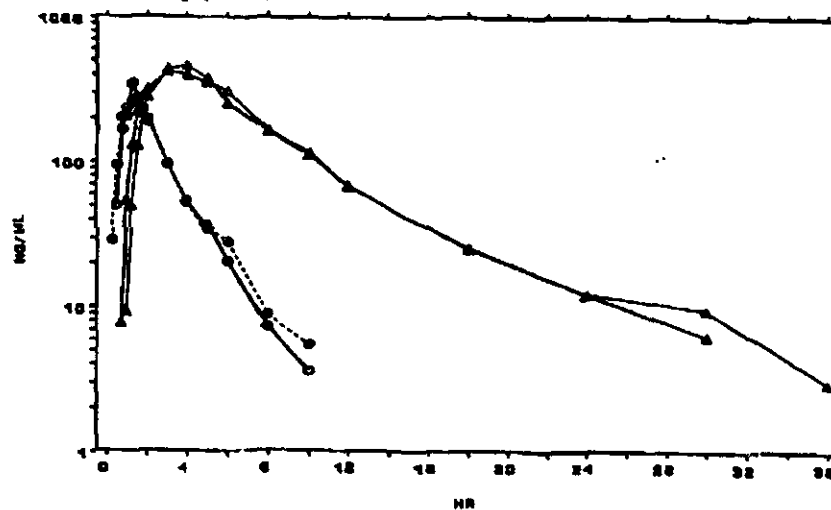
Figure 72.1 plots the mean concentrations for losartan and E-3174.

Figure 72.1. Mean Plasma Concentration vs. Time Profiles For Losartan and L-158,641 in the Groups which Received Phenobarbital (TOP) and Placebo (EOTTOM)

Phenobarbital Group(N=10)



Placebo Group(N=4)



○ = MK-954 Pre-Rx; ● = MK-954 During Rx; △ = L-158,641 Pre-Rx;
▲ = L-158,641 During Rx

The data do indicate that the metabolism of losartan, and probably L-158,641, can be influenced by induction of cytochrome P450. While levels of induction achieved with phenobarbital are minor and are unlikely to result in a clinically important affect on the activity of losartan, the data do not eliminate the possibility of interaction of P450 induction with other patient factors which influence drug metabolism.

Study 70.

This as a double-blind, randomized, placebo-controlled, two-period crossover study in ten normal volunteers. In each period, each subject received, according to a random allocation schedule, either losartan 100 mg orally or matched placebo for 12 days, with a single 30 mg oral dose of sodium warfarin on Day 7. This treatment scheme is illustrated in Table 70.1.

Table 70.1. Treatment Scheme

Day:	1	2	3	4	5	6	7	8	9	10	11	12	13
Warfarin, 30 mg (1 dose)							X						
Losartan or placebo, 100 mg q.d.	X	X	X	X	X	X	X	X	X	X	X	X	X

After the completion of the first treatment period (randomized to losartan or placebo) followed by a 2-week washout period, each subject was crossed over to the complementary treatment period identical except for the substitution of losartan for placebo and vice versa. The two warfarin doses, one in each treatment period, were separated by 4 weeks.

Just prior to and at intervals following warfarin administration, blood was drawn for determination of levels of (R) and (S) warfarin and prothrombin time.

The primary pharmacodynamic measurement was prothrombin time (reported in two units – seconds and INR). Two summary measures were calculated for each subject: area under the curve (0 to 144 hours) with respect to changes from baseline in prothrombin time and the maximum change in prothrombin time by subject. An ANOVA model containing terms for subject, period, and treatment was used to analyze the differences between treatments with respect to these summary measures.

Separate analyses were carried out for the pharmacokinetics of each enantiomer (R and S) of warfarin, based on results of a stereospecific assay. Ln-transformed area under the plasma concentration curve (lnAUC), ln-transformed maximum plasma concentration (lnC_{max}), maximum plasma concentration (C_{max}) and time until maximum plasma concentration (T_{max}) were the primary pharmacokinetic measurements analyzed.

Ten healthy male volunteers ranging in age from 18 to 29 years were enrolled. Patient #3 withdrew prematurely for personal reasons after day 10 of losartan therapy (2nd sequence). Data for patient #3 is not included in the summary by the sponsor. Table 70.2 and 70.2a list the mean pharmacokinetic parameters of the R and S enantiomers of warfarin. There does not appear to be a significant difference between parameters with losartan therapy.

Table 70.2. Pharmacokinetics (arithmetic mean ±S.D.)

Parameter	R-Warfarin		S-Warfarin	
	Losartan	Placebo	Losartan	Placebo
AUC(ng•hr/mL)	87861.0	87195.4	70266.0	70194.9
(± S.D.)	(14941.7)	(22525.9)	(13956.1)	(17945.9)
C _{max} (ng/mL)	1656.3	1496.3	1647.0	1615.6
(± S.D.)	(382.9)	(256.1)	(308.8)	(258.1)
λ(hr ⁻¹)	0.015	0.016	0.020	0.020
(± S.D.)	(0.002)	(0.003)	(0.003)	(0.003)
t _{1/2} (hr) ¹	44.97	44.34	34.97	36.00
(± S.D.)	(2.49)	(3.11)	(2.06)	(2.20)

Table 70.2a. Pharmacokinetics (geometric mean ratios and treatment differences)

Parameter	Least Square Means		Trt Diff ²	90% CI
	Losartan	Placebo		
R-Warfarin				
AUC(ng•hr/mL) ³	87040.29	84199.81	1.034	(.967, 1.105)
C _{max} (ng/mL) ³	1608.71	1489.29	1.080	(.953, 1.224)
T _{max} (hr)	2.90	2.77	.125	(-1.59, 1.836)
S-Warfarin				
AUC(ug•hr/mL) ³	69461.29	67787.18	1.024	(.945, 1.111)
C _{max} (ng/mL) ³	1616.49	1603.22	1.008	(.928, 1.096)
T _{max} (hr)	1.70	2.08	-.375	(-.999, 0.249)

¹ Harmonic mean and pseudo standard deviation.

² Treatment effect estimates are geometric mean ratios for log-transformed values, otherwise treatment estimates reflect arithmetic mean differences (losartan - placebo)

³ Log transformed for analysis by ratio.

Tables 70.3 and 70.3a list the AUC and maximum change in prothrombin time. There is a slight increase with losartan treatment but this difference is not significant. The AUC and C_{max} difference is illustrated in figure 70.1.

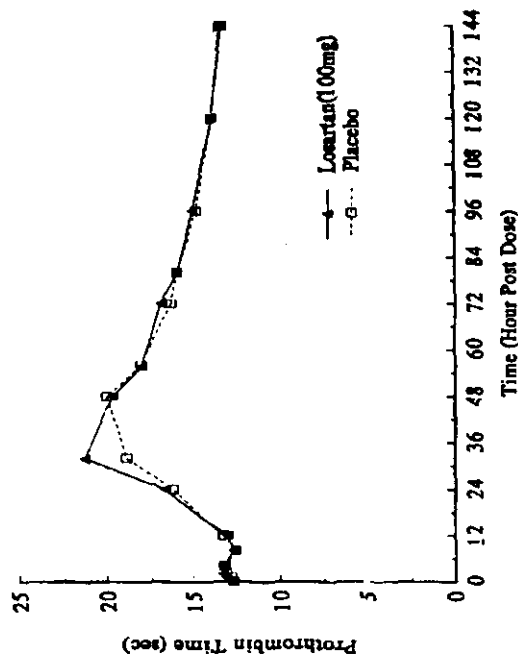
Table 70.3. AUC (0-144 hr) for Prothrombin Time

Subject	Seconds*hr		INR*hr	
	Losartan	Placebo	Losartan	Placebo
0001	661.20	867.70	138.24	197.42
0002	352.20	426.90	63.93	73.47
0004	279.95	225.55	51.59	38.44
0005	577.30	485.55	107.21	86.36
0006	214.00	358.55	38.20	64.65
0007	478.05	499.70	88.25	105.42
0008	785.00	381.60	96.98	69.83
0009	375.80	247.80	73.82	48.34
0010	226.70	194.05	41.46	36.02
Overall				
Mean	438.91	409.71	77.74	80.00
Std	200.71	204.31	33.13	49.40
LS Mean	433.20	415.42	76.64	81.10
Median	375.80	381.60	73.82	69.83
Min	214.00	194.05	39.20	36.02
Max	785.00	867.70	138.24	197.42

Table 70.3a. Maximum Change in Prothrombin Time

Subject	Seconds		INR	
	Losartan	Placebo	Losartan	Placebo
0001	10.30	17.90	2.39	4.94
0002	6.30	5.60	1.22	1.02
0004	4.20	3.00	0.81	0.53
0005	8.70	7.30	1.77	1.41
0006	4.10	6.90	0.76	1.35
0007	7.00	10.90	1.37	2.59
0008	32.00	7.00	2.17	1.37
0009	6.50	5.30	1.36	1.19
0010	4.60	4.20	0.87	0.80
Overall				
Mean	9.30	7.62	1.41	1.69
Std	8.76	4.44	0.59	1.35
LS Mean	9.04	7.88	1.37	1.73
Median	6.50	6.90	1.36	1.35
Min	4.10	3.00	0.76	0.53
Max	32.00	17.90	2.39	4.94

Figure 70.1. Prothrombin Time (Seconds) Means Across Time



This study appears to show a lack of a pharmacokinetic interaction between losartan and warfarin. It is not clear that this has any clinical relevance. The pharmacodynamic conclusions are weak. It is not clear that the design of this study is adequate to make any statement regarding the effect on prothrombin time. The sponsor cites a reference supporting the use of this design (Rocci ML, et al. Norfloxacin does not alter warfarin disposition or anticoagulant effect. *J Clin Pharmacol* 1990;30:728-732.). In the norfloxacin study, warfarin concentration (R and S) measured by AUC and Cmax was not changed by norfloxacin. Prothrombin time measured by AUC and prothrombin time maximum were not different. However, it is recognized, as stated in the labeling, that norfloxacin "may enhance the effects of the anticoagulant warfarin or its derivatives". This interaction may result from increased levels of free warfarin. That is where this study fails. Since < 1% of warfarin is free drug, measuring total drug is inadequate to assess an interaction. The design of this trial failed to predict a pharmacodynamic enhancement of warfarin by another drug. Consequently, the labeling for losartan should not include the results of this study. [Reviewer's Note: Patient #1031 in study 47 had gingival bleeding and an increased prothrombin time when treated with losartan and warfarin.]

Study 063.

This was a single center, open, 2-period, cross-over, single dose pharmacokinetic study in 10 (5 male and 5 female) elderly (>65 years of age) hypertensive patients. Patients were withdrawn from their usual antihypertensive regimen for at least 1 week. On each study day, patients received either the 50 mg losartan tablet or the 10 mg losartan I.V. solution in accordance with a randomized allocation schedule. The intravenous doses were administered over a 20-minute interval and each dose was separated by a 14-day washout period.

The average age of patients was 69.9 years of age (range: 65 - 75). All of the patients were caucasian. Tables and figures 63.1 - 63.4 list the AUC, Cmax, absolute bioavailability and systemic clearance for losartan in study 063 compared to studies that included predominantly healthy males. In study 063, females generally had higher AUC, Cmax and absolute bioavailability compared to males in study 063. Systemic clearance generally was lower in females. Males throughout several studies had similar results where as females differed.

Table 63. 1. $AUC_{0-\infty}$ (ng-hr/ml) for Plasma Losartan Concentration Versus Time

Study	Sex	N	Age Range	Mean	LSmeans	95% Confidence Interval
Hypertensive Subjects						
004	Both	18	32-65	641.29	722	(514.19, 768.39)
004	Female	5	43-58	822.54		(428.81, 1216.27)
004	Male	13	32-65	571.58		(450.61, 692.54)
Young Healthy Males						
007	Male	10	18-31	413.00	678	(283.64, 542.35)
015	Male	8	19-29	416.32	681	(339.90, 492.74)
022	Male	8	21-35	361.22	626	(204.11, 518.32)
Elderly Hypertensives						
063	Both	10	65-75	743.25	743	(494.56, 991.97)
063	Female	5	66-75	1008.38		(671.29, 1345.46)
063	Male	5	65-73	478.15		(291.69, 664.62)

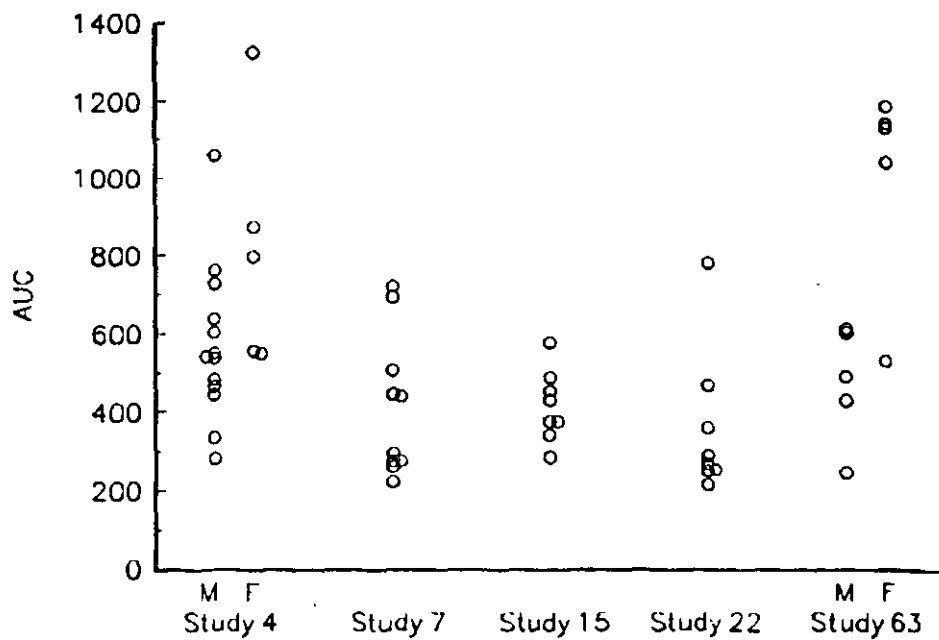
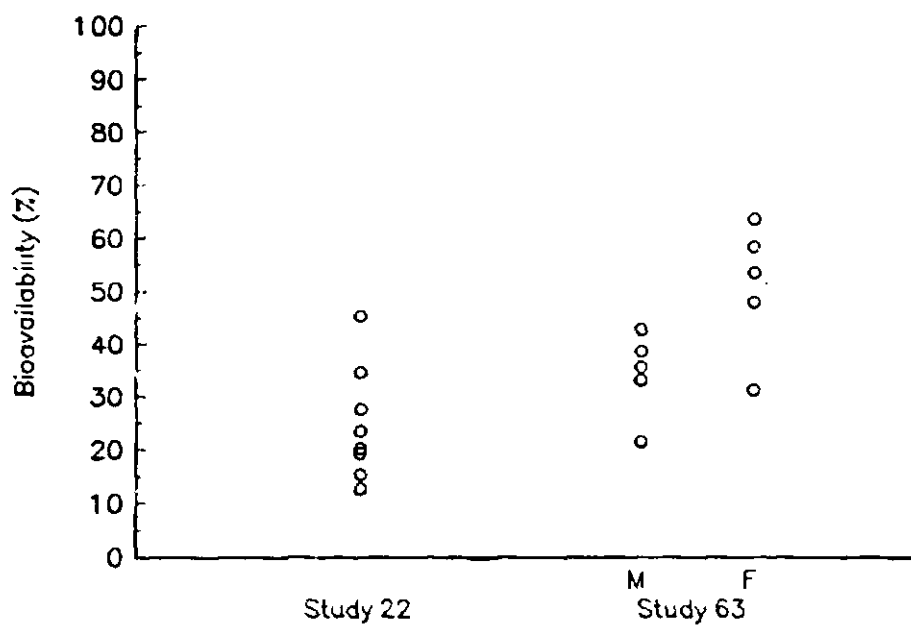
Figure 63.1. $AUC_{0-\infty}$ (ng-hr/ml) for Losartan

Table 63.2. Losartan Absolute Bioavailability

Study	Sex	N	Mean	LSmeans	95% Confidence Interval	Geometric Mean	90% Geometric Mean C.I.
<u>Young Healthy Males</u>							
022	Male	8	25	33	(16, 34)	22.9	(17.3, 30.3)
<u>Elderly Hypertensives</u>							
063	Both	10	43	43	(33, 52)	40.6	(33.5, 49.2)
063	Male	5	34		(24, 44)	33.4	(25.9, 43.0)
063	Female	5	51		(35, 66)	49.4	(37.9, 64.5)

Figure 63.2. Absolute Bioavailability (%) of Losartan

Table 63.3. Maximum Losartan Plasma Concentration (C_{max} ng/ml)

Study	Sex	N	Mean	LSmeans	95% Confidence Interval
<u>Young Healthy Males</u>					
015	Male	8	259.07	401	(175.29, 342.86)
022	Male	8	243.08	385	(146.22, 339.95)
<u>Elderly Hypertensives</u>					
063	Both	10	391.07	391	(230.97, 551.17)
063	Female	5	533.08		(263.42, 802.74)
063	Male	5	249.06		(96.38, 401.74)

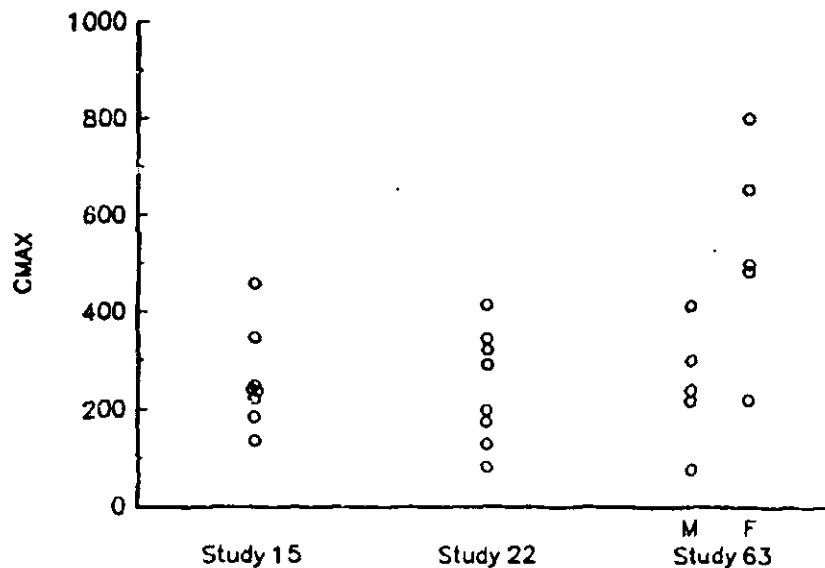
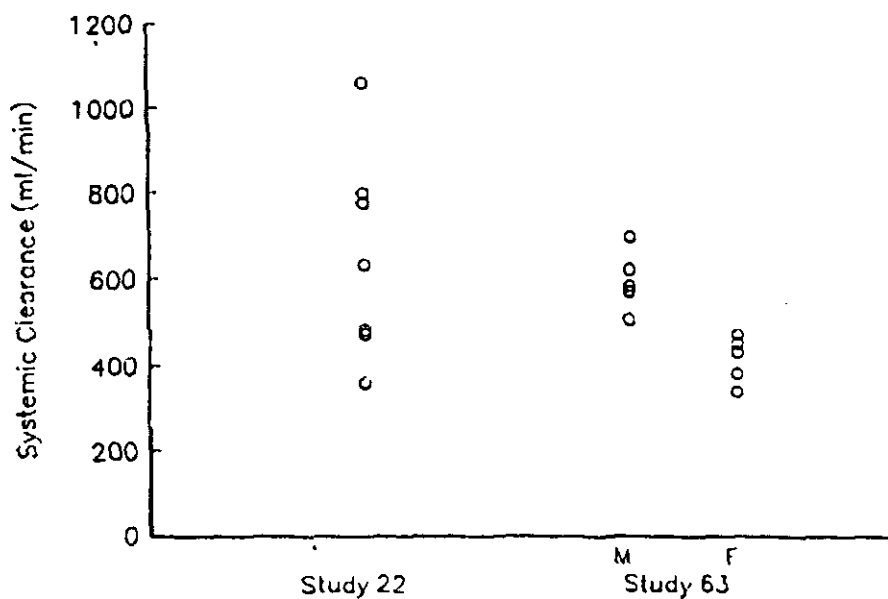
Figure 63.3. C_{max} (ng/ml) for Losartan

Table 63.4. Systemic Clearance (ml/min)

Study	Sex	N	Mean	LSmeans	95% Confidence Interval
Young Healthy Males					
022	Male	8	618.04	527.45	(411.61, 824.46)
Elderly Hypertensives					
063	Both	10	506.57	506.57	(426.18, 586.96)
063	Female	5	416.0		(347.89, 484.09)
063	Male	5	597.16		(510.31, 684.00)

Figure 63.4. Systemic Clearance (ml/min) for Losartan



In general, elderly hypertensive patients had greater AUC but not C_{max} for E-3174 compared to healthy younger males in other studies.

Table 63.5. $AUC_{0-\infty}$ (ng-hr/ml) for Plasma L-158,641

Study	Sex	N	Age Range	Mean	LSmeans	95% Confidence Interval
Hypertensive Subjects						
004	Both	18	32-65	2707.48	2789	(2346.77, 3068.18)
004	Female	5	43-58	2952.59		(2065.79, 3839.39)
004	Male	13	32-65	2613.21		(2168.87, 3057.54)
Young Healthy Males						
007	Male	10	18-31	1843.34	2048	(1443.16, 2243.52)
015	Male	8	19-29	1561.13	1766	(1294.46, 1827.81)
022	Male	8	21-35	1780.36	1985	(1493.63, 2067.09)
Elderly Hypertensives						
063	Both	10	65-75	2681.70	2682	(2128.65, 3234.75)
063	Female	5	66-75	2886.59		(1691.35, 4081.82)
063	Male	5	65-73	2476.81		(1781.87, 3171.76)

Figure 63.5. AUC (ng-hr/ml) for L-158,641

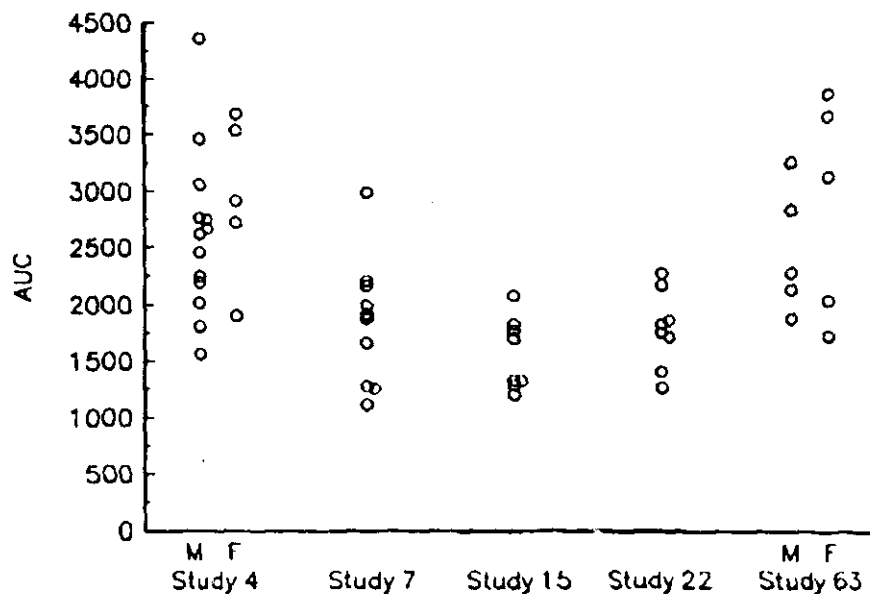
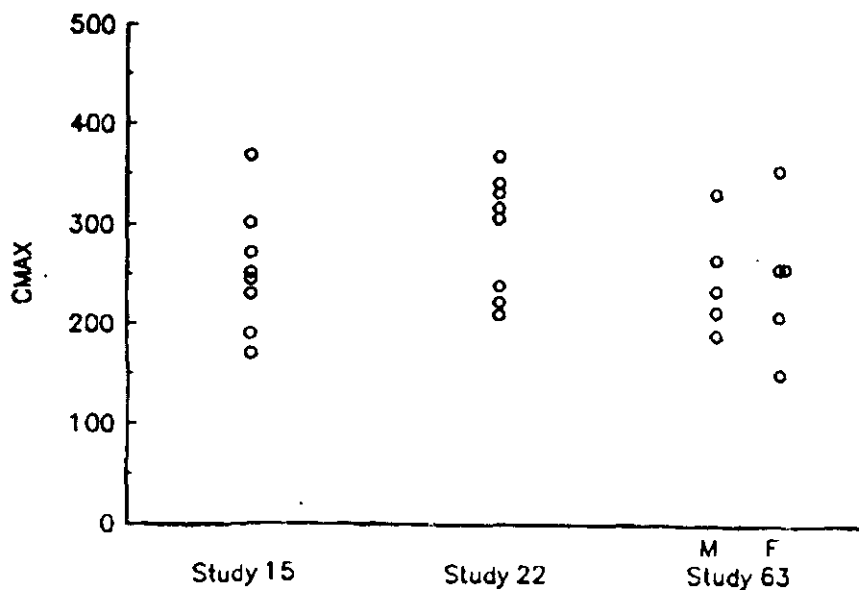
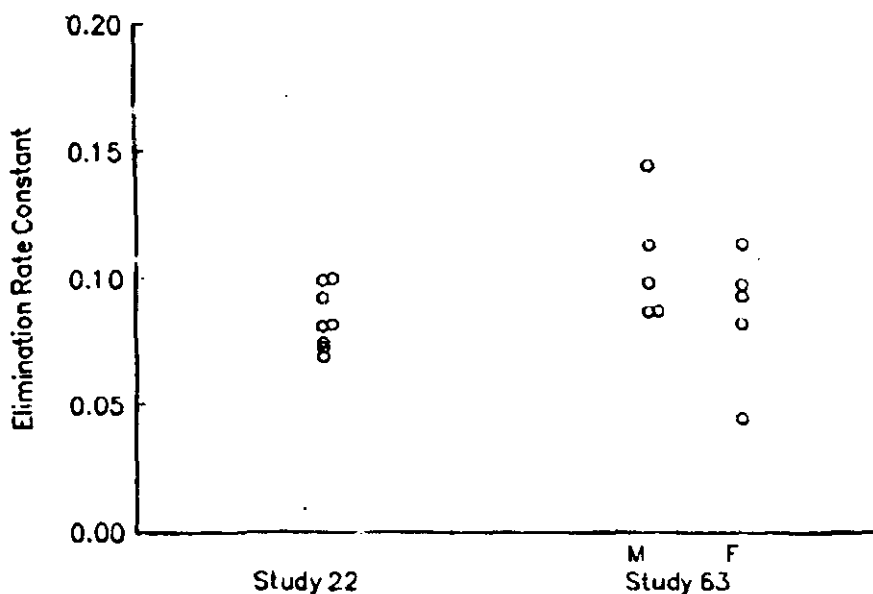


Table 63.6. Maximum L-158,641 Plasma Concentration (C_{max} ng/ml)

Study	Sex	N	Mean	LSmeans	95% Confidence Interval
Young Healthy Males					
015	Male	8	253.16	252	(200.75, 305.58)
022	Male	8	291.98	291	(242.01, 341.95)
Elderly Hypertensives					
063	Both	10	246.62	247	(202.04, 291.20)
063	Female	5	246.02		(152.37, 339.67)
063	Male	5	247.22		(178.68, 315.76)

Figure 63.6. C_{max} (ng/ml) for L-158,641

The elimination rate constant for E-3174 was not different between sexes and studies (figure 63.7).

Figure 63.7. Elimination Rate Constant (hr^{-1}) for L-158,641

Study 79.

This was a double-blind, randomized, two-period crossover study in 13 healthy volunteers. Subjects received 50 mg losartan (MK-954) or placebo daily for 15 days in each period. On Days 4 and 11 of each period, subjects also received single 0.5 mg intravenous (Day 4) and oral (Day 11) doses of digoxin. Thirteen healthy male subjects (10 Caucasians, 2 Haitians, 1 Iranian) between the ages of 19 and 32 years old were deemed acceptable for participation in the study. Eleven subjects completed the study according to protocol. Two subjects were discontinued during the study (AN 0005, adverse laboratory experience; AN 0007, withdrew from study). 1.

Two subjects did not complete the study. Patient # 0005 was discontinued during period 1 (losartan) due to increased liver function tests (ALT, AST). Patient #0007 was discontinued during period 1 (Day 5) since he inadvertently received the

medication for a different subject (patient # 0008) 24 hours post the Day 4 digoxin infusion. The data from these 2 subjects (patient #0005 and patient # 0007) were not included in the pharmacodynamic/pharmacokinetic analysis. Data for all 13 subjects who entered the study were included in the safety analysis.

Some pharmacokinetic data could not be included in the treatment comparisons. In 2 subjects, due to assay sensitivity, AUC_{0-48} could not be calculated for I.V. (patients 0001, 0203) and oral (patients 0009, 0203) digoxin. In four I.V. subjects (patients 0002, 0010, 0011, 0012) and 3 oral subjects (patients 0006, 0011, 0203), incomplete or apparently erroneous urine collections precluded use of their data in the urinary excretion analysis.

Table 79.1 lists the pharmacokinetic parameters for digoxin. There is a slight increase in digoxin C_{max} (13%) and AUC (5%) with losartan therapy.

Table 79.1. Digoxin Pharmacokinetic Parameters (arithmetic mean $\pm$ S.D.)

Parameter	With Losartan				Without Losartan			
	Day 4 (I.V.)	N	Day 11 (Oral)	N	Day 4 (I.V.)	N	Day 11 (Oral)	N
C_{max} (ng/mL)	--	--	3.46 (0.70)	11	--	--	3.07 (0.53)	11
AUC_{0-48} (ng·hr/mL)	28.76 (2.93)	10	23.63 (3.67)	11	28.45 (3.92)	9	22.43 (2.57)	9
AU (% dose)	54.01 (7.20)	7	51.16 (6.30)	8	51.89 (6.48)	7	46.26 (2.44)	8
T_{max} (hr)	--	--	0.64 (0.23)	11	--	--	0.86 (0.74)	11

AU = urinary excretion

Patient 005 had an increase in AST on day 1 (73 IU/L), day 4 (120 IU/L) and day 5 (99 IU/L). ALT was also increased with maximum ALT occurring on day 4 (184 IU/L). It is unlikely that elevations in transaminases are due to losartan since the increases started on day 1.

Study 043. Double-blind, Randomized, Placebo-controlled Study to Investigate the RAAS Effects of MK-954 and Linalapril in Patients With Mild to Moderate Hypertension.

This is a randomized, double-blind, placebo controlled, multi-center trial whose primary hypothesis is that at treatment Week 2 and Week 6, the geometric mean fold-increase from placebo baseline in plasma renin activity and angiotensin II concentrations at 4 and/or 8 hours postdosing with losartan will be ≥ 5 and will be ≥ 2.9 times larger in the losartan dose groups than in the placebo treatment group. The trial consisted of a 2- to 4-week medication tapering/placebo Run-In period followed by a 6-week double-blind treatment period. The trial enrolled nonblack patients, 21 - 70 years of age, with a history of uncomplicated hypertension, no other medical problems and receiving no medication that could affect the RAAS. At the end of the placebo run-in period, patients were required to have a supine DBP between 95 and 110 mmHg on 2 consecutive visits (DBP did not differ by more than 7 mmHg between visits) to be randomized to treatment. Patients could be randomized to either placebo, losartan 25 mg, losartan 100 mg or enalapril 20 mg once daily. Table 43.1 - 43.3a list the outline of the study and the procedures performed during the trial.

Table 43.1 Entire Study Flowsheet

Procedure	Week:				2		3		Bal.		6				10		12	
	Visit:	1	1a**	1b**	1c**	2	3	4	4a	5	6	6a	7	7a	7b	7c	8	9
Medical History	X																	X
Physical Examination	X																	X
Discontinuation of Medications*	X	X*	X*	X*														
q.d. Placebo	X	X	X	X	X	X	X	X	X	X								
Supine/Standing BP/HR	X	X	X	X	X	X	X	X	X		X		X	X	X			X
Laboratory Safety					X	X			X			X					X	X
Body Weight	X				X				X	X		X					X	X
ECG					X				X			X					X	X
Admission (night before)									X	X		X					X	
24-hr Urine Collection									X	X		X					X	
Serial Supine/Standing BP/HR									X	X		X					X	
Serial PRA, All, Aldo., Catecholamine									X	X		X					X	
PRA, All Sampling to 72 hours																	X	
Supine BP/HR to 72 hours																	X	
Drug Level MK 954										X							X	
Overnight Stay (second night)									X	X		X					X	
Randomization										X								
Double-blind Therapy (q.d.)										X	X	X	X	X	X	X	X	
Restart Prior Medication																		X

* Or tapering, if appropriate. ** = occur 1 - 7 days apart. Bas = baseline run-in.

Table 43.3. Hemodynamic and Other Measurements

Measurement	Time Relative to Dose Administration
Supine BP/HR	-30 min, 0, 30 min, 1 hour, 1.5, 2, 3, 4, 6, 8, 12, 24 hours (28, 32, 36, 48, 72 hours Visit 8 only)
Standing BP/HR	0 hour, 1 hour, 2, 4, 4.5*, 6, 8, 12, 24 hours
RAAS*** Profile	0 hour, 4 hours, 4.5*, 8, 12**, 24 hours (1 hour supine except for 4.5 hours) (28, 32, 36, 48, 72 hours Visit 8 only for PRA and All)
Catecholamines	0 hour, 4 hours, 4.5*, 8, 12, 24 hours (1 hour supine except for 4.5 hours)
Plasma Drug Level	0, 2, 4, 6, 8, 12, 24 hours (Visits 6 and 8)
24-Hour Urine for Na ⁺ , K ⁺ , Creatinine, Aldosterone, Protein, Catecholamines	0-24 hours

* Patient ambulated from 4 to 4.5 hours.
 ** PRA and catecholamines only at 12 hours.
 *** RAAS profile is PRA, angiotensin II (by RIA and/or HPLC-RIA) and aldosterone concentrations in plasma.

Study 43.3a. Flowchart for Visits 5, 6, 7, 8 - Sample Collection Days

Procedure	Time (Hours)																				
	-12	-0.5	0	0.5	1	1.5	2	3	4	4.5 [†]	5	6	8	12	24 [‡]	28 [‡]	32 [‡]	36 [‡]	48 [‡]	72 [‡]	
Admission	x																				
Lab Safety (Visits 5, 7, 8)		x													x [§]	x [§]					
ECG		x																			
Discontinuing			x																		
Supine BP/HR		x ^{**}	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x	x	x
Standing BP/HR			x		x		x	x	x	x		x	x	x	x						
Supine PRA, All ^{**} , Aldo., Catecholamines			x ^{††}						x ^{††}				x	x ^{†††}	x	x	x	x	x	x	x
Standing PRA, All, Aldo., Catecholamines										x											
Drug Level ^{††††}			x				x		x			x	x	x	x						
24-Hr Urine NA ⁺ , K ⁺ , Creatinine, Aldo., Protein, Catecholamine										x											
Light Meal						x					x		x	x							
Overnight Stay	x	x											x	x	x						

‡ = visit 8 only; * = Visit 8 only - PRA and All, only
 ** = For -30 minute supine BP/HR and all supine PRA, All, etc., the subjects must be supine for 1 hour prior to sample collection.
 † = Ambulating from 4 to 4.5 hours.
 †† = Two samples for All only - one for RIA, one for HPLC-RIA
 ††† = PRA only
 †††† = Visits 6 and 8 only

Results

Fifty-one patients were randomized (placebo = 14; losartan 25 mg = 11; losartan 100 mg = 14; enalapril 20 mg = 12). All except one patient was caucasian. Thirty-five patients were male. Four centers participated and enrollment ranged from 6 - 17 per center. The mean age was 52.2 years. Forty-eight patients completed the study. Three patients dropped out due to clinical adverse events, two in the placebo group and one in the losartan 100 mg group.

Figures 43.1 - 43.3 show the changes in suDBP blood pressure after the first dose, 2 weeks of dosing and 6 weeks of dosing. Losartan lowers suDBP.

Figure 43.1 - 43.2. Changes from Run-In in Supine Diastolic Blood Pressure

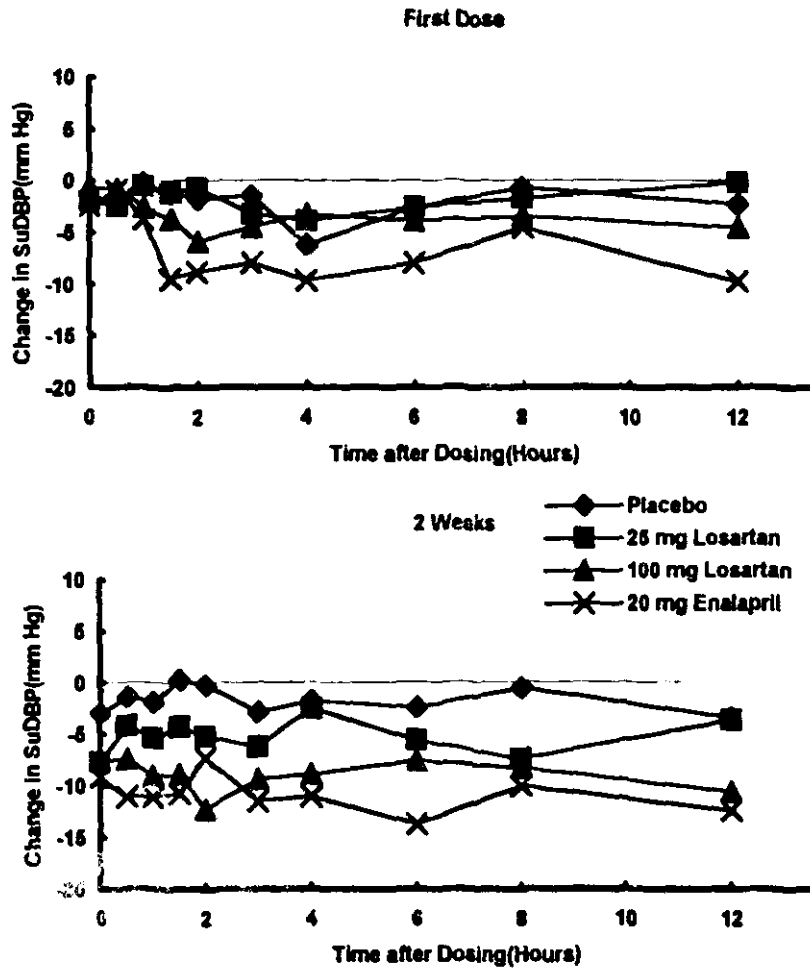


Figure 43.3. Changes from Run-In in Supine Diastolic Blood Pressure

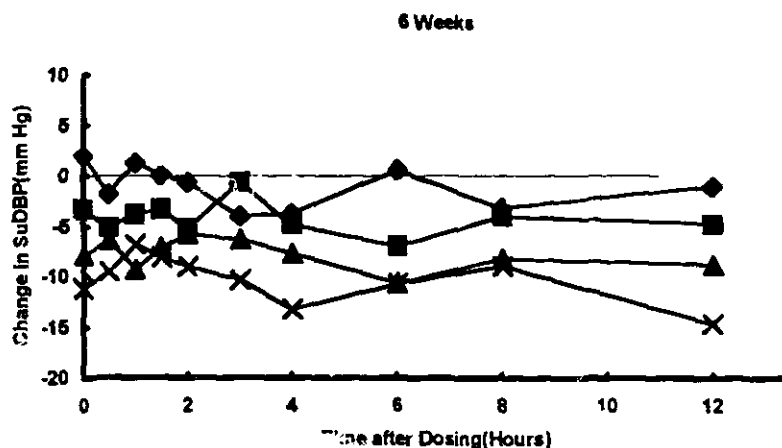


Table 43.4 lists the AUC for neurohormone concentrations. Renin and angiotensin II levels increase. Aldosterone levels decrease and norepinephrine levels are variable. Urinary excretion of aldosterone decreased with both losartan 100 mg and enalapril 20 mg.

Table 43.4. AUC for Neurohormone Concentrations

	N=	Difference or Ratio vs. Run-In		
		First Dose	Week 2	Week 6
Supine Plasma Renin Activity; R; 0-8 h; ng AL/mL/hr				
Placebo	12	-0.923	0.663	0.722
25 mg Losartan	11	0.658 ^a	5.820 ^a	4.178
100 mg Losartan	13	4.721 ^{a,b,d}	11.022 ^{a,b}	7.700 ^{a,b,d}
20 mg Enalapril	12	5.085 ^{a,b,d}	11.787 ^{a,b}	9.981 ^{a,b}
Supine Angiotensin II (Direct RIA); R; 0-8 h; pg/mL/hr				
Placebo	12	-0.486	1.092	0.856
25 mg Losartan	11	0.986 ^c	3.319 ^{a,c}	2.661 ^{a,c}
100 mg Losartan	13	2.927 ^{a,b,c,d}	5.516 ^{a,b,c}	4.682 ^{a,b,c}
20 mg Enalapril	12	-2.815 ^{a,b}	-1.641	-1.885 ^{a,b}
Plasma Aldosterone; D; 0-8 h; ng/dL/hr				
Placebo	12	6.5	15.0	19.9
25 mg Losartan	11	-5.6 ^d	-12.4 ^b	-15.8 ^b
100 mg Losartan	13	-23.1 ^{a,b}	-17.8 ^{a,b}	-40.3 ^{a,b,d}
20 mg Enalapril	12	-18.1 ^d	-26.2 ^{a,b}	-25.9 ^{a,b}
Plasma Norepinephrine; D; 0-12 h; pg/mL/hr				
Placebo	11	33.4	-349.7	-240.6
25 mg Losartan	11	360.5	757.6 ^{a,b,c}	81.5
100 mg Losartan	11	198.7	617.3 ^{a,b}	-238.7 ^d
20 mg Enalapril	10	-165.7	-65.4	-479.7

* For each variable: Name; R (=ratio) or D (=difference); AUC interval (hours); AUC units. N is the number of patients with 6-week data for analysis. a = p<.05 vs. Run-In; b = p<.05 vs. Placebo; c = p<.05 vs. Enalapril; d = p<.05 vs. Week 2

Table 43.5 shows that the AUC and C_{max} for losartan increases approximately 20% with multiple dosing compared to the first dose. The AUC for E-3174 increased by 5% but there is little change in the C_{max}.

Table 43.5. Mean AUC and C_{max} for Losartan and L-158,641 (E-3174) after the First Dose and 6 Weeks of Once-Daily Administration at Doses of 25 and 100 mg/day

	25 mg Losartan				100 mg Losartan			
	Losartan		L-158,641		Losartan		L-158,641	
	AUC*	C _{max}	AUC	C _{max}	AUC	C _{max}	AUC	C _{max}
First Dose	244	57	945	26	647	222	3656	471
6 Weeks	248	56	1088	45	779	269	3821	474
Ratio (Wk6/First Dose)	1.04	1.04	1.13	1.11	1.17	1.17	1.04	0.97
90% C.I.	(0.90, 1.18)	(0.80, 1.13)	(1.04, 1.23)	(0.99, 1.23)	(0.87, 1.56)	(0.82, 1.64)	(0.98, 1.11)	(0.84, 1.12)

*AUC_{0-24 hr} = ng•hr/mL, C_{max} = ng/mL

In the sponsor's clinical summary of study 043, multiple analysis comparing neurohormone levels or drug concentrations with the change in blood pressure were performed. Refer to study 043 clinical summary report for a discussion of these analysis.

Safety

Table 43.6 shows that similar numbers of patients in each treatment group experienced adverse events. Headache was the most common adverse experience.

Table 43.6. Clinical Adverse Experience

Clinical Adverse Experience	Losartan 25 mg	Losartan 100 mg	Enalapril 20 mg	Placebo
Summary				
Number (%) of Patients	N=11	N=14	N=12	N=14
With One or More Adverse Experiences	9 (82%)	9 (64%)	8 (67%)	7 (50%)
With Serious Adverse Experiences	0	0	0	1 (7%)
Withdrawn Due to Adverse Experiences	0	1 (7%)	0	2 (14%)

Table 43.7 lists three patients who were discontinued for adverse events. In all cases, the patients recovered after therapy was stopped.

Table 43.7. Patients Discontinued for Clinical Adverse Experiences

AN	Age (Years)	Sex	Dose	Adverse Reaction	Onset (Day)	Duration	Relative Day of Discontinuation	Serious
0052	65	F	Placebo	Chest Pain	21	1 Hour	21	Yes
0055	62	M	Placebo	Arm Pain	4	3 Days	4	No
				Blood Pressure Increased	4	3 Days	4	No
0056	62	M	Losartan 100 mg	Hypotension	1	30 mins.	1	No

Patient 52 experienced severe chest pain of 1-hour duration, with nausea, which required subsequent hospitalization.

Patient 56 discontinued on relative Study Day 1 of the randomized treatment phase (100 mg losartan) following a severe hypotensive episode which was probably related to drug therapy. Predose, his respective supine and standing blood pressures (heart rate) were 149/92 mmHg (62 bpm) and 134/96 mmHg (66 bpm). Four hours after dosing, when standing for blood pressure measurements, symptoms included diaphoresis, lightheadedness and blurring of vision. At that time, his respective supine and standing blood pressures (heart rate) were 140/80 mmHg (64 bpm) and 122/96 mmHg (120 bpm). He appeared extremely pale when symptomatic and standing. Symptoms were promptly relieved by resumption of the supine position. However, for the next 3-4 hours, he was unable to stand for upright blood pressure measurements. Twenty-four hours after dosing, he felt well and was discharged. A detailed evaluation of this patient (captopril challenge/imaging study) did not reveal any underlying basis for his apparently greater sensitivity to losartan. Of note, his supine PRA predose and on the Run-In day was low (0.12 to 0.28 ng Al/mL/hr), as were his supine plasma aldosterone levels (3-5 ng/dL).

Patient 19 (losartan 25 mg) had an unexplained decrease in hemoglobin from a baseline of 13.1 Gm/dl to 10.3 Gm/dl on day 43. A repeat hemoglobin on day 58 off drug was 13.3 Gm/dl.

Study 018. A 12-week, Single-blind, Longitudinal, Pilot Study of the Effect of Losartan on Prostaglandin Synthesis in Patients With Mild to Moderate Hypertension

Protocol

This study attempted to determine the effect of losartan on prostaglandin synthesis by measuring renal and extrarenal prostaglandin synthesis. Since prostaglandin synthesis is stimulated by increased levels of angiotensin II, blockage of the angiotensin II receptor could potentially cause changes in prostaglandin synthesis. This was a single-blind, single center study

[Michael J. Dunn, M.D., University Hospitals of Cleveland] in female hypertensive patients consisting of a 4 week placebo baseline period, a 4 week losartan 50 mg treatment period and a 4 week placebo washout period. Table 18.1 lists the renal and systemic prostaglandins measured during the trial. PGE₂ is synthesized mainly in the kidney and its measurement is based on urinary excretion of unmetabolized compound. Prostacyclin is synthesized in the kidney and in the systemic vasculature. The prostacyclin metabolites, 6-keto-PGF_{1α} and urinary 2,3-dinor-6-keto-PGF_{1α}, are indicative of renal prostacyclin synthesis (6-keto-PGF_{1α}) and systemic prostacyclin synthesis (urinary 2,3-dinor-6-keto-PGF_{1α}). Thromboxane A₂ is primarily synthesized by platelets but also in the kidney and is detected in urine as the metabolites 2,3-dinor-TXB₂ and TXB₂, respectively.

Table 18.1. Prostaglandins Measured.

Prostaglandin	Metabolite	Source
PGE ₂	*	Renal
Prostacyclin	6-keto-PGF _{1α}	Renal
	2,3-dinor-6-keto-PGF _{1α}	Systemic
Thromboxane A ₂	TXB ₂	Renal
	2,3-dinor-TXB ₂	Systemic

* Detected in urine as unmetabolized compound.

The study enrolled non-black, female hypertensive patients within 30% of ideal body weight and with supine DBP 95 - 115 mmHg at week -1 and day -1 of the baseline placebo period. Table 18.2 lists the procedures performed during the study. In brief, prostaglandin measurements were obtained during baseline at week -1 and day -1 visits, during losartan treatment at week 2 and 4 and during placebo washout at weeks 6 and 8.

Table 18.2. Study Procedures.

	Placebo Baseline					Losartan				Placebo Washout			
	Week				Day	Week				Week			
	-4	-3	-2	-1	-1	1	2	3	4	5	6	7	8
History	X												
PE	X												X
12-Lead ECG	X												X
Study Medication	X				X				X				
Dispensing													
Study Med.		X	X	X	X	X	X	X	X	X	X	X	X
Accounting													
Concomitant med.		X	X	X	X	X	X	X	X	X	X	X	X
Recording													
BP/HR/Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Experience		X	X	X	X	X	X	X	X	X	X	X	X
Recording													
24-Hour Urine for Creatinine Clear.		X		X									X
24-Hour Urine*				X	X		X		X		X		X
PRA and Aldosterone				X	X				X				X
Chem/Hem/UA	X**			X**					X				X

* 24-hour urine for sodium, creatinine, PGE-2, 6-Keto-PGF_{1α}, urinary 2,3-dinor 6 keto-PG_{1α}, TXB₂, and 2,3-dinor TXB₂

** Clinically significant abnormalities from these tests were repeated.

Renal PGE-2 was measured by RIA. Systemic metabolites were measured by gas chromatograph mass spectroscopy.

No analysis of the data was pre-specified in the protocol. Changes from baseline in prostaglandin levels, blood pressure, heart rate, weight, ECG, and laboratory parameters were analyzed using the signed rank test to test the null hypothesis that the median change was zero.

Sixteen female hypertensive patients (sDBP 95 - 115 mmHg) were enrolled. They ranged in age from 51 to 66 years with a mean age of 59 years. They had been diagnosed as being hypertensive from 0 to 42 years ago, with a mean duration of disease of 13 years. All but one of the 16 patients who entered the study completed it. One patient (# 7) was discontinued during the first week of losartan therapy when it was discovered that nitrate therapy (protocol deviation) was to be initiated by the patient's private physician because of an increase in shoulder pain for which an exercise stress test was performed. The protocol stated that any patient who discontinued must be replaced; however, #7 was not replaced due to difficulty in recruiting patients for the study.

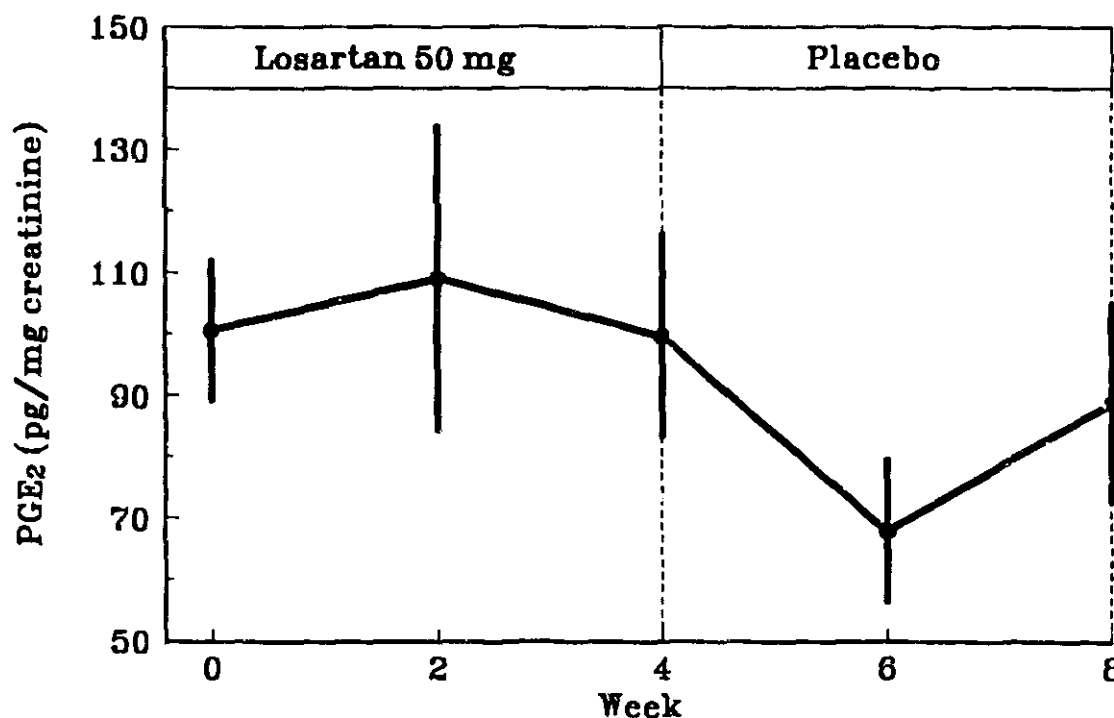
PGE₂ is synthesized mainly in the kidney and is excreted in the urine as unmetabolized compound. There was no significant change from baseline in the 24-hour urinary excretion of PGE₂ after 2 or 4 weeks of treatment with losartan (Table 18.3 and Figure 18.1). At Week 6, 2 weeks into the placebo washout period, the amount of PGE₂ excreted in 24 hours

was significantly lower than during baseline ($p=0.015$). At Week 8, after 4 weeks on placebo, there was no significant difference from baseline in urinary PGE₂ excretion.

Table 18.3 24-Hour Urine PGE₂ (pg/mg creatinine). Change From Average Baseline Measurement

Week	N	Average Baseline Value			Weekly Response			Change from Baseline			Within Grp Comparison (p-Value)
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	
2	15	100.6	110.5	44.1	109.1	97.0	95.7	8.5	-13.0	67.7	0.901
4	15	100.6	110.5	44.1	99.7	77.0	63.4	-0.9	-6.0	45.9	0.890
6	15	100.6	110.5	44.1	67.9	56.0	44.0	-32.8	-35.5	45.6	0.015
8	15	100.6	110.5	44.1	88.8	64.0	62.3	-11.8	-17.5	50.9	0.303

Figure 18.1. Mean $\pm$ Standard Error of 24-Hour Urinary PGE₂ Excretion



Note: Baseline measurement (Week 0) is the average of the last two measurements of the placebo baseline period. N=15 at all time points.

Examining the average value for each patient in each treatment period (averaging the week 2 + 4 and 6 + 8 visits), there was no significant change from baseline during treatment with losartan in PGE₂ excretion (Table 18.4). However, the average excretion during the placebo washout period was significantly lower than during placebo baseline ($p=0.035$). [Note: It would also be significantly different from the treatment period.]

Table 18.4 24-Hour Urine PGE₂ (pg/mg creatinine) - Average Measurement. Change From Average Baseline Measurement

Treatment Period	N	Average Baseline Value			Average Response			Change from Baseline			Within Grp Comparison (p-Value)
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	
Losartan	15	100.6	110.5	44.1	104.4	77.5	74.9	3.8	-10.0	48.6	0.922
Placebo Washout	15	100.6	110.5	44.1	78.3	68.0	44.6	-22.3	-26.5	37.6	0.035

Prostacyclin is synthesized in the kidney and in the systemic vasculature. The prostacyclin metabolites, 6-keto-PGF_{1 α} and 2,3-dinor 6-keto-PGF_{1 α} , are indicative of renal and systemic prostacyclin synthesis, respectively.

There was no significant change from baseline in the 24-hour excretion of 6-keto-PGF_{1α} during treatment with losartan or with placebo (Tables 18.5).

Table 18.5 24-Hour Urine 6-keto-PGF_{1α} (pg/mg creatinine). Change From Average Baseline Measurement

Week	N	Average Baseline Value			Weekly Response			Change from Baseline			Within Grp Comparison (p-Value)
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	
2	15	45.1	42.0	16.7	52.8	52.0	15.5	7.7	5.0	18.9	0.127
4	15	45.1	42.0	16.7	41.0	37.0	17.0	-4.1	-1.5	14.7	0.446
6	15	45.1	42.0	16.7	48.7	48.0	21.2	3.6	4.5	18.3	0.277
8	15	45.1	42.0	16.7	45.9	48.0	13.4	0.7	3.0	13.9	0.934

There was a notable ($p=0.066$) increase from baseline in 24-hour urinary excretion of 2,3-dinor 6-keto-PGF_{1α} at Week 2, but at Week 4 there was no significant change from baseline (Table 18.6). The amount of metabolite excreted at Week 6 and Week 8 was also similar to baseline. Average excretion during treatment (averaging the week 2 + 4 and 6 + 8 visits) with losartan and placebo was similar to baseline.

Table 18.6 24-Hour Urine 2,3-dinor 6-keto-PGF_{1α} (pg/mg creatinine). Change From Average Baseline Measurement.

Week	N	Average Baseline Value			Weekly Response			Change from Baseline			Within Grp Comparison p-Value)
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	
2	15	124.2	121.0	36.4	139.3	135.0	41.3	15.0	8.5	41.9	0.066
4	15	124.2	121.0	36.4	130.7	137.0	41.9	6.5	3.5	50.5	0.429
6	15	124.2	121.0	36.4	143.0	146.0	56.5	18.8	-5.5	53.5	0.389
8	15	124.2	121.0	36.4	124.0	111.0	54.5	-0.2	-11.5	62.9	0.561

Thromboxane A₂ is primarily synthesized by platelets, but it is also synthesized in the kidney. It is detected in the urine as the metabolites 2,3-dinor TXB₂ and TXB₂, respectively.

There was no significant difference from baseline in the amount of TXB₂ excreted after 2 or 4 weeks of treatment with losartan (Table 18.7). After 2 weeks of treatment with placebo, there was no significant difference from baseline in the excretion of TXB₂. However, after four weeks of treatment with placebo, there was a notable decrease ($p=0.085$). The mean and median decreases were similar to those at other weeks, but there was less variability in the changes. The average excretion during the losartan and placebo periods (averaging the week 2 + 4 and 6 + 8 visits) was similar to that during baseline.

Table 18.7 24-Hour Urine TXB₂ (pg/mg creatinine) Change From Average Baseline Measurement

Week	N	Average Baseline Value			Weekly Response			Change from Baseline			Within Grp Comparison (p-Value)
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	
2	15	37.1	26.5	22.2	32.8	26.0	19.9	-4.3	-2.0	12.7	0.246
4	15	37.1	26.5	22.2	29.3	29.0	12.8	-7.8	-3.5	18.9	0.247
6	15	37.1	26.5	22.2	31.5	22.0	30.9	-5.6	-8.5	26.4	0.147
8	15	37.1	26.5	22.2	29.8	27.0	20.4	-7.3	-3.5	16.0	0.085

After 2 weeks of treatment with losartan, the excretion of 2,3-dinor TXB₂ was significantly greater than during baseline ($p=0.003$) (Table 18.8). However, at Week 4 there was no significant difference from baseline. Urinary excretion of 2,3-dinor TXB₂ at Weeks 6 and 8 during treatment with placebo was also similar to baseline.

Table 18.8 24-Hour Urine 2,3-dinor TXB₂ (pg/mg creatinine) Change From Average Baseline Measurement

Week	N	Average Baseline Value			Weekly Response			Change from Baseline			Within Grp Comparison (p-Value)
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	
2	15	180.0	187.0	69.1	218.7	206.0	89.2	38.7	40.5	38.2	0.003
4	15	180.0	187.0	69.1	191.1	186.0	87.9	11.1	23.0	96.3	0.669
6	15	180.0	187.0	69.1	163.9	143.0	79.3	-16.0	-12.5	79.9	0.762
8	15	180.0	187.0	69.1	170.6	127.0	107.1	-9.4	-7.5	84.1	0.730

There was a significant decrease in mean SBP and DBP. Plasma renin activity increased significantly ($p = .001$) at week 4. There was a significant ($p=0.002$) decrease from baseline in aldosterone at Week 4 (Table 18.9). At Week 8 there was no significant change from baseline for aldosterone levels.

Table 18.9. Aldosterone (ng/dl) Change From Baseline

Week	N	Baseline Value			Weekly Response			Change from Baseline			Within Grp Comparison (p-Value)
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	
4	15	9.7	6.0	6.5	5.1	3.0	3.9	-4.6	-3.0	4.6	0.002
8	15	9.7	6.0	6.5	7.4	6.0	3.8	-2.3	-1.0	5.4	0.198

Study 069. A Double-Blind, Placebo-Controlled, Parallel Study to Evaluate the Pharmacodynamic Activity of Intravenous E-3174, An Angiotensin II Receptor Antagonist, in Hypertensive Patients.

Protocol

Study 69 was performed at a single center to assess the relationship between blood pressure changes and plasma drug levels of E-3174 when E-3174 20 mg is given as a 4-hour infusion to hypertensive patients. The study consisted of a 2 week outpatient placebo baseline period, a one day in-patient period during which a 4 hour placebo infusion was administered and a 1 day in-patient double-blind period during which a 4 hour infusion of either placebo or E-3174 (an active metabolite of losartan in humans) 20 mg was administered. Patients were between 21 and 65 years of age, non-black and fulfilled blood pressure criteria as outlined in table 69.1 prior to randomization.

Table 69.1. Blood Pressure Criteria for Randomization.

Study Day	Mean suDBP**
Day 1 (after 1 week washout of antihypertensive meds)	90-120 mmHg
Day 8 (after 1 week on oral placebo)	100-120 mmHg
Day 15 (after 2 weeks on oral placebo)	100-120 mmHg
Day 16: 20 minutes & immediately prior to initiation of I.V. placebo	95-120 mmHg and mean, values must not differ by more than 7 mmHg
1, 2, 3, 4, 5, 7, 8 & 9 hours after the initiation of placebo infusion	All values ≥ 90 mmHg and 5 of the 8 values 95-120 mmHg
Day 17: 20 minutes & immediately prior to initiation of I.V. double-blind drug	≥ 90 mmHg and mean values must not differ by more than 7 mmHg

* Mean supine diastolic blood pressure (suDBP). the calculated average of three consecutive readings at 1-minute intervals. All individual readings were to be read to the nearest 2 mmHg.

None of the 3 readings may have differed from the average by >5 mmHg

Results

Twenty patients were randomized to treatment on day 17. Twelve (5 male, 7 female; 3 caucasian, 9 hispanic) received E-3174 and eight (5 male, 3 female; 1 caucasian, 7 hispanic) received placebo. The ages of patients ranged from 37 to 63 years. There were no dropouts. The number of patients screened for enrollment is not provided. In addition to blood pressure and E-3174 concentration measurements, plasma renin activity, aldosterone levels, 24-hour electrolyte excretion (i.e., sodium, potassium and chloride), fractional excretion of uric acid, plasma uric acid levels, creatinine clearance and urine volume output were evaluated. Within-group changes from baseline were analyzed using a Wilcoxon Signed-Rank test. Between-group analyses were done using Wilcoxon Rank sum test using mean rank for ties. The comparison of Day 16 to Day 17 was done using a Paired T-test.

Figure 62.1 shows the change in suDBP on day 17. Twelve of 17 post-baseline E-3174 supine DBP measurements were significantly different from placebo measurements (comparing change from day 17 baseline between treatments).

Figure 69.1. Supine Diastolic Blood Pressure

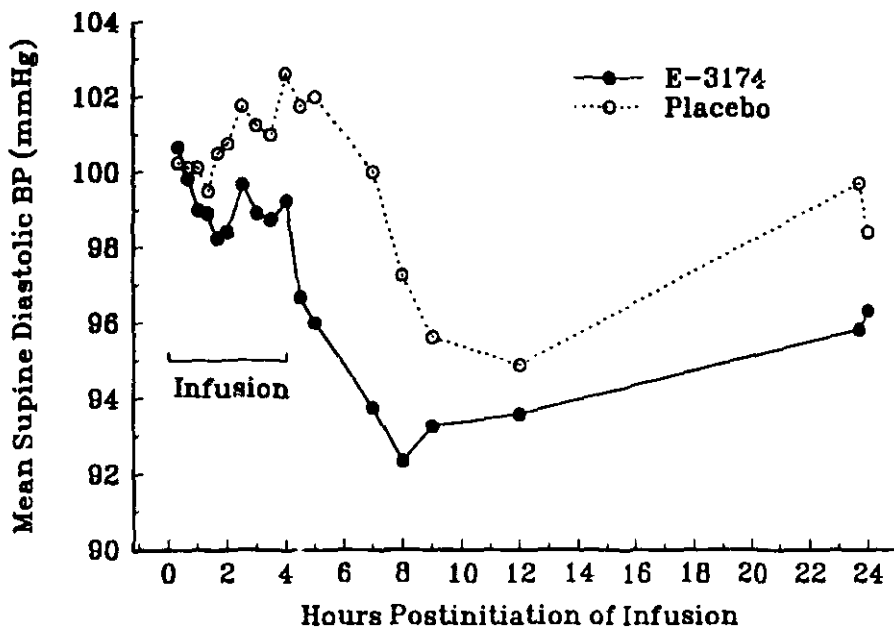
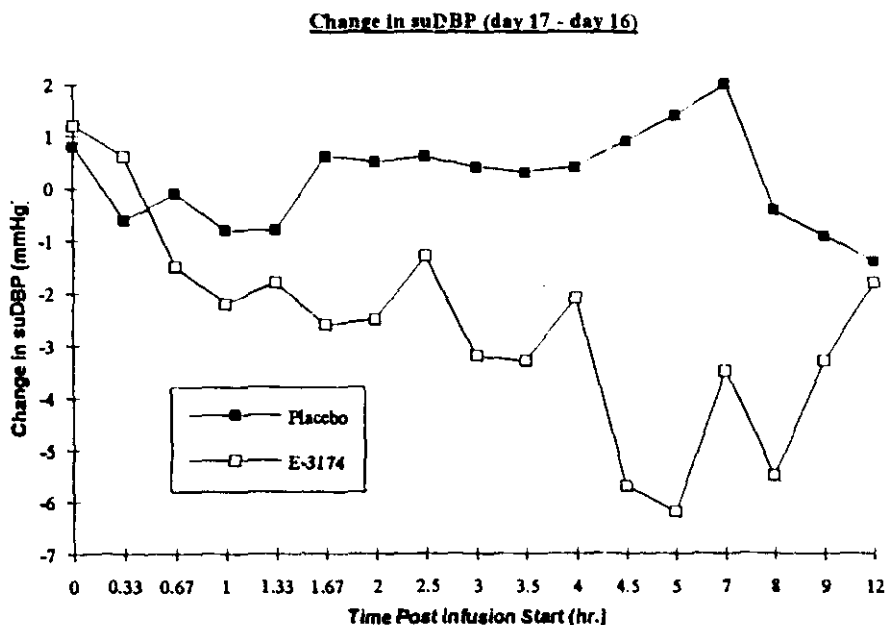


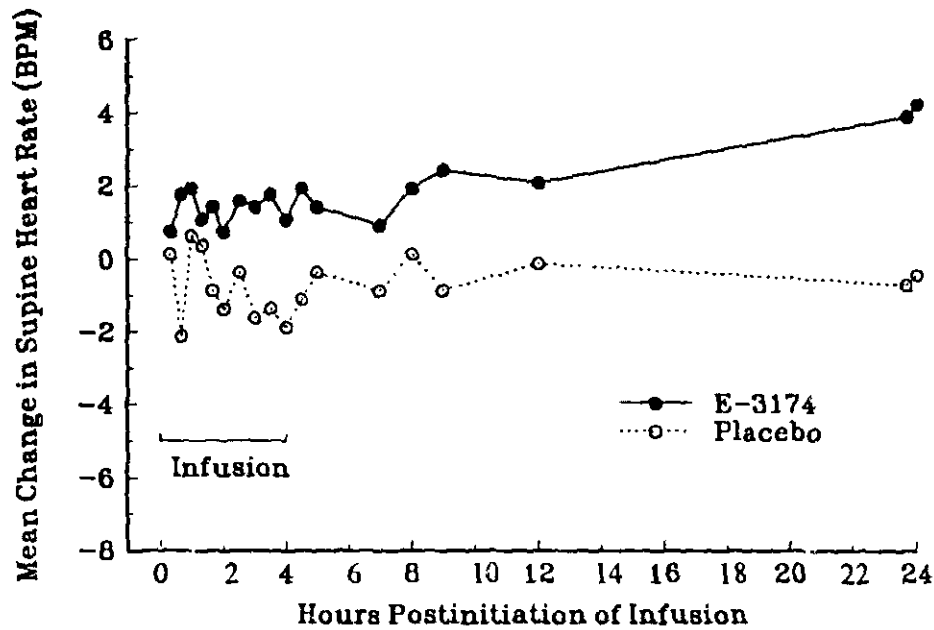
Figure 69.1a shows the change in suDBP between comparable timepoints on day 17 and day 16 for each treatment. The change in suDBP equals the change on day 17 minus the change on day 16 for each measurement post start of infusion (data from appendix 6, volume 1.137). Note that the time axis does not reflect equal time intervals. The maximum effect on blood pressure occurs after the infusion was completed.

Figure 69.1a.



There is a 1 - 2 bpm increase in supine heart rate in the E-3174 treatment group compared to placebo. Figure 69.1b illustrates the change in heart over time. This effect on heart rate is not seen with standing heart rate.

Figure 69.1b. Supine Heart Rate: Mean Change From Baseline



Figures 69.1c and 69.1d plot the between treatment change in suDBP on day 17 and the concentrations of E-3174 versus time respectively

Figure 69.1c. Plasma Drug Levels of E-3174 in Relation to Supine Diastolic Blood Pressure (Δ Between Treatments) Over 24 Hours

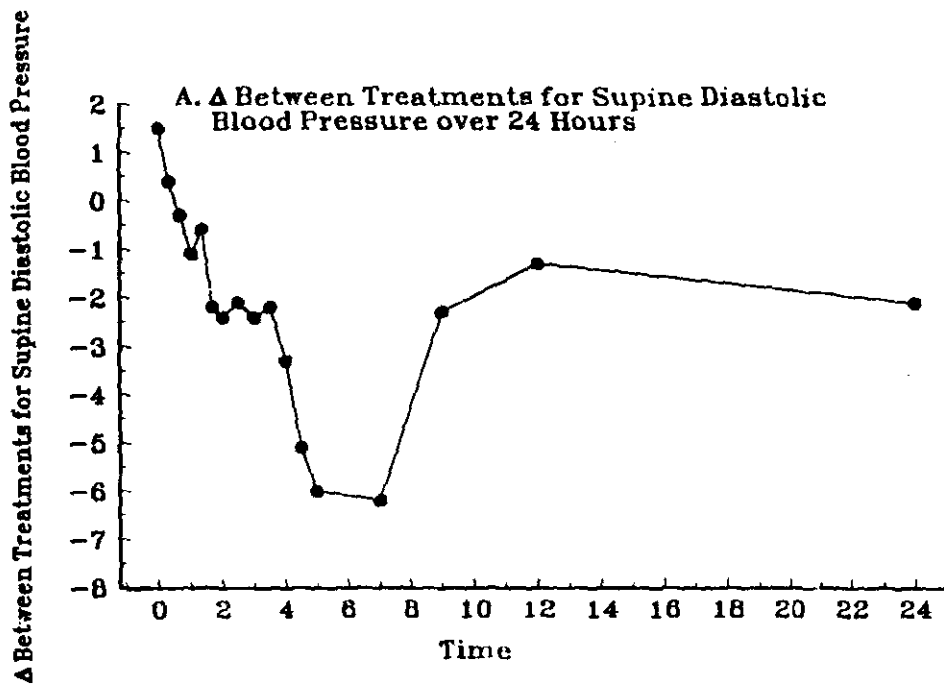
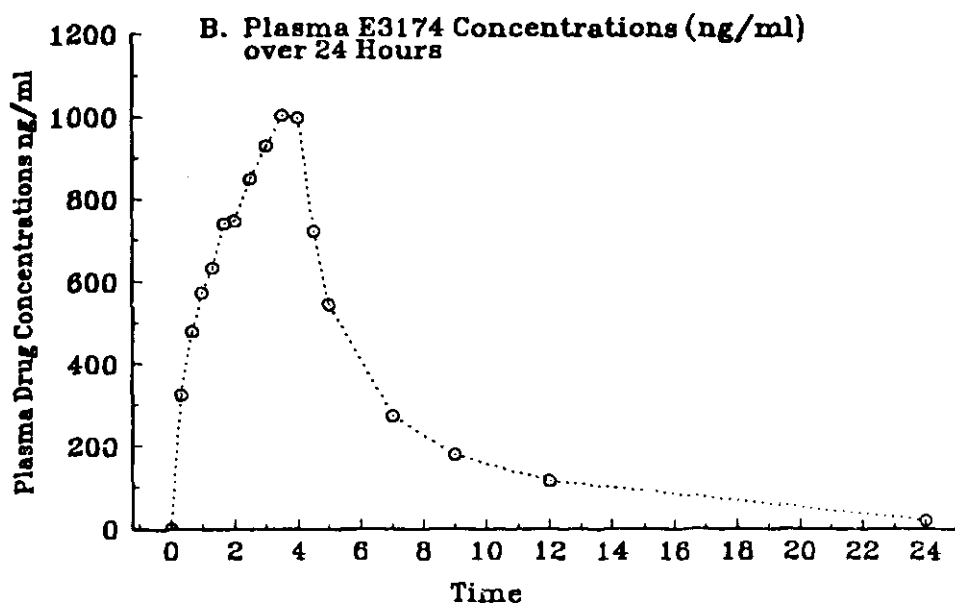


Figure 69.1d.



There was no difference between treatments in urinary electrolyte excretion, urinary aldosterone, plasma uric acid, fractional excretion of uric acid, creatinine clearance and urinary volume. As shown in figure 69.2, mean renin levels increased slightly with E-3174 infusion but this increase was not significantly different from the placebo group measurements and was comparable magnitude to changes noted during the infusion of placebo on day 16 in the same patients (table 69.3).

Figure 69.2. Plasma Renin Activity Following Double-Blind Test Drug

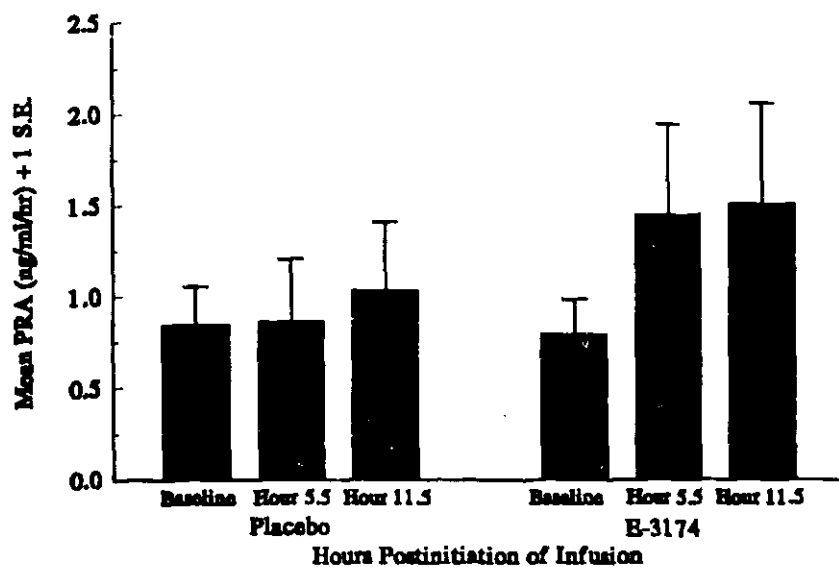


Table 59.3. Summary Statistics For Plasma Renin Activity (ng/mL/hr) Comparison Of Day 17 To Day 16

HOUR	TREATMENT	N	Day 16			Day 17			Change			Comparison	
			Mean	S.D.	Median	Mean	S.D.	Median	Mean	S.D.	Median	vs. B	COMPARISON
-1	PLACEBO	8	0.95	0.63	0.96	0.85	0.59	0.8	-0.11	0.72	-0.26	0.259	0.692
	E-3174	11	0.9	0.75	0.7	0.8	0.63	0.7	-0.1	0.5	0	--	0.506
5.5	PLACEBO	8	1.68	2.19	0.65	0.87	0.97	0.56	-0.81	1.79	-0.12	0.949	0.241
	E-3174	11	1.05	0.85	0.92	1.45	1.65	0.92	0.4	1.3	0.05	--	0.329
11.5	PLACEBO	8	0.79	0.75	0.5	1.04	1.06	0.52	0.24	0.51	0	0.812	0.222
	E-3174	11	1.07	0.92	1.1	1.51	1.83	1	0.44	1.14	0	--	0.229

Of the 20 patients who entered the trial, only 1 had an adverse experience. Patient #7 reported mild chills 3.5 hours after the start of the E-3174 infusion.

Active Control Trials						
Study #	Design/ Patient Population	Treatment Groups	N	Primary Endpoint	Other Measures	Page
044	- r, db, ac, 12 wk Rx period - hypertensives - International Trial - 30% of patients will have moderate HTN	- losartan 50 mg od - captopril 50 mg od (titrate to 100 mg at wk 6 if siDBP $\geq$ 90 mmHg)	109 54	Change in trough sitting DBP from baseline at week 12.	- plasma renin	142
045	- r, db, ac, 12 week Rx period - hypertensives - International Trial (non-U.S.)	- losartan 50 mg od - atenolol 50 mg od (titrate to 100 mg at wk 6 if siDBP $>$ 90 mmHg)	134 68	Change in trough sitting DBP from baseline at week 12.	- check for rebound increased bp	146
055	- r, db, ac, $>$ 64 years of age, 12 wk Rx period - hypertensives - International Trial - no more than 30% black, 33% to have moderate (106 - 115 mmHg) HTN	- losartan 50 - 100 mg od - Felodipine ER 5 - 10 mg od	89** 43**	Change in siDBP at weeks 6 and 12 of db treatment		151
056	Three phase study. 1) positive control, 2) placebo control, 3) db treatment period. Phase 3 is db, r, ac, 8 wk Rx period. Hypertensives with hx of ACEI induced cough	- losartan 50 mg od - lisinopril 20 mg od - HCTZ 25 mg od	48 46 41	incidence of dry cough on 2 consecutive visits		156
064	- r, db, ac, p, 12 wk Rx period - severe hypertensives (siDBP $>$ 115 mmHg)	- losartan 50 mg - enalapril 20 mg Titration. Dose doubled then +/- HCTZ 25 mg _{P2} atenolol 100 mg. Ca channel blocker	50 25	Change in siDBP		161

wk = week, db = double-blind, ol = open label, od = once a day, bid = twice a day, r = randomized, ac = active control, pc = placebo control, nc = no control, p = parallel, co = crossover, hx = history, HTN = hypertension, ACEI = angiotensin converting enzyme inhibitor, NE = norepinephrine, Epi. = epinephrine, PRA = plasma renin activity

** = does not include data from 1 of 17 centers due to cut-off date restrictions.

Study 044. A Randomized, Double-blind, Parallel Study of the Safety and Antihypertensive Efficacy of Losartan Compared to Captopril in Patients with Mild to Moderate Hypertension.

Protocol

This is a randomized, double-blind, multicenter, parallel dose trial comparing the clinical efficacy of losartan and captopril administered once a day. Hypertensive patients had to have a baseline siDBP between 95 and 115 mmHg on 2 consecutive baseline visits in order to be randomized (2:1 for losartan:captopril) to either losartan 50 mg or captopril 50 mg once a day for 12 weeks of therapy. Patients were stratified based on the severity of hypertension. After 6 weeks of therapy, the doses of losartan and captopril could be increased to 100 mg once a day if the siDBP remained ≥ 90 mmHg. Procedures performed in the trial are outlined in table 44.1. The primary efficacy parameter to be analyzed in this study was change from baseline in sitting diastolic blood pressure after 12 Weeks on double-blind therapy.

Table 44.1. Study Procedures Performed at Each Study Week

Procedure	Pre-Placebo	Baseline		Double-blind Treatment				Off-Drug Period	
		2	4	7	10	13	16	17 ³	17 ⁴
Medical History	X								
Obtain Informed Consent	X								
Complete Physical Exam	X						X		X
Body Weight	X	X	X	X	X	X	X	X	X
Fasting Trough BP and HR ¹	X	X	X	X	X	X	X	X	X
Fasting Laboratory Tests	X ²	X			X		X		X
12-Lead ECG		X					X		
Plasma Renin Activity			X		X		X	X	X
Assess Adverse Experiences		X	X	X	X	X	X	X	X

1 = Measurements made in both the sitting and standing positions and taken 24 hours (range 22-26 hours) after the last study dose, if applicable.

2 = Evaluation performed if patient did not have known history or if prior tests were not available.

3 = Visit occurred 2 to 3 days after last study dose.

4 = Visit occurred 7 days after last study dose.

Result

Demographics

Sixteen centers received drug shipments. Fourteen of the centers were in Europe and 2 in Central America. Fourteen (14) investigators recruited patients and submitted case report forms as of the cut-off date for the NDA. One center did not recruit patients. One center recruited patients but did not submit the case report forms by the due date (3/31/93) and as a result, information on these patients are not included. One hundred and nine were randomized to losartan 50 mg and 54 patients were randomized to Captopril 50 mg. The median number of patients recruited at each site was 12 and the range was 2-21. There was no significant difference in demographic parameters between treatment groups. Sixty-one percent of the patients were male. The mean age was 54.1 years of age. Table 44.1 lists the distribution of patients based on race, severity of hypertension and the mean baseline siDBP. There were no statistically significant differences between treatment groups.

Table 44.1a. Baseline Patient Demographic Characteristics.

	Losartan (N=109)	Captopril (N=54)	Total (N=163)
Racial Origin:			
Caucasian	97 (89%)	48 (89%)	145 (89%)
Oriental	2 (2%)	0	2 (1%)
Latin American	6 (6%)	3 (6%)	9 (6%)
Black	3 (3%)	1 (2%)	4 (2%)
Asian	1 (1%)	2 (4%)	3 (2%)
Severity of Hypertension (siDBP, mmHg)			
Mild (95-105)	73 (67%)	36 (67%)	109 (67%)
Moderate (106-115)	36 (33%)	18 (33%)	54 (33%)
siDBP (mmHg)			
Mean	103.1	103.3	103.2
Median	101	103	102
Range	95-115	95-115	95-115

Disposition

Table 44.2 provides information on patients disposition during the trial. Twenty-one patients, including thirteen losartan patients, discontinued the trial prematurely. Ten losartan patients withdrew due to adverse events.

Table 44.2. Patient Accounting

	LOSARTAN (N=109)	CAPTAPRIL (N=54)
	n (%)	n (%)
Completed Double-blind Phase/Not Continuing Into Extension Protocol	38 (34.9)	15 (27.8)
Completed Double-blind Phase/Continuing into Extension Protocol	58 (53.2)	31 (57.4)
Discontinued Double-blind Phase	13 (11.9)	8 (14.8)
Clinical Adverse Experience	10 (9.2)	5 (9.3)
Laboratory Adverse Experience	0 (0.0)	0 (0.0)
Clinical & Laboratory Adverse Experience	0 (0.0)	0 (0.0)
Therapy Ineffective	0 (0.0)	1 (1.9)
Patient Uncooperative	0 (0.0)	0 (0.0)
Patient Withdrew	1 (0.9)	0 (0.0)
Protocol Deviation	1 (0.9)	0 (0.0)
Lost to Follow-up	1 (0.9)	2 (3.7)

Table 44.2a lists the patients withdrawn and the reason for discontinuation.

Table 44.2a. Premature Withdrawals

Patient Number	Treatment Regimen	Reason Discontinued	Days on Treatment
3025	Losartan	Clinical AE	21
3035	Captopril	Clinical AE	80
3036	Losartan	Clinical AE	19
3043	Losartan	Clinical AE	24
3044	Losartan	Clinical AE	62
3048	Losartan	Clinical AE	55
3049	Losartan	Clinical AE	18
3050	Captopril	Clinical AE	55
3078	Losartan	Clinical AE	70
3120	Captopril	Clinical AE	20
3125	Losartan	Clinical AE	68
3142	Losartan	Clinical AE	74
3182	Captopril	Clinical AE	5
3190	Captopril	Clinical AE	4
3191	Losartan	Clinical AE	53
3045	Captopril	Lost to Follow-up	87
3135	Losartan	Lost to Follow-up	89
3153	Captopril	Lost to Follow-up	1
3089	Losartan	Protocol Deviation	7
3001	Captopril	Therapy Ineffective	20
3092	Losartan	Patient Withdrew	44

Discussion

There is an inherent problem with the design of this trial. The purpose of the study was to test the hypotheses that losartan and captopril have equivalent antihypertensive efficacy in patients with mild to moderate essential hypertension, as measured by a decrease in sitting diastolic blood pressure. Captopril is at best a twice a day therapy in the treatment of hypertension. Consequently, any study that doses captopril once a day is going to underestimate the blood pressure effect. Since captopril is given only once a day in this trial, there is little that can be said about the comparison of captopril with losartan. Additionally, data from one center is not included from the analysis provided in the NDA. Only the safety portion of this trial will be reported in this review.

Safety

Thirty nine percent (39%) of the losartan patients in the study reported at least one adverse experience vs. 37% of the captopril patients. There was no significant difference between treatments for adverse experiences based on body system. Headache was the most common reported adverse event. For the most part, there is no difference in the incidence of specific adverse events between treatment groups. "Orthostatic effects" were reported in three losartan and none of the captopril

patients. However, these adverse experiences were not associated with standing blood pressure changes that are normally associated with symptoms. Thus, the symptoms are not related to changes in blood pressure.

Table 44.3 lists the patients withdrawn for clinical adverse events. Dizziness was a factor in discontinuing three losartan and two captopril patients. In two of the losartan patients with dizziness (#3043, #3078), elevated blood pressures may have been the contributing factor.

Table 44.3. Patients Withdrawn for Adverse Events.

Patient Number	Treatment	Adverse Event	Day Discontinued	AE Start Day	AE Stop Day
3182	Captopril	PALPITATION	5	1	7
		DIZZINESS	5	3	7
3075	Losartan	COUGH	21	2	24
		RHINITIS, ALLERGIC	21	2	24
3049	Losartan	PSORIASIS	18	3	19
3120	Captopril	DEPRESSION	20	3	20
		DYSPNEA	20	3	20
		HEADACHE	20	3	20
		DIZZINESS	4	4	4
3048	Losartan	DIZZINESS	55	4	56
		SWEATING	55	4	56
3050	Captopril	PAIN, CHEST	55	13	13
		PAIN CHEST/LEF	55	13	13
		PAIN, CHEST	55	15	15
		PAIN, ANKLE	84	18	18
		PAIN, CHEST	55	22	51
		PAIN, CHEST	55	52	56
3036	Losartan	ORTHOSTATIC EFFECTS	19	19	24
3043	Losartan	DIZZINESS	24	23	23
		RETINOPATHY, HYPERTENSIVE	24	24	24
3044	Losartan	HEADACHE	62	38	41
3191	Losartan	INFLUENZA	53	38	43
3035	Captopril	HEADACHE	80	53	63
3078	Losartan	NAUSEA	70	59	59
		DIZZINESS	70	59	61
		PAIN, CHEST	70	62	62
		HYPERTENSION INCREASED	70	62	70
3035	Captopril	HEADACHE	80	64	83
3125	Losartan	SALPINGO-OOPHORITIS	69	66	75
3142	Losartan	ARTHRITIS	84	34	43
		NAUSEA	53	42	53
		ANGINA PECTORIS	84	84	91
		PHARYNGITIS	84	84	91

Two losartan patients and two captopril patients had serious adverse experiences. Summaries for the losartan patients are provided in table 44.3a.

Table 44.3a. Losartan Patients with Serious Adverse Event

Patient #	Summary of Adverse Event
3125	60-year-old female with a history of cholecystectomy in 1989 began treatment with losartan 50 mg on June 3, 1992. The dosage was increased to 100 mg on July 15. On July 19 the patient developed a high fever, pain and swelling in the lower abdomen. Subsequently the patient's condition worsened and she was hospitalized on July 22 with a probable diagnosis of ovarian abscess. Study drug was discontinued on July 22.
3142	38-year-old male with hyperuricemia and a history of knee and ankle gout, hepatomegaly, and arrhythmia began treatment with losartan 50 mg on October, 14, 1992. During the placebo baseline phase of the study the patient complained of leg pain. On October 31 the patient developed ankle pain which recurred throughout remainder of the trial. The investigator commented on the case report form that the event may have been gout but decided that the experience should be termed "arthritis" since gout could not be confirmed. On November 25 the losartan dosage was increased to 100 mg once-daily. In early January, 1993, the patient developed pharyngitis, tonsillitis, and angina and was treated with ciprofloxacin, metallic bismuth and codeine. Due to ankle pain, study drug was discontinued on January 5, 1993. On January 18 the patient was hospitalized. A rheumatological examination revealed a probable diagnosis of gout. The patient's uric acid levels are listed in table 44.3b.

Table 44.3b. Patient # 3142 Uric Acid Levels

Uric Acid Levels: (Normal Range: 140-460 umol/l)	
14Sep92	596 umol/l (prestudy)
30Sep92	529 umol/l (prestudy)
25Nov92	463 umol/l (after 6 weeks on losartan 50 mg)
11Jan93	365 umol/l (6 days after drug discontinued)
18Jan93	360 umol/l (13 days after drug discontinued)

Ten patients (7 losartan, 3 captopril) had laboratory adverse events during the double blind treatment period. Most were of no clinical significance. However, three losartan (#3020, #3181, #3238) and one captopril patient (#3023) had increased creatinine. Patient 3020 had a minimal increase from a baseline of 1.1 mg/dl to a maximum value of 1.25 mg/dl. The other patients had clinically relevant increases which are depicted in table 44.4. Two losartan patient had an increase of the serum potassium. These cases are listed in table 44.4.

Table 44.4. Patients With Increased Creatinine or Potassium

Patient	Treatment	Baseline Creatinine (mg/dl)	Maximum Creatinine (mg/dl)	Comment
3181	losartan	1.4	2.3	Creatinine decreased, but not to baseline, after losartan discontinued. Baseline BUN = 61 mg/dl, Maximum BUN = 72 mg/dl
3238	losartan	1.1	1.5	Creatinine decreased, but not to baseline, after losartan discontinued. Baseline BUN = 26 mg/dl, Maximum BUN = 53 mg/dl
3023	captopril	1.25	2.4	Creatinine decreased, but not to baseline, after losartan discontinued. Baseline BUN = 17 mg/dl, Maximum BUN = 32 mg/dl
Patient	Treatment	Baseline Potassium (Meq/dl)	Maximum Potassium (Meq/dl)	Comment
3078	losartan	4.6	5.9	No changes in other electrolytes
3240	losartan	4.9	5.32	After drug discontinued, potassium 5.75. Creatinine unchanged. BUN increased from 23 mg/dl to 32 mg/dl.

There were no significant mean changes in laboratory parameters. Uric acid did decrease by .41 mg/dl in the losartan group. Table 44.5 shows the mean change in plasma renin compared to baseline. It is not clear why only approximately half of the patients randomized have renin values included in the mean values. The mean values for both groups decreased after drug therapy was discontinued.

Table 44.5 Mean Changes in Plasma Renin Activity

Week	Treatment	N	BASELINE			TREATMENT			CHANGE			COMPARISON	
			Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	vs. B	COMPARISON
6	Losartan (A)	60	1.94	1.24	2.37	3.59	1.717	4.787	1.649	0.408	4.009	0.216	0
	Captopril (B)	29	1.863	1.4	1.539	2.351	1.8	1.957	0.489	0.4	1.453	-	0.041
12	Losartan (A)	49	1.426	1.1	1.345	2.685	1.8	2.625	1.259	0.7	2.034	0.205	0
	Captopril (B)	30	1.711	1.365	1.407	2.294	1.55	1.925	0.583	0.261	1.874	-	0.077

The sponsor analyzed the number of patients with lab changes during treatment outside of predefined limits. Table 44.6 lists some lab parameters that require additional discussion. Serum uric acid decreased by > 2.0 mg/dl in 6.6% of losartan and in 2.0% of captopril patients. Serum sodium decreased by > 5 Meq/L in 5.7% of losartan and in 2.0% of captopril. Serum sodium did not decrease below 132 Meq/L on any patient. None of the captopril patients who had increases of serum sodium > 5.0 Meq/L exceeded a sodium of 148 Meq/L. Patients with increases in serum potassium greater than 5.5 Meq/L in the losartan group have been reviewed in table 44.4.

Table 44.6 Number of Patients (%) With Laboratory Test Result Changes From Baseline Outside Predefined Limits

Lab Test	Predefined Limit	Treatment	Decrease > Limit	Within Limits	Increase > Limit	Total
Serum Uric Acid ^c	Change > 2.0 mg/dl	Losartan	7 (6.6%)	98 (92.5%)	1 (0.9%)	106 (100%)
		Captopril	1 (2.0%)	47 (95.9%)	1 (2.0%)	49 (100%)
Serum Sodium ^c	Change > 5.0 mEq/L	Losartan	6 (5.7%)	99 (94.3%)	0 (0.0%)*	105 (100%)
		Captopril	1 (2.0%)	45 (91.8%)	3 (6.1%)	49 (100%)
Serum Potassium ^c	Change > 0.5 mEq/L	Losartan	7 (6.7%)	84 (80.0%)	14 (13.3%)	105 (100%)
		Captopril	4 (8.2%)	42 (85.7%)	3 (6.1%)	49 (100%)

^c The distribution of patients was compared between treatment groups using Kruskal-Wallis test (based on Rdit Scores).

* Statistically significant difference between groups (p < 0.05).

Study 045. A Randomized, Double-Blind Parallel Study of the Safety and Antihypertensive Efficacy of Losartan (MK-954, DuP 753) as Compared to Atenolol in Patients with Mild to Moderate Hypertension

Protocol

This is a randomized, double-blind, parallel, international (non-U.S.) multi-center trial attempting to show that losartan has similar anti-hypertensive efficacy and safety as atenolol after 12 weeks of therapy. The trial consisted of a placebo baseline period of 4 weeks duration. Sitting trough DBP during this period between 95 - 115 mmHg at week 2 and 4 visits was required for randomization into a 12 week double blind treatment period. Patients were randomized (2:1) to either losartan 50 mg once a day or atenolol 50 mg once a day. After 6 weeks of treatment in the double blind period, any patients with siDBP $\geq$ 90 mmHg had the dose of therapy increased to 100 mg. Patients with siDBP < 90 mmHg continued on 50 mg. After 12 weeks of therapy, patients had BP measured 3 and 7 days after discontinuing therapy. Participation in an open label follow-up study was optional. The open label study data was not included in this NDA. Table 45.1 outline the procedures performed during the trial.

Table 45.1. Clinical and Laboratory Measurements Study Week⁵

Procedure	Baseline			Double-blind Treatment			Off-Drug Period	
	Pre-Placebo	Week 2	Week 4	Week 7	Week 10	Week 13	Week 16	Week 17 ^{3,4}
Medical History	X							
Obtain Informed Consent	X							
Complete Physical Exam	X						X	X ⁴
Body Weight	X	X	X	X	X	X	X	X ^{3,4}
Fasting Trough BP and HR ¹	X	X	X	X	X	X	X	X ^{3,4}
Fasting Laboratory Tests	X ²	X	X ⁶		X		X	X ⁴
12-Lead ECG		X					X	
Assess Adverse Experiences		X	X	X	X	X	X	X ^{3,4}

1 Measurements made in both the sitting and standing positions and taken 24 hours (range 22-26 hours) after the last study dose, if applicable.

2 Evaluation performed if patient does not have known history or if prior tests are not available.

3 Visit occurred 2 to 3 days after last study dose

4 Visit occurred 7 days after last study dose

5 Note that throughout the Protocol and the study design section of CSR, baseline is referred to as Weeks 1-4, double-blind as Weeks 5-16 and off-drug as Week 17, however, throughout the results and analyses sections baseline is referred to as Weeks -4 to -1, double-blind as Weeks 1-12 and off-drug as Week 13.

6 Repeat labs, if necessary.

The study was powered so that if 117 patients completed the study, there would be 80% probability of detecting a 5 mmHg difference between treatment groups in sitting diastolic blood pressure (SiDBP), assuming a standard deviation of 9 mmHg or less, and a 5% level of significance for a 2-sided test. Based upon the resulting sample sizes from this study (132 patients in the losartan group and 66 patients in the atenolol group at Week 12) and the mean squared error from the analysis of covariance model [$64 (\text{mmHg})^2$ for Week 12 change from baseline in trough SiDBP], the observed power to detect a 5 mmHg difference between treatment groups was 99%. There was at least 80% power to detect a 3.4 mmHg difference. Comparisons between treatment groups with respect to change from baseline sitting blood pressures were performed using adjusted means based upon an analysis of covariance for a randomized block (investigators as blocks) design with baseline blood pressure as the covariate.

Results

Two hundred and nine patients were randomized to 15 centers. Only data from 14 centers was validated by the cut-off date of the NDA. Consequently, data for 202 patients (134 losartan and 68 atenolol) is included in the NDA. The number of patients per center ranged from 1 to 24 with a median of 15. Table 45.2 lists the demographic characteristics of the treatment groups.

Table 45.2. Baseline Patient Demographic Characteristics

	Losartan (N=134)	Atenolol (N=68)	Total (N=202)
Sex			
Female	59 (44%)	22 (32%)	81 (40%)
Male	75 (56%)	46 (68%)	121 (60%)
Age (years)			
Mean	52.4	53.9	52.9
S.D.	10.1	9.3	9.8
Range	28-73	34-74	28-74
Racial Origin			
Caucasian	112 (84%)	59 (87%)	171 (85%)
Oriental	1 (1%)	0	1 (0%)
Black	3 (2%)	0	3 (1%)
Hispanic	16 (12%)	9 (13%)	25 (12%)
Mulatto	2 (1%)	0	2 (1%)
Duration of Primary Diagnosis (years)			
Mean	8.5	8.2	8.4
S.D.	8.9	6.9	8.3
Median	6	6	6
Range	0.5-51	0.5-47	0.5-51
Severity of Hypertension (SiDBP, mmHg)			
Mild (95-105)	90 (67%)	44 (65%)	134 (66%)
Moderate (106-115)	44 (33%)	24 (35%)	68 (34%)
SiDBP (mmHg)			
Mean	103.1	103.6	103.3
Median	102.5	102	102
Range	94-115	95-115	94-115

There were no significant differences in demographics between treatment groups.

Table 45.3 presents the patient disposition during the trial. Sixteen patients discontinued from the study during the double-blind phase, 9 patients discontinued on or before week 6 and therefore did not have the option to titrate at week 6: 4 patients in the losartan group (#4058, #4220, #4217, #4129) and 5 patients in the atenolol group (#4032, #4053, #4045, #4111, #4126). Thus, for the all-patients-treated analyses, there were a total of 193 patients available to evaluate the effect of titration on blood pressure response between weeks 6 and 12: 130 patients in the losartan group and 63 patients in the atenolol group.

Table 45.3. Patient Disposition

	Losartan (n=134)	Atenolol (n=68)
	n (%)	n (%)
Completed Double-blind Phase/Not Continuing into Extension	36 (26.9)	21 (30.9)
Completed Double-blind Phase/Continuing into Extension	87 (64.9)	42 (61.8)
Discontinued Double-blind Phase	11 (8.2)	5 (7.3)
Clinical Adverse Experience	2* (1.5)	5* (8.8)
Laboratory Adverse Experience	0 (0.0)	0 (0.0)
Clinical & Laboratory AE	0 (0.0)	0 (0.0)
Therapy Ineffective	4 (3.0)	0 (0.0)
Patient Uncooperative	0 (0.0)	0 (0.0)
Patient Withdrew	2 (1.5)	0 (0.0)
Protocol Deviation	1 (0.7)	0 (0.0)
Lost to Follow-up	2 (1.5)	0 (0.0)

* Statistically significant difference between groups ($p < 0.05$).

+ 1 atenolol patient discontinued during off-drug follow-up week is not included as a dropout

Table 45.3a lists the patients withdrawn from the study.

Table 45.3a. Patients Withdrawn

Patient Number	Treatment Regimen	Reason Discontinued	Day Discontinued
4032	Atenolol	Clinical AE	4
4053	Atenolol	Clinical AE	4
4111	Atenolol	Clinical AE	21
4126	Atenolol	Clinical AE	26
4045	Atenolol	Clinical AE	35
4129	Losartan	Clinical AE	40
4061	Losartan	Clinical AE	78
4058	Losartan	Lost To Follow-up	2
4217	Losartan	Lost To Follow-up	49
4102	Losartan	Protocol Deviation	62
4254	Losartan	Therapy Ineffective	55
4224	Losartan	Therapy Ineffective	58
4187	Losartan	Therapy Ineffective	62
4225	Losartan	Therapy Ineffective	62
4220	Losartan	Patient Withdrew	22
4167	Losartan	Patient Withdrew	52

Tables 45.4 and 45.5 list the mean change in trough siDBP and siSBP at weeks 6 and 12. There was no significant difference between treatments at 6 and 12 weeks.

Table 45.4. Mean Change in Trough Sitting Diastolic Blood Pressure (mmHg) at Week 6 and 12
All-Patients-Treated Approach

Week	Treatment Group	N	Baseline		Treatment		Change		Change	Comparison
			Mean	S.D.	Mean	S.D.	Mean	S.D.	Adj Mean	vs. B
6	Losartan (A)	132	103.1	5.8	94.1	8.8	-9.0	7.7	-9.2	NS
	Atenolol (B)	66	103.6	6.1	92.7	9.3	-11.0	8.5	-10.8	--
12	Losartan (A)	132	103.1	5.8	94.5	9.7	-8.6	9.8	-8.3	NS
	Atenolol (B)	66	103.6	6.1	93.1	10.0	-10.6	8.2	-10.1	--

NS = not statistically significant [analysis of covariance for a randomized block (investigators as blocks) design with baseline blood pressure as the covariate]

Table 45.5. Mean Change in Trough Sitting Systolic Blood Pressure (mmHg) at Week 6 and 12
All-Patients-Treated Approach

Week	Treatment Group	N	Baseline		Treatment		Change		Change	Comparison
			Mean	S.D.	Mean	S.D.	Mean	S.D.	Adj Mean	vs. B
6	Losartan (A)	132	156.9	19.8	145.1	18.4	-11.8	12.2	-13.8	NS
	Atenolol (B)	66	160.2	16.7	147.8	21.9	-12.4	18.3	-13.1	--
12	Losartan (A)	132	156.9	19.8	145.4	19.5	-11.4	16.4	-12.2	NS
	Atenolol (B)	66	160.2	16.7	148.3	22.4	-11.9	19.9	-11.3	--

NS = not statistically significant [analysis of covariance for a randomized block (investigators as blocks) design with baseline blood pressure as the covariate]

Blood pressure measurements post-treatment withdrawal were not obtained for the majority of patients.

Figure 45.1 and figure 45.2 displays the response rate for each treatment. At both 6 and 12 weeks, the response rate was greater with atenolol but the difference was not statistically significant.

Figure 45.1. and 45.2. Trough Sitting DBP-Categories of Antihypertensive Response at Weeks 6 (fig. 45.1) and 12 (fig. 45.2).

Figure 45.1. Week 6 Response Rates

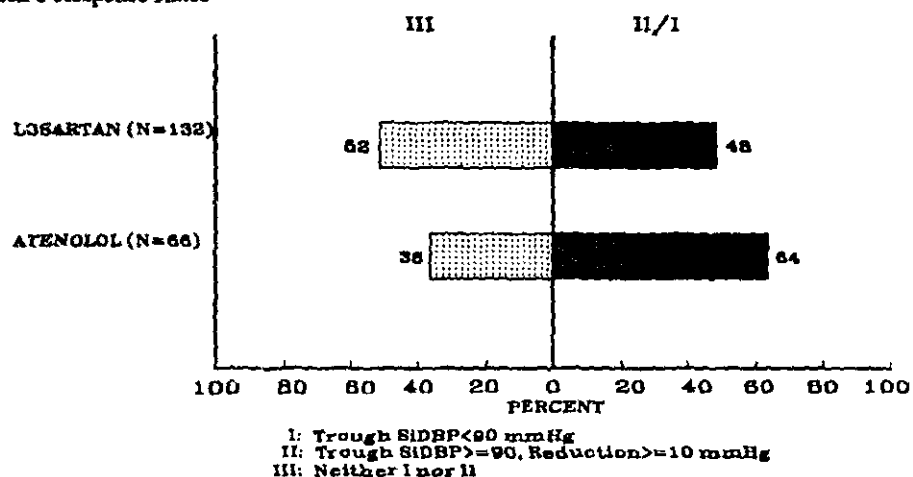
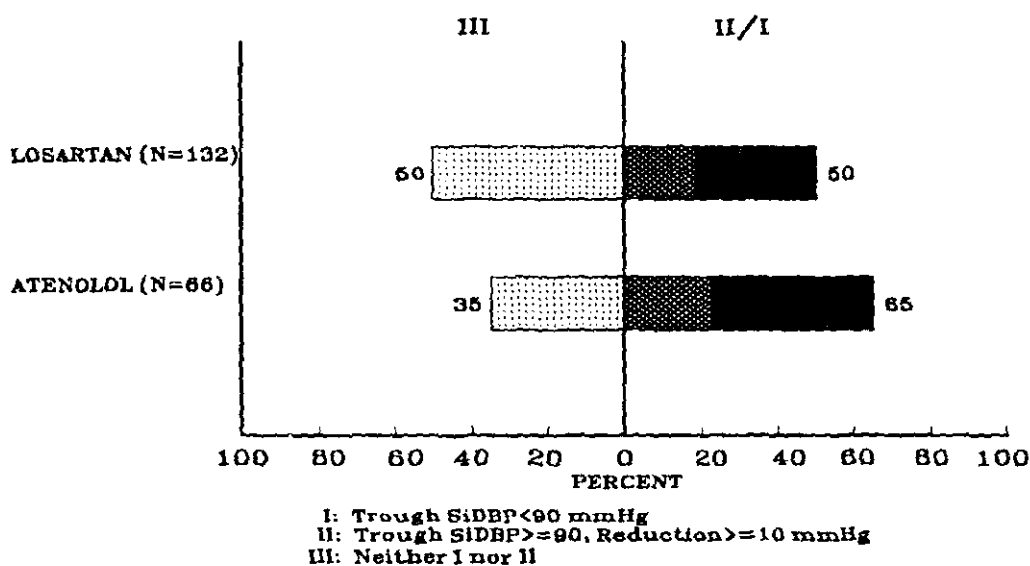


Figure 45.2. Week 12 Response Rates



Sixty-seven losartan (50%) patients and 38 (56%) atenolol patients experienced at least one adverse event in the double blind treatment period. Bradycardia occurred in 3 atenolol patients and none of the losartan patients. URI occurred in 8 (6%) losartan and 1 (1.5%) atenolol patients. Other adverse event incidence rates did not appear to be different between treatments. An inquiry into the database comparing the incidence of adverse events between treatments based on gender showed no difference in male patients. However, in female patients, table 45.5a. lists several adverse events that appear to be more prevalent in losartan treated females than in atenolol treated females. However, when the incidence rates of adverse events in female losartan treated patients are compared to male losartan treated patients, there does not appear to be a higher frequency in females relative to males.

Table 45.5a. Adverse Events in Female Patients

Adverse Event	Losartan (N = 59)	Atenolol (N = 22)
asthenia/fatigue	5 (8.5%)	1 (4.5%)
dizziness	6 (10.2%)	1 (4.5%)
headache	12 (20.3%)	3 (13.6%)
URI	5 (8.5%)	0 (0%)
Abdominal Pain	5 (8.5%)	1 (4.5%)

Within the losartan treatment group, 58% of the female patients and 44% of the male patients experienced at least one adverse event.

A total of 7 patients (4.0%) were discontinued from the study due to a clinical adverse experience. Two (1.5%) of the patients in the losartan group and 5 (7.4%) in the atenolol group were discontinued due to a clinical adverse experience. Table 45.6 lists the patients discontinued due to adverse experiences.

Table 45.6. Patients Withdrawn due to Clinical Adverse Events

Patient Number	Treatment	Adverse Event	AE Start Day	AE Stop Day	Day Withdrawn
4129	Losartan	PAIN, ABDOMINAL	-22	1	40
		PAIN, ABDOMINAL	2	41	
4053	Atenolol	ALKALINE PHOSPHATASE INCREASED	-14		4
		ALT INCREASED	-14		
		PAIN, ABDOMINAL	-14	-11	
		PAIN, ABDOMINAL	4	8	
		NAUSEA	8	8	
4032	Atenolol	ALKALINE PHOSPHATASE INCREASED	25		4
		HEADACHE	1	5	
		SOMNOLENCE	1	6	
		COLD EXTREMITIES	4	5	
		SWELLING, JOINT	4	5	
		RASH	4	7	
4111	Atenolol	BRADYCARDIA	5	22	21
4126	Atenolol	ASTHENIA/FATIGUE	10	28	26
		DIZZINESS	10	28	
		RASH	24	44	
		EOSINOPHILS INCREASED	44		
4045	Atenolol	ASTHENIA/FATIGUE	19	36	35
		CRAMP, MUSCLE	19	36	
		PAIN, NECK	19	36	
		PHARYNGITIS	19	36	
		SWEATING	19	36	
4061	Losartan	DIZZINESS	43	43	78
		DIZZINESS	64	82	

Four patients (two from each treatment group) experienced serious adverse experiences. Summaries for the losartan patients with serious adverse events are presented in table 45.6a.

Table 45.6a. Losartan Patients with Serious Adverse Events

Patient #	Summary
4189	57-year-old male hypertensive patient with a history of myocardial infarction (1975), diverticulitis (1984) and psoriasis (1989) was hospitalized for a pulmonary embolism/infarct while on losartan 100 mg. He had begun treatment with losartan 50 mg and was subsequently titrated to losartan 100 mg after 45 days. There was no concomitant therapy. After 23 days on losartan 100 mg, the patient complained of pain in the left calf which resolved in 4 days. Ten days after the onset of the calf pain, the patient developed sudden pleuritic chest pain on the left side. He was hospitalized and a severe pulmonary embolism/infarct was confirmed. Study drug therapy was interrupted for one day. The patient was treated with heparin 10,000 IU and warfarin 5 mg; he subsequently recovered.
4129	70-year-old female hypertensive patient with a history of arthrosis (1982) and acute pancreatitis (1991) had been on losartan 50 mg for 2 days when she developed severe abdominal pain. During the placebo baseline phase of the study she had complained of moderate abdominal pain which increased in severity to severe pain during the blinded phase. The patient was discontinued from the study.

No patient in the study was discontinued due to a laboratory adverse experience. Eleven losartan and 4 atenolol patients had laboratory adverse experiences. None of the laboratory adverse events were of clinical relevance. There was no significant change in mean weight, pulse or ECG intervals in the losartan group. Mean pulse and ECG rate decreased in the atenolol group as expected. An analysis examining the number of patients who exceeded pre-defined changes in laboratory parameters was performed. This was generally unremarkable. Of note, was the observation that 21.5% of losartan patients had changes in alkaline phosphatase greater than 20 U/L as opposed to 7.8% of the atenolol patients. Alkaline phosphatase decreased greater than 20 U/L in 15.6% of atenolol and 4.6% of the losartan patients.

Study 055. A Randomized, Double-blind, Parallel Study of the Safety and Antihypertensive Efficacy of Losartan (MK-954, DuP-753) Compared to Felodipine Extended Release (ER) in Elderly Patients with Mild to Moderate Hypertension

Protocol

This is a randomized, double-blind, parallel, international (Europe, S. America, Mexico, Australia, Hong Kong) multi-center trial in hypertensive patients greater than 64 years of age. Trial consisted of a 4 week placebo period and a 12 week treatment period. To be randomized, patients were required to have a siDBP between 95 and 115 mmHg on 2 consecutive visits in the placebo period. The difference in siDBP between the two visits could not be greater than 7 mmHg. Eligible patients were randomized to either felodipine ER 5 mg or losartan 50 mg. During the double blind treatment period, patients had trough sitting and standing blood pressures measured every 3 weeks. After 6 weeks of treatment, if the trough siDBP was ≥ 90 mmHg, the patient could have the dose felodipine or losartan doubled. Table 55.1 lists the procedures performed throughout the trial.

Table 55.1. Procedures Performed During the Trial.

Study Weeks	Pre-Placebo	Baseline		Treatment			
		2	4	7	10	13	16
Medical History	X						
Complete Physical Exam	X						X
Sign Informed Consent	X						
Body Weight	X	X	X	X	X	X	X
Clinic Visits ^a	X	X	X	X	X	X	X
Sitting and standing BP and HR ^c	X ^{c,1}	X ^f	X ^g	X	X	X	X
Chest X-ray		X ^j					
Laboratory Safety Tests ^h	X ^b	X	X ^d		X		X
12-lead ECG		X			X		X
AE Evaluation		X	X	X	X	X	X
Dispense Baseline Medication	X ⁱ						
Dispense Double-blind Medications			X	X	X	X	
Discontinue double-blind Medications							X

^a Clinic Visits (Weeks 2-16) occurred as indicated between 0630 and 1000 hours. Patients were to be in the fasted state at all clinic visits (i.e., no food or liquids were to be taken during the 8 hours prior to each clinic visit)

NOTE: Amendment 1 allowed for patients not to be fasted prior to clinic visits

^b Perform tests if patient does not have known history or if prior tests are not available.

^c Measurements were to be taken 24 hours (range 22 to 26 hours) after the last morning study dose.

^d Repeat labs, if necessary.

^e Mean SiDBP was 90-115 mmHg or patient could not continue in the study.

^f Mean SiDBP was 95-115 mmHg or patient could not continue in study

^g Mean SiDBP was 95-115 and Week 2 and Week 4 values must be ≤ 7 mmHg or patient could not continue in study

^h Fasting hematology, blood chemistry and urinalysis

NOTE: Amendment 1 allowed for patients not to be fasted for laboratory tests.

ⁱ Patient was off antihypertensive medication at least 7 full days or patient returned for another evaluation when an adequate washout period was achieved.

^j A chest X-ray was taken if one was not available from the previous 12-month period

NOTE: If a patient did not complete the study, all procedures scheduled for treatment Week 16 were done on the day the patient discontinued treatment.

The primary efficacy parameter to be analyzed in this study was the change from baseline in sitting diastolic blood pressure after 12 weeks on double-blind therapy, although other blood pressure measurements (e.g., sitting systolic blood pressure) and timepoints were also analyzed.

The study was powered such that if at least 117 patients (78 in the losartan group and 39 in the felodipine group) completed the study there would be 80% (61%) probability of detecting a 5 (4) mmHg difference between treatment groups with respect to change in blood pressure (assuming a standard deviation of 9 mmHg or less, and a 5% level of significance for a 2-sided test).

Results

Demographics and Disposition

One hundred and forty patients were randomized at seventeen centers. One center enrolled no patients. The median number of patients recruited at each site was 9 and the range was 2-29. The summary report of the sponsor contains information on 132 patients. Data on eight patients is not included because their data was not received by the CANDA data cut-off date of 3/31/93. This includes all seven patients from site #13 and one patient from site #12 (patient 5308). Of the 132 patients with information in the CANDA, 89 were randomized to losartan and 43 to felodipine ER.

Table 55.2 lists the demographic characteristics of the 132 patients included in the summary. Fifty-five percent (55%) of the patients were female. The mean age was 70 years and the range was 65 to 87 years; 81% of the patients were between 65 and 74 years of age. More than half of the patients (58%) were Caucasian, 22% were Asian, 11% were Hispanic, and 9% were Mestizo. Although the protocol allowed for up to one-third of the patients to be black, no black patients were enrolled.

Table 55.2. Baseline Patient Demographic Characteristics

	Losartan (N=89)	Felodipine (N=43)	Total (N=132)
<u>Sex</u>			
Female	48 (54%)	25 (58%)	73 (55%)
Male	41 (46%)	18 (42%)	59 (45%)
<u>Age (years)</u>			
Mean	70.4	69.9	70.2
S.D.	4.5	5.3	4.8
Range	65-82	65-87	65-87
<u>Racial Origin</u>			
Caucasian	52 (58%)	24 (56%)	76 (58%)
Asian	19 (21%)	10 (23%)	29 (22%)
Hispanic	10 (11%)	5 (12%)	15 (11%)
Mestizo	8 (9%)	4 (9%)	12 (9%)
<u>Duration of Primary Diagnosis (years)</u>			
Mean	9.6	7.9	9.0
S.D.	8.1	7.1	7.8
<u>Severity of Hypertension(SiDBP, mmHg)</u>			
Mild (95-105)	65 (73%)	32 (74%)	97 (73%)
Moderate (106-115)	24 (27%)	11 (26%)	35 (27%)
Mean	102.0	102.5	102.1
S.D.	5.6	5.6	5.6
Range	95-115	95-115	95-115

There were no statistically significant differences between treatment groups.

Table 55.3 outlines the disposition of patients in the trial. One hundred twenty-one (121, 91.7%) out of 132 patients completed the study according to protocol. Seventy-eight (78) of those patients continued into an open-label extension. Eleven (11, 8.3%) patients discontinued the study: 5 patients in the losartan group (5.6%) and 6 patients in the felodipine group (14.0%).

Table 55.3. Patient Disposition

	LOSARTAN (N= 89) n (%)	FELODIPINE (N=43) n (%)
Completed Double-blind Phase/Not Continuing Into Extension	32 (36.0)	11 (25.6)
Completed double-blind Phase/Continuing into Extension	52 (58.4)	26 (60.5)
Discontinued double-blind Phase	5 (5.6)	6 (14.0)
Clinical Adverse Experience	3 (3.4)	5 (11.6) +
Laboratory Adverse Experience	0 (0.0)	0 (0.0)
Clinical & Laboratory		
Therapy Ineffective	1 (1.1)	0 (0.0)
Patient Uncooperative	0 (0.0)	0 (0.0)
Patient Withdrew	0 (0.0)	0 (0.0)
Protocol Deviation	0 (0.0)	0 (0.0)
Lost to Follow-up	1 (1.1)	1 (2.3)

+One patient (AN 5085) had a clinical adverse experience during placebo baseline that continued without change into double-blind.

Table 55.3a. lists the patients withdrawn prematurely and reasons for withdrawal. The primary reason for discontinuing the study was due to a clinical adverse experience both in the losartan (3.4%) and felodipine (11.6%) treatment groups. One patient in the losartan group discontinued the study because of ineffective therapy and one patient in each treatment group was lost to follow-up. Two patients who discontinued the study were lost to follow-up. Patient #5275 who entered the study with a baseline sitting blood pressure of 150/107 mmHg was randomized to treatment with felodipine ER 5 mg. No adverse experiences were reported at the final (Week 3) clinic visit and the mean trough sitting blood pressure at this visit was 125/86 mmHg. After approximately 6 weeks of treatment, the patient's wife phoned the investigator to cancel his appointment. At this time she indicated that he was without symptoms. The patient never returned for his Week 6 visit. The actual duration of treatment is therefore unknown. Patient #5160 who entered the study with a baseline sitting blood pressure of 146/101 mmHg was randomized to treatment with losartan 50 mg. After 6 weeks of treatment, his mean trough sitting blood pressure was 129/87 mmHg and no adverse events were reported. He did not return for his Week 9 visit and no additional information was provided regarding his status.

Table 55.3a. Withdrawals

Patient Number	Treatment Regimen	Reason Discontinued	Day Discontinued
5158	Felodipine	Clinical AE	2
5271	Losartan	Clinical AE	3
5085	Felodipine	Clinical AE	4
5053	Losartan	Clinical AE	10
5036	Felodipine	Clinical AE	24
5273	Losartan	Clinical AE	42
5221	Felodipine	Clinical AE	47
5045	Felodipine	Clinical AE	68
5275	Felodipine	Lost To Follow-up	38
5160	Losartan	Lost To Follow-up	41
5230	Losartan	Therapy Ineffective	78

Efficacy

One hundred and twenty-nine of 132 patients had efficacy data available. One hundred and twenty-four patient had week 6 efficacy data and were eligible for dose titration. Tables 55.4 and 55.5 list the mean change in siDBP and siSBP at weeks 6 and 12. There was a significant difference between treatments at week 6 but this difference was not apparent at week 12.

Table 55.4 Mean Change In Trough Sitting Diastolic Blood Pressure At Week 6 And 12 All-Patients-Treated Approach (mmHg)

WEEK	TREATMENT GROUP	N	BASELINE		Treatment		Change		Change	COMPARISON vs. B
			Mean	S.D.	Mean	S.D.	Mean	S.D.	Adj Mean	
6	Losartan (A)	88	101.9	5.5	93.0	10.3	-8.8	8.4	-9.5	**
	felodipine (B)	41	102.2	5.6	89.1	9.2	-13.1	7.7	-13.7	--
12	Losartan (A)	88	101.9	5.5	88.7	9.6	-13.2	7.8	-12.9	NS
	Felodipine (B)	41	102.2	5.6	88.2	9.1	-14.0	7.6	-13.4	--

NS - NOT STATISTICALLY SIGNIFICANT

** - TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, P<0.01

Table 55.5 Mean Change In Trough Sitting Systolic Blood Pressure At Week 6 And 12 All-Patients-Treated Approach (mmHg)

WEEK	TREATMENT GROUP	N	BASELINE		Treatment		CHANGE		CHANGE	COMPARISON vs. B
			Mean	S.D.	Mean	S.D.	Mean	S.D.	Adj Mean	
6	Losartan (A)	88	171.5	19.1	158.9	21.1	-12.6	16.4	-13.5	NS
	Felodipine (B)	41	171.8	18.8	155.6	20.4	-16.2	13.1	-16.7	--
12	Losartan (A)	88	171.5	19.1	154.3	20.7	-17.2	16.5	-17.0	NS
	Felodipine (B)	41	171.8	18.8	152.9	21.5	-19.0	15.0	-18.3	--

NS - NOT STATISTICALLY SIGNIFICANT

Sixty percent of the losartan and 44 percent of the felodipine patients underwent dose titration at week 6 (for siDBP > 90 mmHg). Table 55.6 shows the change in siDBP at weeks 6 and 12 based on titration status.

Table 55. Mean Change In Blood Pressure At Weeks 6 And 12 By Titration Status All-Patients-Treated Approach

TROUGH SITTING DIASTOLIC BLOOD PRESSURE (mmHg)

	TREATMENT	N	Baseline		Week 6		Week 12		Change					
			Mean	S.D.	Mean	S.D.	Mean	S.D.	Week 6 to 12	Baseline to Week 12	Mean	S.D.	Mean	S.D.
NO	Losartan	34	98.6	4.2	84.2	5.8	82.5	8.1	-1.7	6.4	-16.1	7.9		
	Felodipine	22	99.9	5.1	83.4	7.8	84	8.9	0.7	8.9	-15.8	8.9		
YES	Losartan	51	104.2	5.2	99.7	6.8	93.4	7.5	-6.3	7.6	-10.8	6.7		
	Felodipine	17	104.8	5.2	96.6	5.1	93.5	7	-3.1	6.2	-11.3	4.7		

Note: Patient titrated at Week 6 if SiDBP ≥ 90 mmHg

Safety

Approximately half (57.6%) of the patients reported at least one adverse experience. The treatment groups were very similar with respect to all adverse experiences reported. Table 55.7 describes the adverse experience incidence in the trial.

Table 55.7. Clinical Adverse Experience

	LOSARTAN (N=89)	FELODIPINE (N=43)
Number (%) of Patients	N (%)	N (%)
With One Or More Adverse Experiences	53 (59.6)	23 (53.5)
Without Any Adverse Experiences	36 (40.4)	20 (46.5)
With Serious Adverse	1 (1.1)	3 (7.0)
Withdrawn Due To Adverse Experiences	3 (3.4)	5 (11.6) +
Who Died	0	0
With Drug-Related Adverse Experiences	24 (27.0)	10 (23.3)

There were no statistically significant differences between treatment groups.

Eight patients, 3 losartan and 5 felodipine, withdrew due to adverse events. Table 55.8 lists the adverse events in patients who withdrew due to adverse experiences. Patient #5273 withdrew due to hypotension and angina pectoris. Patient #5271 withdrew due to vomiting. Patient #5053 developed ataxia on day 9 and withdrew on day 10.

Table 55.8. Adverse Events in Patients Withdrawn for Adverse Experiences

Patient Number	Treatment	Adverse Event	AE Start Day	AE Stop Day	Discontinued Day
5035	FELODIPINE	RHINITIS	-4	15	24
		VERTIGO	-4	15	
		COUGH	1	24	
		EDEMA/SWELLING	3	16	
		EDEMA/SWELLING	17	24	
		HEADACHE	20	20	
5045	FELODIPINE	RHINITIS	21	22	
		SWEATING	3	23	68
		EDEMA/SWELLING	3	68	
		PAIN, FINGER	6	68	
		DRY MOUTH	28	68	
		THIRST	28	68	
5053	LOSARTAN	ALK PHOS INCREASED	45		
		HYPERCHLOREMIA	45		
5085	FELODIPINE	ATAXIA	9	12	10
		HEADACHE	-1	3	4
5158	FELODIPINE	FLUSHING	-1	5	
		EDEMA/SWELLING	-1	9	
		HEADACHE	-16	1	2
5221	FELODIPINE	T-WAVE ABNORMALITY	-5		
		HEADACHE	1	1	
		NAUSEA	1	1	
		HEADACHE	2	2	
		HEADACHE	7	8	
5271	LOSARTAN	PREMATURE BEAT	-18	-18	47
		EPISTAXIS	-11	-4	
		SLEEP DISORDER	7	63	
		EDEMA/SWELLING	27	47	
		EDEMA/SWELLING	48	63	
5273	LOSARTAN	PAIN, FOOT	48	63	
		HEADACHE	-6	2	3
		NERVOUSNESS	-6	2	
		WARM SENSATION	-6	2	
		MALAISE	1	2	
5273	LOSARTAN	VOMITING	1	2	
		ANGINA PECTORIS	40	43	42
		HYPOTENSION	43	43	

Table 55.9 lists the most common adverse experiences (> 4% in any treatment group) in either treatment group. There was no significant difference between treatment groups.

**Table 55.9. Most Common Clinical Adverse Experiences
(Patient Incidence $\geq 4\%$ in Any One Treatment Group)**

	LOSARTAN (N=89)	FELODIPINE (N=43)
	N (%)	N (%)
Body As A Whole/Site Unspec.	15 (16.9)	8 (18.6)
Edema/Swelling	6 (6.7)	6 (14.0)
Anthemia/Fatigue	7 (7.9)	0 (0.0)
Digestive System	10 (11.2)	8 (18.6)
Diarrhea	1 (1.1)	2 (4.7)
Nausea	2 (2.2)	2 (4.7)
Musculoskeletal System	16 (18.0)	7 (16.3)
Pain, Back	4 (4.5)	2 (4.7)
Pain, Foot	1 (1.1)	2 (4.7)
Pain, Knee	0 (0.0)	2 (4.7)
Nervous System & Psychiatric	20 (22.5)	5 (20.9)
Headache	8 (9.0)	6 (14.0)
Respiratory System	18 (20.2)	6 (14.0)
Infection, Respiratory, Upper	10 (11.2)	3 (7.0)
Cough	4 (4.5)	1 (2.3)
Pharyngitis	4 (4.5)	1 (2.3)
Skin & Skin Appendage	4 (4.5)	2 (4.7)
Urogenital System	4 (4.5)	1 (2.3)

Note: This table contains counts of patients. If a patient experienced more than one clinical adverse experience, the patient was counted once with each adverse experience in a body system category, and the patient was counted only once in the body system total. For this reason, the separate adverse experience totals may not add up to the body system total.

There were no statistically significant differences between treatment groups.

There was no significant change in mean laboratory values. Three losartan patients had laboratory changes worthy of comment. Patient #5035 had an increase in serum sodium from a baseline of 144 Meq/L to a week 12 values of 162 Meq/L. Patient #5274 had a baseline creatinine of 1.1 mg/dl and a week 12 value of 1.6 mg/dl. Patient #5188 had a baseline serum potassium of 3.5 Meq/L and a 12 week value of 3.0 Meq/L.

Study 56. A Multicenter, Double-Blind, Randomized, Parallel-Group Study to Investigate the Incidence of Cough in Patients Receiving Losartan (MK-954, DuP 753) (50 mg q.d.) Lisinopril (20 mg q.d.) or Hydrochlorothiazide (25 mg q.d.) who Have Reported Cough with an Angiotensin Converting Enzyme Inhibitor

Protocol

This is a randomized, double-blind study designed to test the hypothesis that the percentage of patients who report a "dry cough" while being treated with losartan 50 mg q.d. will be lower than the percentage of patients who report a "dry cough" while being treated with an ACEI (lisinopril 20 mg q.d.). Hypertensive patients who have previously reported a "dry cough" with an angiotensin converting enzyme inhibitor were enrolled. Patients older than 21 years of age with a history of ACE inhibitor induced "dry cough", a history of a sitting diastolic blood pressure (SiDBP) of 90-110 mmHg and with no history of reversible airway disease or chronic lung disease were eligible for enrollment. Drugs that could affect the incidence of cough (NSAID, codeine, cough suppressants) were not permitted. Cough was assessed by a questionnaire and by a 10 cm visual analog scale (questionnaire can be found in the appendix). The study was divided into 3 phases. Phase 1 was a six week (? - the investigator is unblinded in this phase, it is not clear if the patient is unblinded) positive challenge filter period with lisinopril 20 mg q.d. On two (2) consecutive visits, patients must respond positively for cough (i.e., "moderately", "quite a bit" or "extremely" on the questionnaire - "a little" is not considered a positive response). After the initial visit at which the patient complained of cough, the presence of cough had to be documented on a subsequent visit ≥ 1 day later. Once cough was documented in phase 1, the patient entered phase 2, a single-blind (?) placebo washout period of at least 4 weeks duration. Within 4 weeks, but after a minimum of 2 weeks after starting Phase II, patients must respond negatively for cough (i.e., "not at all" on the questionnaire), documented on 2 consecutive visits which are ≥ 1 day apart. Once the lack of cough was documented in phase 2, patients entered phase 3, a double-blind treatment phase in which they were randomized to either losartan 50 mg daily, lisinopril 20 daily or HCTZ 25 mg daily for up to 8 weeks. Clinic visits are scheduled bi-weekly but may

occur earlier, or more frequently, if clinically indicated. That is, the patient may return to the clinic following the development of a cough that persists for ≥ 1 day. The presence of cough had to be documented on a subsequent visit > 1 day later. At each visit, the patient will independently complete the questionnaire and visual analog scale prior to seeing the physician or study nurse. Additionally, at each visit, safety evaluations of blood pressure, heart rate and adverse experiences will be obtained. If clinically appropriate, patients who respond positively for cough on two (2) consecutive visits will be considered to have completed Phase III of the study.

Procedures performed during the study are outlined in table 56.1.

Table 56.1 Flowchart of Study Visits and Procedures

	Visit	** Challenge*									
		Prestudy	Lisinopril			Placebo		Double-Blind Treatment			
		Visit	Filter			Washout					
Day	1	2	3	4	5	6	7	8	9	10	
Week		14	28	42	56	70	84	98	112	126	
		2	4	6	8	10	12	14	16	18	
Medical History	X									X	
Physical Examination	X									X	
12-lead ECG	X									X*	
Laboratory Tests	X						X			X*	
Chest X-ray	X										
Signed informed consent	X										
Body weight	X	X	X	X	X	X	X	X	X	X	
Review inclusion/exclusion criteria	X			X		X					
Dispense medications	X			X		X					
Provide patient instructions	X	X			X		X				
Questionnaire	X	X	X	X	X	X	X	X	X	X	
Visual analog scale	X	X	X	X	X	X	X	X	X	X	
Sitting and standing blood pressure	X	X	X	X	X	X	X	X	X	X	
Adverse experiences evaluation		X	X	X	X	X	X	X	X	X	
Tablet counts		X	X	X	X	X	X	X	X	X	

* Follow-up if abnormal at Visit 10

NOTE: PATIENTS DISCONTINUED EARLY WERE TO BE COMPLETELY EVALUATED, I.E., VISIT 10 PROCEDURES (SEE SECTION XI.8)

An interim analysis of the data from the two control groups was scheduled to occur after 30 patients completed the study. The sole purpose of this analysis was to assess the accuracy of the "positive" cough definition to be used in the final analysis. Only the two control groups were to be utilized for this assessment. No statistical tests were to be performed, therefore, the size and power of the statistical tests described above will remain unaffected. These data was not shared with the investigators. An interim analysis was performed after 70 patients completed the study. Contrary to what was proposed by the protocol, the results of losartan 50 mg treatment were also included in the summary statistics.

Results

One hundred and thirty-five (135) patients from twenty (20) centers were randomized into the study. Approximately one half (53.3%) of all patients were recruited by four investigators. The number of patients randomized per center ranged from 1 to 25. Table 56.2 lists the demographic characteristics of each treatment group.

Table 56.2. Baseline Patient Demographic Characteristics

	LOSARTAN (N=48)	LISINAPRIL (N=46)	HCTZ (N=41)	TOTAL (N=135)
Sex				
Female	31 (65%)	30 (65%)	26 (63%)	87 (64%)
Male	17 (35%)	16 (35%)	15 (37%)	48 (36%)
Age (years)				
Mean	54.3	57.6	56.9	56.2
S.D.	10.6	12	9	10.7
Range	26-77	37-81	40-77	26-81
Racial Origin				
Caucasian	39 (81%)	45 (98%) ^a	36 (88%)	120 (89%)
Black	5 (10%)	0	3 (7%)	8 (6%)
Oriental	0	0	1 (2%)	1 (1%)
Hispanic	0	1 (2%)	0	1 (1%)
Indian	1 (2%)	0	1 (2%)	2 (1%)
Mestizo	1 (2%)	0	0	1 (1%)
Mulatto	1 (2%)	0	0	1 (1%)
Maori	1 (2%)	0	0	1 (1%)

^a - Statistically significantly different from LOSARTAN treatment group, p<0.05

Table 56.3 lists the severity of the dry cough at the end of the lisinopril positive control period categorized by description from the questionnaire.

Table 56.3. Severity of Dry Cough at the End of Lisinopril Filter Period, By Treatment

Treatment	Number and Percentage of Patients with Dry Cough					Total No.
	Not at All No. (%)	A Little No. (%)	Moderately No. (%)	Quite a Bit No. (%)	Extremely No. (%)	
Losartan 50	0 (0.0)	0 (0.0)	22 (45.8)	18 (37.5)	8 (16.7)	48
Lisinopril 20	0 (0.0)	0 (0.0)	28 (60.9)	12 (26.1)	6 (13.0)	46
HCTZ 25	0 (0.0)	0 (0.0)	28 (68.3)	10 (24.4)	3 (7.3)	41
All	0 (0.0)	0 (0.0)	78 (57.7)	40 (29.6)	17 (12.6)	135

Table 56.4 lists the patient disposition in the study. One hundred and twenty-nine patients completed the study. Six withdrew prematurely from double-blind treatment. One losartan patient withdrew due to an adverse event. Patient #3694 took double-blind therapy for 9 days, at which time the patient was withdrawn for severe asthenia/fatigue. The patient's sitting blood pressure at randomization was 125/76 and on the day of discontinuation was 91/61. One lisinopril patient (#3699) was discontinued for asthenia/fatigue which started in the placebo washout phase. One HCTZ patient (#3683) was discontinued for weight gain and increased blood pressure.

Table 56.4. Patient Accounting

	Losartan (N=48) No. (%)	Lisinopril (N=46) No. (%)	HCTZ (N=41) No. (%)
Completed Double-blind Phase Not Continuing into Extension	20 (41.7)	20 (43.5)	13 (31.7)
Completed Double-blind Phase/ Continuing into Extension	27 (56.3)	25 (54.3)	24 (58.5)
Discontinued Double-blind Phase Clinical Adverse Experience	1 (2.1)	1 (2.2)	4 (9.8)
Patient Withdrew	1 (2.1)	1 (2.2) [†]	1 (2.4)
Protocol Deviation	0 (0.0)	0 (0.0)	2 (4.9)
	0 (0.0)	0 (0.0)	1 (2.4)

[†] This patient (AN 3699) was discontinued for a clinical adverse experience which started in baseline and continued into double-blind without change in intensity or frequency.

In order to recognize the differences between the various phases with regard to the definition of a positive or negative response for cough, it is worthwhile to review the questionnaire used in the trial. The definitions for a positive response by treatment phase are outlined in table 56.5. The questionnaire consisted of nine symptoms. In order, they are: dry mouth, cramps in legs, dry cough, racing heart, heartburn, headache, sore throat, getting up at night to pass urine and flushing in the face. For each symptom, based on the previous weeks experience, the patient described it as occurring "not at all", "a little", "moderately", "quite a bit" or "extremely". In phase one (lisinopril positive challenge phase), all patients had to exhibit a positive challenge for dry cough which was defined as a dry cough of moderate severity or greater on 2 consecutive visits. Visits had to be ≥ 1 day apart. In phase two (placebo washout), all patients had to exhibit a negative response which was a response of "not at all" for dry cough on 2 consecutive visits. In phase 3, a positive response for dry cough was defined as a dry

cough of "a little" or greater severity for 2 consecutive visits > 1 day apart. In conclusion, there is a distinction between the definition of a positive response for a dry cough in the positive challenge phase and the double blind treatment phase. The definition in the double blind treatment phase is less rigorous.

Table 56.5. Definition of Positive and Negative Response to Dry Cough

	Positive Response	Negative Response
Phase 1 (lisinopril positive challenge)	moderately, quite a bit, extremely *	Not at all, a little
Phase 2 (placebo washout)	a little, moderately, quite a bit, extremely	Not at all *
Phase 3 (double-blind treatment)	a little, moderately, quite a bit, extremely	Not at all

* Required on two consecutive visits to get to the next phase.

The sponsor has provided 2 different analysis for the data, all patients treated analysis and a per protocol analysis. Neither was specified as the primary analysis in the protocol. The sponsor suggests that the primary analysis of this study included all-patients-treated in the eight-week double-blind phase of the study. However, for some reason the sponsor has chosen to change the definition of the primary endpoint in this analysis. These revised definitions are outlined in table 56.5a. The primary endpoint in the protocol is cough on 2 consecutive visits greater than 1 day apart.

Table 56.5a.

Possible Scenarios	Dry Cough Responses	Disposition for Dry Cough All-Patients-Treated	Disposition for Dry Cough Per-Protocol
Patient completed 8 weeks	1,1,1,1	Negative	Negative
Patient completed 8 weeks	1,1,1,4	Positive	Negative
Patient completed 8 weeks	2,2,1,1 or 1,2,2,1	Positive	Positive
Patient completed 8 weeks	1,2,1,2	Positive	Negative
Patient completed < 8 weeks	2,2	Positive	Positive
Patient completed < 8 weeks	1,2,1	Negative	Not Included
Patient completed < 8 weeks Withdrawn due to extreme cough	5	Positive	Not Included

1 = Not at All (negative), 2 = A Little (positive), 3 = Moderately (positive), 4 = Quite a Bit (positive), 5 = Extremely (positive)

Table 56.6 displays the percentage of patients responding positively to dry cough during the double-blind treatment period, by treatment. This is an all patients treated analysis. It includes patients who were protocol violators and patients who did not fulfill the protocol specified criteria for a positive cough in phase 3 but were counted as positive under a revised criteria for analysis. The criteria for the all patients treated approach were not included in the protocol. One must be concerned that their derivation was data driven. In the sponsors all patients treated analysis and per protocol analysis, the percentage of patients responding positively to dry cough was significantly higher in the lisinopril treatment group compared to both the losartan and HCTZ treatments groups, ($p \leq 0.01$).

Table 56.6 All-Patients-Treated Analysis for Dry Cough

Treatment	Dry Cough		Total No.
	No. (%)	Yes (%)	
Losartan 50	34 (70.8)	14 (29.2)	48
Lisinopril 20	13 (23.3)	33 (71.7) **,†	46
HCTZ 25	27 (65.9)	14 (34.1)	41

** Lisinopril vs. losartan, $p \leq 0.01$. Fisher's Exact Test.
† Lisinopril vs. HCTZ, $p \leq 0.01$ Fisher's Exact Test.
Losartan vs. HCTZ: not statistically significant

Table 56.6a is a per protocol analysis of the primary endpoint. Twenty-one patients were excluded mainly for not having 2 "positive" visits in phase one, 2 "negative" visits in phase two, used concomitant antihypertensive therapy at any phase or did not ingest the correct amount of medication. Patient #3688 (losartan) was not included in the Merck list but should have been because of a failure to have 2 negative visits in phase 2. Of the 49 patients who had dry cough (designated yes) during phase three, 14 of these patients (9 lisinopril, 2 HCTZ, 3 losartan) did not actually fulfill the protocol criteria for cough because the consecutive visits were not greater than one day apart. Six patients (4 losartan, 1 lisinopril, 1 HCTZ) had only one visit positive for cough (last visit). Table 56.6b is the correct per protocol analysis. Losartan versus lisinopril is significantly different ($p < .001$; Chi-square).

Table 56.6a. Number and Percentage of Patients with Dry Cough By Treatment Per-Protocol Analysis. Sponsors Analysis

Treatment	Dry Cough		Total No.
	No. (%)	Yes No. (%)	
Losartan 50	32 (78.1)	9 (22.0)	41
Lisinopril 20	10 (25.6)	29 (74.4)**,†	39
HCTZ 25	23 (67.7)	11 (32.4)	34

** Lisinopril vs. losartan, $p \leq 0.01$; † = Lisinopril vs. HCTZ, $p \leq 0.01$;
Losartan vs. HCTZ: not statistically significant

Table 56.6b. Number and Percentage of Patients with Dry Cough By Treatment Per-Protocol Analysis. Medical Officer Analysis (Excludes patients with only one day between "yes" visits and patients with only one "yes" visit.)

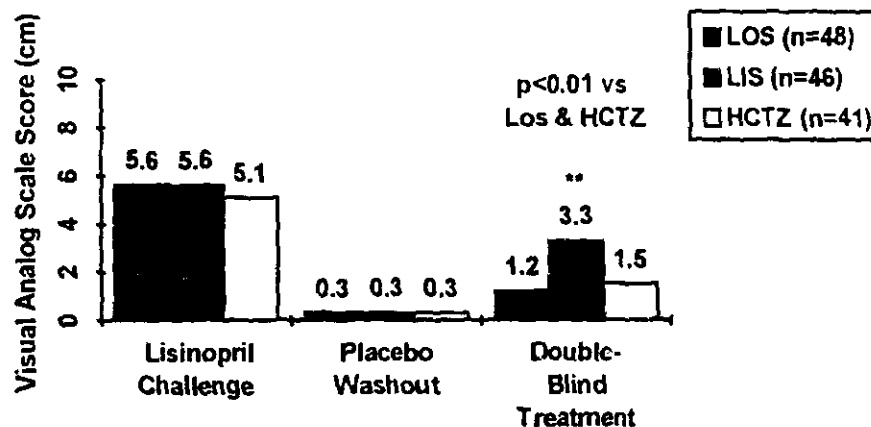
Treatment	Dry Cough		Total No.
	No. (%)	Yes No. (%)	
Losartan 50	30 (83.3)	6 (16.7)	36
Lisinopril 20	9 (31.0)	20 (69.0)	29
HCTZ 25	24 (75.0)	8 (25.0)	32

Table 56.7 lists the results based on the severity of cough for the all patients treated analysis. Most losartan patients with cough described the severity as "a little". Male and female patients had less cough with losartan than with lisinopril.

Table 56.7. Severity of Dry Cough, By Treatment (All-Patients-Treated Analysis)

Treatment	Not at All	A Little	Moderately	Quite a Bit	Extremely	Total
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No.
Losartan 50	34 (70.8)	9 (18.8)	4 (8.3)	1 (2.1)	0 (0.0)	48
Lisinopril 20	13 (28.3)	12 (26.1)	6 (13.0)	13 (28.3)	2 (4.4)	46
HCTZ 25	27 (65.9)	4 (9.8)	5 (12.2)	5 (12.2)	0 (0.0)	41

Figure 56.1 illustrates the difference in visual analog scores based on treatment group.

Figure 56.1 Visual Analog Scale Scores

The relationship between dry cough and all other symptom scores, in addition to treatment and gender, was analyzed with a multiple logistic regression analysis in order to determine if the presence of any of the other symptoms was related to the presence of dry cough, either independent of or dependent upon treatment. The results of this analysis indicated that the presence of both dry mouth and headache were associated with dry cough independently of treatment ($p \leq 0.01$). The relationship between treatment and the presence of dry cough was the same whether or not dry mouth was present, and reflected the relationship in the total population.

The mean changes for sitting systolic and diastolic blood pressure (mmHg) from the end of the placebo washout period to the end of the double-blind treatment period are presented in Tables 56.8 and 56.9. Presumably, this data represents the last double blind value carried forward. The change in blood pressure is better with lisinopril suggesting the doses of medication were not equipotent. The lowest recommended dose of lisinopril is 10 mg per day. The lowest dose recommended by the sponsor is 50 mg. If there is truly not a dose response for cough with ACE inhibitors, then this difference in potency may not be relevant. Obviously, had losartan 100 mg been used rather than 50 mg, these results would be more impressive.

Table 56.8. Mean Change in Sitting Systolic Blood Pressure (mmHg) From Placebo Washout

TREATMENT	N	PLACEBO WASHOUT		DOUBLE BLIND		CHANGE	
		Mean	S.D.	Mean	S.D.	Mean	S.D.
LOS 50	48	149.6	18.9	139.9	20.5	-9.6	14.6
LIS 20	46	154.5	19.1	140.6	21.3	-13.9	13.4
HCTZ 25	40	151.3	20.0	143.9	15.3	-7.4	13.2

Table 56.9 Mean Change in Sitting Diastolic Blood Pressure (mmHg) From Placebo Washout

TREATMENT	N	PLACEBO WASHOUT		DOUBLE BLIND		CHANGE	
		Mean	S.D.	Mean	S.D.	Mean	S.D.
LOS 50	48	94.8	10.1	89.6	9.3	-5.2	7.8
LIS 20	46	94.1	8.4	85.6	9.6	-8.5	8.2
HCTZ 25	40	95.8	9.1	91.1	7.5	-4.7	9.1

Conclusion:

The sponsor performed a specified interim analysis. They did not follow the protocol for the timing of the analysis (performed after 70 rather than 30 completed patients) and looked at the results of the losartan treated patients (should have looked only at the results of the lisinopril and HCTZ patients). The results of the trial are sufficiently robust so that any statistical adjustment still yields a significant outcome.

Although the definition of a positive cough response was not the same in the lisinopril treatment period and the double blind treatment period, it is apparent from table 56.7 that more lisinopril than losartan patients had cough defined as moderately severe or greater. The difference between therapies with regard to antihypertensive response suggest that lisinopril 20 mg had a greater antihypertensive effect compared to losartan 20 mg. If a more potent dose of lisinopril was used compared to losartan then an argument could be made that this study does no prove anything. A dose response for cough has not been defined for most ACE inhibitors. In general, the Cardio-Renal division has assumed that cough is not a dose dependent side effect. If this assumption is true, then the study does show something. If this assumption is false, then the study does not prove that the incidence of cough is less with losartan.

Study 64. A Double-blind, Randomized, Parallel, Active-controlled Study to Evaluate the Antihypertensive Efficacy and Safety of Losartan (MK-954, DuP 753) in Patients With Severe Hypertension.

Protocol

This is a randomized, double blind, parallel, enalapril controlled trial in patients with severe hypertension (siDBP = 115 - 130 mmHg). Eligible patients with severe hypertension whose previous antihypertensive medications could be safely discontinued, whose mean siDBP was 115 to 130 mmHg (on two readings, 30 minutes apart, with the 2 consecutive means being no more than 7 mmHg different) at least 24 hours and no more than 7 days off previous antihypertensive medications, and whose sitting systolic blood pressure was ≤ 220 mmHg, were stratified according to race (black or non-black) and were randomly assigned to one of two treatment groups. Patients were randomized in a ratio of 2:1 to receive once-daily therapy of either losartan 50 mg or enalapril 20 mg. Patients received double-blind therapy for 12 weeks. If siDBP remained ≥ 90 mmHg, losartan or enalapril doses were doubled. Over the course of therapy, HCTZ 25 mg, atenolol 100 mg and a dihydropyridine calcium channel blocker were added sequentially if siDBP remained ≥ 90 mmHg. A study outline of procedures and measurements performed is outlined in table 64.1.

Table 64.1. Procedures Performed During Trial.

Visit:	Double-Blind Period								
	Prestudy	1	2	3	4	5	6	7 ^a	8 ^b
Days:		1	8	15	29	43	57	71	85
Week:		0	1	2	4	6	8	10	12
Signed Informed Consent	X								
Medical History	X								
Complete Physical Examination	X								X
Clinic Visit ^c	X	X	X	X	X	X	X	X	X
BP and HR (trough [T] and peak [P] sitting and standing) ^d	X	T,P	T	T	T,P ^h	T	T	T	T,P
Routine Laboratory Examinations	X				X	X ^g			X
Electrocardiogram (12-lead)	X								X
Chest X-ray ^e	X								
AE Evaluation		X	X	X	X	X	X	X	X
Count/Dispense Double-Blind Medication ^f		X	X	X	X	X	X	X	X

a Follow Visit 7 schedule for additional visits; b Complete all procedures scheduled for Visit 8 if patient discontinues study for any reason prior to Visit 8.

c Clinic visits will occur as indicated between 0630 and 1000 hours. Patients are to be in the fasted state at all clinic visits (i.e., no food is to be taken during the 8 hours prior to each clinic visit).

d Measurements must be taken between 0630 and 1000 hours, 24 hours (range 22 to 26 hours) after last dose of study medication (for Visits 2 through 8) and prior to medication taken at the clinic visit. Peak measurements must be taken 6 hours (range 5 to 8 hours) after last dose.

e If none available within past 6 months; f According to titration schedule; g Complete abbreviated panel.

h Peak blood pressure measurements obtained at end of monotherapy.

Results

Seventy five (75) patients were entered into the study. Fifty (50) patients were randomized to the losartan group and 25 were randomized to the enalapril group. The distribution of patients by treatment group for each investigator is presented in Table 64.2.

Table 64.2 Baseline Patient Demographic Characteristics

		Losartan (N=50)	Enalapril (N=25)	Total (N=75)
Sex	Female	19 (38%)	11 (44%)	30 (40%)
	Male	31 (62%)	14 (56%)	45 (60%)
Age (years)	Mean	49.8	53	50.9
	S.D.	11.6	11.5	11.6
	Range	23-74	34-72	23-74
Racial Origin	Caucasian	25 (50%)	15 (60%)	40 (53%)
	Black	22 (44%)	10 (40%)	32 (43%)
	Hispanic	2 (4%)	0	2 (3%)
	Native Amer.	1 (2%)	0	1 (1%)
Duration of Primary Diagnosis (years)	Mean	10.7	11.9	11.1
	S.D.	9.3	9.3	9.2
	Median	6.5	11	10
	Range	0.5-34	6.5-36	0.5-36
Baseline Blood Pressures (SISBP/SIDBP)	Mean	173.7/118.5	176.5/119.3	

Six losartan patients and two enalapril patients discontinued therapy prior to completion of 12 weeks of therapy. Table 64.2a. lists the patients who did not complete the 12 week double-blind period of treatment.

Table 64.2a.

Patient #	Treatment	Day Discontinued	Reason Discontinued
4518	losartan	39	lost to follow-up
4559	losartan	69	lost to follow-up
4617	losartan	8	lost to follow-up
4573	losartan	51	protocol deviation
4577	losartan	97	protocol deviation
4601	losartan	46	uncooperative
4613	enalapril	29	lost to follow-up
4560	enalapril	25	laboratory adverse experience Increased creatinine (1.1 → 2.2 mg/dl) and BUN (15 → 62 mg/dl) compared to baseline.

Table 64.3 and 64.4 provide the mean change in trough siDBP and trough siSBP at weeks 4 and 12.

Table 64.3 Mean Change in Trough Sitting Diastolic Blood Pressure by Week All-Patients-Treated Approach (mmHg)

WEEK	TREATMENT GROUP	N	BASELINE		POST-TREATMENT		CHANGE		CHANGE	BETWEEN-GROUP COMPARISON
			Mean	S.D.	Mean	S.D.	Mean	S.D.	Adj Mean	
4	Losartan	50	118.5	3.5	99.4	9.8	-19.1	9.7	-19.1	0.355
	Enalapril	25	119.3	3.1	98.2	8.5	-21.0	7.9	-21.0	--
12	Losartan	50	118.5	3.5	90.8	8.7	-27.7	8.0	-29.0	0.051
	Enalapril	25	119.3	3.1	88.4	5.1	-30.9	4.8	-32.4	--

Table 64.4 Mean Change in Trough Sitting Systolic Blood Pressure by Week All-Patients-Treated Approach (mmHg)

WEEK	TREATMENT GROUP	N	BASELINE		POST-TREATMENT		CHANGE		CHANGE	BETWEEN-GROUP COMPARISON
			Mean	S.D.	Mean	S.D.	Mean	S.D.	Adj Mean	
4	Losartan	50	173.7	14.5	154.5	16.8	-19.2	17.9	-19.1	0.412
	Enalapril	25	176.5	14.9	152.7	16.4	-23.8	15.7	-22.0	--
12	Losartan	50	173.7	14.5	140.3	16.1	-33.4	17.8	-33.4	0.082
	Enalapril	25	176.5	14.9	133.8	14.5	-42.7	17.8	-39.6	--

At 12 weeks, all but one losartan treated patient were considered to be responders to therapy (siDBP < 90 mmHg or trough siDBP ≥ 90, reduction ≥ 10 mmHg). The significance of this definition of responder is suspect since patients could be markedly hypertensive but because they decreased their siDBP by 10 mmHg they are considered responders. The majority of losartan and enalapril patients required combination therapy. Sixty percent in each treatment group received 3 or more drugs to control blood pressure.

Table 64.5 lists the mean change in siDBP at week 4 and 12 based on racial subgroup. At week 4, most if not all patients should be on losartan monotherapy (50 or 100 mg). Although the mean change in siDBP in black patients at week 4 is impressive (-16.9 mmHg), it is not sufficient evidence that losartan is effective in black patients. There is no placebo group with which to compare. Since the pivotal studies (all placebo controlled) included in the NDA suggest that losartan is ineffective in black patients, nothing short of a placebo controlled trial can refute this observation. The week 12 results which suggest no difference between black and caucasian patients is not unexpected because other therapies contribute to the treatment effect.

Table 64.5 Summary Statistics for Trough Sitting Diastolic BP by Treatment Group and Race

WEEK	TREATMENT	RACE	N	Baseline		Post-Treatment		Change	
				Mean	S.D.	Mean	S.D.	Mean	S.D.
4	Losartan	BLACK	22	118.9	3.9	102	9.2	-16.9	9.7
		NON-BLACK	28	118.2	3.2	97.4	10	-20.8	9.5
	Enalapril	BLACK	10	120.3	3.7	102.6	7.9	-17.7	6.2
		NON-BLACK	15	118.6	2.5	95.3	7.8	-23.3	8.2
12	Losartan	BLACK	22	118.9	3.9	90.5	6.9	-28.4	6.8
		NON-BLACK	28	118.2	3.2	91.1	10	-27.1	8.9
	Enalapril	BLACK	10	120.3	3.7	88.7	6.2	-31.6	5
		NON-BLACK	15	118.6	2.5	88.2	4.4	-30.4	4.9

The incidence of adverse experiences is quite similar between treatment groups. There were no serious adverse events reported. A detailed summary of the results is not warranted since most patients were on multiple drug therapy to control blood pressure. As a consequence, adverse events could not be attributed to any one therapy. One enalapril patient (#4560) withdrew due to elevated creatinine.

The mean glucose in losartan treated patients increased from 102.8 mg/dl at baseline to 124.0 mg/dl at week 12. Two patients had marked increases in glucose. Patient #4551 a day 1 blood glucose of 197 mg/dl and a day 102 glucose of 417 mg/dl. Patient #4611 had a day -21 glucose of 166 and a day 92 glucose of 262.

Patient # 4551 had elevations in the ALT and AST during treatment. ALT increased from 57 U/L at baseline to 170 U/L at day 92. AST increased from 51 U/L at baseline to 101 U/L at day 92.

Open Label - Hypertensives						
Study #	Design/ Patient Population	Treatment Groups	N	Primary Endpoint	Other Measures	Page
012	- ol, nc, 2 center, 7 day Rx period - hypertensives with renal insufficiency - includes hemodialysis patients	- losartan 100 mg daily		pharmacokinetic parameters (losartan and E-3174)	- plasma renin - plasma aldosterone - urine creatinine clearance - urine sodium, urea nitrogen - hemodynamics	165
014	- sb, ol, nc, single center, 8 week Rx - hypertensives with renal nephropathy, proteinuria, non-black	- losartan 50 mg x 4 wks then 100 mg x 4 wks.	13	Change in 24 hour protein excretion	- GFR, Renal Plasma Flow - plasma renin	170
058	Preliminary results included in NDA were not reviewed at this time. Enrollment is ongoing.					
059	- ol, nc, 12 week treatment period - severe hypertensives - International Trial (U.S., S. Amer., Europe) - 50% have sDBP 115 - 125 mmHg	one treatment group, medication titrated based on response; losartan 50 - 100 mg +/- HCTZ 12.5 - 25 mg +/- atenolol 50 - 100 mg or felodipine 5 - 10 mg	180	no primary endpoint defined		173
L21 L11 L50 L49 L54	- ol extensions of db trials	- losartan +/- combination	659	Safety	- Change in DBP	178

wk = week, db = double-blind, ol = open label, od = once a day, bid = twice a day, r = randomized, ac = active control, pc = placebo control, nc = no control, p = parallel, co = crossover, hx = history, HTN = hypertension, ACEI = angiotensin converting enzyme inhibitor, NE = norepinephrine, Epi = epinephrine, PRA = plasma renin activity

Study 012. An Open, Multicenter Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Losartan after Chronic Dosing in Patients with Various Degrees of Renal Insufficiency

Objective: To determine the pharmacokinetics of losartan and E-3174 and hemodynamic in patients with various degrees of renal insufficiency

Design: open label, multicenter (2 centers), multi-dose; 1 week baseline washout period, 1 week treatment period.

Treatment Regimens: Losartan 100mg daily for 7 days

Population Studied: 24 patients with renal insufficiency defined by the creatinine clearance of two 24 hour urines obtained during baseline. The patients were subdivided based on the severity of renal insufficiency into 4 groups.

Group I: Creatinine clearance 75 mL/min or higher

Group II: Creatinine clearance 30-74 mL/min

Group III: Creatinine clearance 10-29 mL/min

Group IV: Creatinine clearance <10 mL/min (hemodialysis)

Six patients per renal clearance group completing the trial provided 80% power to detect a 114% difference in the AUC₂₄ of (LOSARTAN) between the normal group of subjects and any of the other three groups. The power to detect a 100% difference (2 fold) between the normal renal function group and any one of the other groups was 73%. Power estimates were based on two-sided t-test, with alpha=0.05.

Inclusion/Exclusion Criteria: Untreated DBP 95 - 115 mmHg, male or non-pregnant female, renal insufficiency as defined by creatinine clearance, no other relevant medical problems, not > 30% of ideal body weight.

Trial Description: All patients discontinued any prior antihypertensive medications (except diuretics in patients who required them) for a 1-week washout period (2 weeks if on prior angiotensin-converting enzyme inhibitor), during which their clinical status was closely monitored. Following the washout period, patients in Groups I, II, and III received losartan 100 mg for 7 days. Hemodialysis patients (Group IV) followed a similar pattern as patients in Groups I-III. Patients took 100 mg losartan at 8:00 a.m. at the clinic for 7 days, with the dose being taken 4 hours before dialysis on dialysis days. Dialysis was performed on a three-times-per-week schedule (Days 2, 4, 6, 9 of the study).

Endpoints/Parameters Measured:

1) Pharmacokinetic Parameters for losartan and E-3174 [the study is powered based on a difference between the AUC between creatinine clearance groups]

2) Table 12.1 and 12.2 list the parameters measured during the clinical trial.

Table 12.1. Clinical and Laboratory Measurements. Group I, II, and III (Non-hemodialysis Patients)

Study Day	Washout							Chronic Treatment/Pharmacokinetics								
	-7	-6	-5	-4	-3	-2	-1	1	2	3	4	5	6	7	8	9
Physical Examination	x															x
Medical History	x															
Inpatient														x	x	
Losartan 100 mg								x	x	x	x	x	x	x		
Plasma Losartan/E-3174 ***								x					x	x	x	
Vital Signs	x	x				x		x	x	x	x	x	x	x	x	x
Laboratory Evaluation*		x				x		x						x		x
24 hr Urine**		x	x			x								x	x	
Creatinine Clearance		x	x			x								x	x	
Electrocardiogram	x															x

*Laboratory Evaluation

Hematology: hemoglobin, hematocrit, RBC count, WBC count, WBC differential, platelet count

Serum Chemistry: AST (SGOT), ALT (SGPT), alkaline phosphatase, GGT, LDH, creatinine, total bilirubin, BUN, fasting serum glucose, uric acid, sodium, potassium, chloride, calcium, phosphates, total protein, albumin, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides

Urinalysis: pH, glucose, microscopic (RBC, WBC, casts, epithelial), drug abuse screen (Days -6, 1)

Renin-Angiotensin System: plasma renin activity, aldosterone

Miscellaneous: HIV antibody (Day -6), pregnancy test (females of childbearing potential, Days -6 and 9)

**24 hr Urine: creatinine (creatinine clearance), sodium, urea nitrogen, total protein. Urine was collected 0-4, 4-8, 8-12, and 12-24 hours postdose on Day 7

*** On Day 6, a trough blood specimen was taken, and on Day 7, the patient was admitted to the study clinic for 30 to 60 hours. Blood specimens were collected predose and at 10, 20, 30, 45, 60, 75, and 90 minutes, and 2, 3, 4, 6, 8, 10, 12, 15, and 18 hours postdose on Day 7, then on Days 8-9 at timepoints 24, 30, 36, 48, and 60 hours after the Day 7 dose.

Table 12.2. Clinical and Laboratory Measurements. Group IV (Hemodialysis Patients)

Study Day	Washout							Chronic Treatment/Pharmacokinetics								
	-7	-6	-5	-4	-3	-2	-1	1	2	3	4	5	6	7	8	9
Physical Examination	x															x
Medical History	x															
Hemodialysis		x		x		x			x		x		x			x
Inpatient														x	x	
Losartan 100 mg (pre-dialysis)								x	x	x	x	x	x	x		
Plasma Losartan/E-3174***																
Peripheral Venous Pre-Hemodialysis****								x						x		x
Vital Signs	x	x		x		x		x	x	x	x	x	x	x	x	x
Laboratory Evaluation*		x				x		x						x		x
Electrocardiogram	x															x

*Laboratory Evaluation

Hematology: hemoglobin, hematocrit, RBC count, WBC count, WBC differential, platelet count

Serum Chemistry: AST (SGOT), ALT (SGPT), alkaline phosphatase, GGT, LDH, creatinine, total bilirubin, BUN, fasting serum glucose, uric acid, sodium, potassium, chloride, calcium, phosphates, total protein, albumin, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides

Renin-Angiotensin System: plasma renin activity, aldosterone

Miscellaneous: HIV antibody (Day -6), pregnancy test (females of childbearing potential, Days -6 and 9), serum drug abuse screen (Days -6, 1)

*** On Day 6, a trough blood specimen was taken, and on Day 7, the patient was admitted to the study clinic for 30 to 60 hours. Blood specimens were collected predose and at 10, 20, 30, 45, 60, 75, and 90 minutes, and 2, 3, 4, 6, 8, 10, 12, 15, and 18 hours postdose on Day 7, then on Days 8-9 at timepoints 24, 30, 36, 48, and 60 hours after the Day 7 dose. **** Pre- and post-dialysis blood specimens were taken from the dialysis shunt circuit at Hours 0, 1, 2, 3, and 4 of dialysis on Day 6 to evaluate the clearance of losartan and E-3174 by hemodialysis.

Enrolled/Randomized: 24 patients with 6 in each creatinine clearance classification group

Demographics/Disposition: All patients completed the study.

Group	Male/Female	Black/White	Mean Age (Years)	Mean Baseline Cr. Cl. (ml/min)	Range Baseline Creatinine Clearance (ml/min)
I	4/2	0/6	48.7	112	81 - 167
II	2/4	1/5	45.0	58.8	47.6 - 74.5
III	4/2	2/4	58.8	16.6	12 - 28.5
IV	2/4	4/2	38.5	-	-

Efficacy Results:

Two patients had incomplete urine collection (# 113 and # 123). In addition, half-lives could not be calculated for 5 patients; Losartan: #231 and #143, E-3174: #222, #241 and #242.

Table 12.3 lists the pharmacokinetic parameters calculated for losartan. AUC tended to increase with increasing dose. C_{max} increased in hemodialysis patients. Elimination half-life was similar in all groups. Urinary recovery of losartan was less than 40% of the dose.

Table 12.3. Summary Pharmacokinetics Parameters for Losartan

Parameter	I (>75)			II (30-74)		
	n	Mean	Std	n	Mean	Std
C_{max}^1 (ng/mL)	6	854.22	315.23	6	1164.63	748.03
T_{max} (hr)	6	0.79	0.37	6	0.68	0.23
AUC ² (ng hr/mL)	6	1108.90	265.05	6	1212.20	755.06
$t_{1/2}$ (hr) ^A	6	2.13	0.68	6	2.17	0.97
CL_r^3 (mL/min)	6	50.24	19.36	6	16.51	8.46
Urinary Recovery ⁴ (% Dose)	5	3.25	1.23	5	1.33	1.03
Parameter	III (10-29)			IV (Dialysis)		
	n	Mean	Std	n	Mean	Std
C_{max}^1 (ng/mL)	6	801.00	445.41	6	1615.05	417.36
T_{max} (hr)	6	0.88	0.41	6	0.68	0.32
AUC ² (ng hr/mL)	6	1760.61	1389.85	6	2065.63	551.01
$t_{1/2}$ (hr) ^A	5	3.22	2.19	5	2.64	1.02
CL_r^3 (mL/min)	6	2.31	0.89		NA	
Urinary Recovery ⁴ (% Dose)	6	0.27	0.32		NA	

A Harmonic mean and pseudo-standard deviation used for half life.

1 C_{max} was significantly higher in Group IV than in Group I ($p=0.020$) and Group III ($p=0.013$). There was a notable trend ($p=0.072$).

2 AUC²⁴ was significantly higher in Group IV than in Group I ($p=0.008$) and notably higher in Group IV than Group II ($p=0.066$). There was a significant trend, $p=0.021$.

3 Renal clearance was significantly greater in Group I than in Groups II and III, $p=0.008$ and $p=0.005$, and significantly higher in Group II than in Group III, $p=0.005$.

There was a highly significant trend, $p<0.001$.

4 Urinary Recovery was significantly greater in Group I than in Groups II and III, $p=0.037$ and $p=0.008$, and significantly higher in Group II than in Group III, $p=0.035$.

There was a highly significant trend, $p<0.001$.

Figure 12.1 plots the mean losartan concentration on day 7. Group IV does not have a value at any time after 16 hours and, as a consequence, it is not clear that the elimination $t_{1/2}$ has been accurately determined.

Figure 12.1 LOSARTAN Mean Plasma Concentrations After Dose Day 7

Mean MK-954 Plasma Concentration (ng/ml)

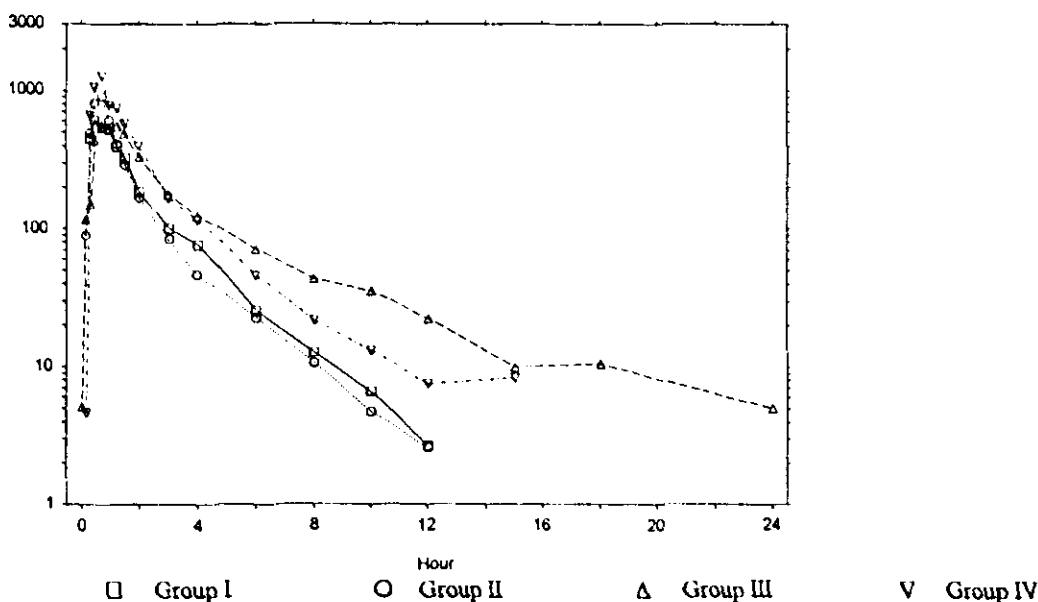


Table 12.4. Summary Pharmacokinetics Parameters for E-3174. Group (Creatinine Clearance - mL/min)

Parameter	I (>75)			II (30-74)		
	n	Mean	Std	n	Mean	Std
C_{max} (ng/mL)	6	681.28	210.49	6	622.98	214.06
T_{max} (hr)	6	2.42	0.92	6	2.08	0.49
AUC (ng hr/mL)	6	4362.15	1143.24	6	3624.26	953.12
$t_{1/2}$ (hr) ^A	6	9.55	3.47	5	11.04	5.44
CL_{cr} (mL/min)	6	16.10	4.14	6	6.92	2.55
Urinary Recovery ³ (% Dose)	5	4.44	1.34	5	1.85	0.92
Parameter	III (10-29)			IV (Dialysis)		
	n	Mean	Std	n	Mean	Std
C_{max} (ng/mL)	6	402.60	344.18	6	715.28	579.02
T_{max} (hr)	6	4.17	1.60	6	2.50	1.00
AUC (ng hr/mL)	6	3912.44	2766.13	6	5011.61	4037.50
$t_{1/2}$ (hr) ^A	6	13.45	5.78	4	11.25	9.06
CL_{cr} (mL/min)	6	1.29	0.78		NA	
Urinary Recovery ³ (% Dose)	6	0.24	0.08		NA	

A Harmonic mean and pseudo-standard deviation used for half life.

1 T_{max} was significantly later in Group III than in Group II, $p=0.015$ and notably later in Group III than in Group I ($p=0.058$) and Group IV ($p=0.072$). There was no significant trend.

2 Renal clearance was significantly greater in Group I than in Groups II and III, $p=0.006$ and $p=0.005$, and significantly higher in Group II than in Group III, $p=0.008$. There was a highly significant trend, $p<0.001$.

3 Urinary Recovery was significantly greater in Group I than in Groups II and III, $p=0.012$ and $p=0.008$, and significantly higher in Group II than in Group III, $p=0.008$. There was a highly significant trend, $p<0.001$.

Figure 12.2. E-3174 Mean Plasma Concentrations After Dose Day 7

Mean E-3174 Plasma Concentration (ng/ml)

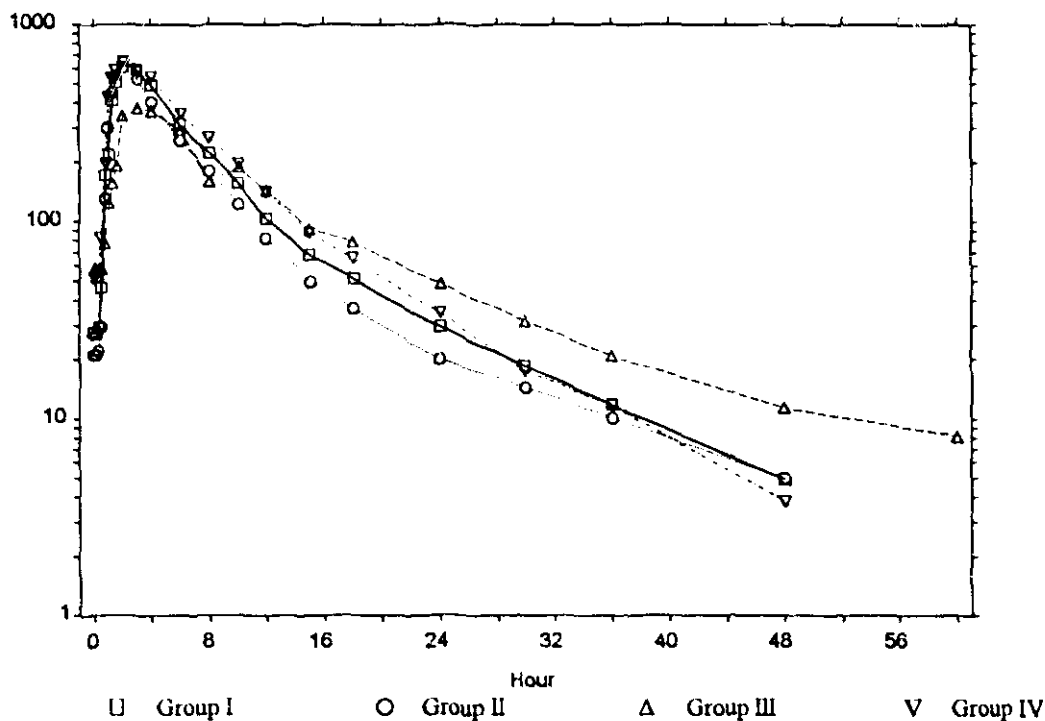


Table 12.5 list the mean losartan and E-3174 concentration during dialysis. Dialysis does not remove losartan or active drug.

Table 12.5. Plasma Concentrations Across Dialyzer - Hemodialysis Patients (Day 6)

Hour	Post-Dose	Sampling Location	Mean (S.D.) Plasma Concentrations			
			n	LOSARTAN	n	E-3174
4 ^a		Predialyzer	6	193.0 (191.2)	6	469.4 (419.0)
		Postdialyzer	6	142.7 (151.2)	6	404.5 (422.5)
5		Predialyzer	6	133.5 (152.5)	6	497.4 (466.9)
		Postdialyzer	6	131.8 (141.3)	6	530.4 (508.6)
6		Predialyzer	6	79.4 (83.7)	6	499.1 (496.5)
		Postdialyzer	6	85.1 (88.4)	6	545.6 (569.7)
7		Predialyzer	6	53.6 (56.3)	6	518.3 (592.8)
		Postdialyzer	6	54.4 (54.5)	6	509.7 (549.6)
8		Predialyzer	4	62.7 (59.2)	4	625.0 (681.8)
		Postdialyzer	4	57.8 (59.9)	4	549.9 (558.7)

^aBeginning of dialysis

Table 12.6 Correlation of Pharmacokinetics Parameters with Creatinine Clearance. For Renal Function Groups I, II and III. Day 7. Correlation with Creatinine Clearance

Parameter	LOSARTAN			E-3174		
	n	Corr	p-value	n	Corr	p-value
C _{max} (ng/mL)	17	0.064	0.808	17	0.407	0.105
T _{max} (hr)	17	-0.123	0.637	17	-0.601	0.011
AUC (ng*hr/mL)	17	-0.164	0.529	17	0.252	0.328
t _{1/2} (hr)	16	-0.153	0.572	16	-0.212	0.431
CL _r (mL/min)	17	0.892	<0.001	17	0.958	<0.001
Urinary Recovery (% Dose)	15	0.792	<0.001	15	0.913	<0.001

*,** Correlation coefficient significantly different from zero, p<0.050, p<0.01, respectively.

For all patient groups, SBP and DBP declined with losartan therapy compared to baseline. There was no correlation between change in blood pressure and plasma concentration of losartan or E-3174 on day 7 (for 12 hours post drug administration).

Table 12.7. PRA, Aldosterone and 24-Hour Urine Tests. Day 7.

Parameter	Group I				Group II			
	Baseline		Day 7	Mean	Baseline		Day 7	Mean
	n	Mean	Mean	Change	n	Mean	Mean	Change
Aldosterone (pg/mL)	6	12.15	9.57	-2.58	6	17.58	17.97	0.38
PRA (ng/mL/hr)	6	0.81	2.59	1.78*	6	1.45	3.46	2.01*
U 24 hr Protein (mg/24 hr)	6	117.2	43.83	-73.33	6	621.5	363.17	-258.3
U Urea Nitrogen (gm/24 hr)	6	12.04	12.27	0.22	6	9.05	9.58	0.53
Protein/Creatinine	5	0.06	0.02	-0.03	6	0.32	0.21	-0.11
U 24 hr Sodium (mEq/24 hr)	6	159.2	161.67	2.50	6	151.8	165.17	13.33
U 24 hr Creat (mg/24 hr)	6	1888	1732	-156.5	6	1327	1361	34.00
Creat Clearance (mL/min)	6	110.3	117.33	7.05	5	55.07	61.72	6.65
Parameter	Group III				Group IV			
	Baseline		Day 7	Mean	Baseline		Day 7	Mean
	n	Mean	Mean	Change	n	Mean	Mean	Change
Aldosterone (pg/mL)	6	38.93	28.72	-10.22	6	48.42	16.98	-31.43
PRA (ng/mL/hr)	6	2.79	6.20	3.41*	6	1.26	3.55	2.29
U 24 hr Protein (mg/24 hr)	6	2092	1607.6	-484.0			N/A	
U Urea Nitrogen (gm/24 hr)	6	7.52	8.05	0.53			N/A	
Protein/Creatinine	6	2.30	1.39	-0.91			N/A	
U 24 hr Sodium (mEq/24 hr)	6	133.7	164.50	30.83			N/A	
U 24 hr Creat (mg/24 hr)	6	1328	1282	-46.7			N/A	
Creat Clearance (mL/min)	6	17.13	17.23	0.10			N/A	

Within Group Test is Signed Rank Test

p<0.05*

p<0.01**

Note: Baseline 24-hour urine was collected on Day -3. Collection began Day 7 for on treatment 24-hour urine values.

PRA/aldosterone measured immediately prior to first dose for baseline and immediately prior to Day 7 dose or on treatment assessment.

Safety Results:

Seven patients experienced adverse events. Table 12.8 lists the adverse experiences.

Table 12.8. Clinical Adverse Experiences

Patient No	Adverse Experience	Renal Group	Study Day of Onset	Intensity
Investigator: Keane (#012001)				
111	Pharyngitis	I	4	Mild
	Laryngitis		4	Moderate
112	Headache	I	1	Mild
121	Stiffness	II	1	Moderate
	Neck Pain		2	Moderate
122	Somnolence	II	3	Moderate
	Somnolence		3	Mild
	Somnolence		7	Mild
131	Flatulence	III	2	Mild
	Muscle Cramp		3	Mild
	Headache		6	Mild
	Dizziness		7	Mild
	Contusion		7	Mild
	Fever		8	Mild
			(Off Drug)	
	Epistaxis		9	Mild
			(Off Drug)	
142	Somnolence	IV	1	Mild
Investigator: Sica (#012002)				
231	Dizziness	III	7	Unknown
	Orthostatic Hypotension		7	Unknown

Study 014. A Single-blind, Longitudinal, Pilot Study to Investigate the Effects of Losartan (DuP 753) on Urinary Protein Excretion in Nondiabetic Patients with Proteinuria

Protocol

Objective: To evaluate the effect of losartan on total urinary protein excretion in nondiabetic patients with ≥ 2.0 gms/24 hours total urinary protein excretion, and mild to moderate hypertension; To evaluate the effect of losartan on the fractional urinary clearance of albumin and IgG.

Design: single-blind, longitudinal, pilot clinical trial, single center (Holland), 4 week placebo baseline period, 8 week treatment period, 4 week washout period.

Population Studied: hypertensive patients with renal nephropathy and proteinuria

Inclusion/Exclusion Criteria: (This is not a comprehensive list.)

To be included in the trial, patients fulfilled the following criteria:

- (1) mild to moderate hypertension [untreated supine diastolic blood pressure (suDBP) of 90-115 mmHg, based upon the mean of the last two baseline determinations of suDBP (i.e., end of Weeks -2 and -1)] and historically documented or renal-biopsy-proven nephropathy,
- (2) non-black,
- (3) at least 21 years of age but <70 years,
- (4) stable proteinuria defined as total urinary protein excretion ≥ 2.0 gms/24 hours based upon the mean of three single 24-hour urine results taken at the end of study weeks -4, -3, and -2. None of the three 24-hour urine results should have been < 1.0 gms/24 hours. [NOTE: Entry eligibility was based on the mean of the Week -4, -3, and -2 results, however, the mean of three 24-hour urine results at the end of Week -1 was used as the baseline value],
- (5) creatinine clearance of ≥ 60 mL/min based upon the mean of the Week -4, -3, and -2 baseline values. [NOTE: Entry eligibility was based upon the mean of Week -4, -3, and -2 creatinine clearances, however, the creatinine clearance calculated based upon the mean of the three collections at the end of Week -1 was used as the baseline value],
- (6) No history of diabetes mellitus.

Treatments: losartan 50 mg daily for the first four weeks and 100 mg daily for the second four weeks.

Trial Description: The trial consisted of a 4 week placebo baseline period, an 8 week treatment period and a 4 week placebo washout period.

Endpoints/Parameters Measured:

Primary efficacy evaluation was based on the effect of losartan on total 24-hour urinary protein excretion in nondiabetic patients with ≥ 2.0 gm/24-hour total urinary protein excretion and mild to moderate hypertension.

Table 14.1. Clinical and Laboratory Evaluation Flowchart

	Day Week -28	Baseline				Treatment								Maintenance			
		-4	-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12
Clinical Evaluations																	
1.	IDC/PE	X															
2.	BP/Pulse	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Evaluations																	
3.	Hematology	X			X	X							X				X
4.	Chemistry																
	Creatinine	X	X	X	X	X				X				X			X
	Albumin	X			X	X				X				X			X
	IgG	X			X	X				X				X			X
	Total Protein	X			X	X				X				X			X
	Uric Acid	X			X	X				X				X			X
	Fasting Glucose*	X			X	X				X				X			X
	LFTs	X			X	X				X				X			X
	Lipids*				X	X				X				X			X

* NOTE: Fasting glucose and lipid profiles were done at the end of Week -1, and on days of the renal function tests (at the end of Weeks 4, 8, and 12). All other labs during the study were nonfasting.

Table 14.2. Clinical and Laboratory Evaluation Flowchart

	Day Week -28	Baseline				Treatment								Maintenance			
		-4	-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12
Clinical Evaluations																	
5.	24-Hour Urine																
	Sodium	X	XX	X	X#		X#		X	X#			X		X#		X
	Urea Nitrogen	X	X	X	X#		X		X			X		X		X	X
	Tot. Protein	X		X	X#		X		X			X		X		X	X
	Creatinine	X	X	X			X		X			X		X		X	X
6.	Fractional Clearances				X				X				X				X
	Albumin and IgG				X				X				X				X
7.	GFR*				X				X				X				X
8.	RBF (PAH)				X				X				X				X
9.	Plasma Renin Activity (PRA) (Supine)		X		X				X				X				X
10.	Creatinine Clearance	X		X	X#				X				X				X
11.	Pregnancy Test				X**				X				X**				X*
12.	Urine Drug Screen (See pg 41)	X							**								*

NOTE: At the end of Weeks -1, 4, 8 and 12, patients will collect three consecutive daily 24-hour urine collections, the mean of which will be used for baseline (Week -1), and efficacy (Weeks 4, 8 and 12)

* Iothalamate, inulin, or DTPA may be used to determine GFR, however, the method used must be consistent within institution and patient.

** A pregnancy test must be done and negative results obtained within 72 hours prior to the GFRs done at the end of Weeks

-1, 4, 8, and 12. Results must be obtained prior to the start of the GFR procedure

GFR and ERPF were analyzed after adjusting for body surface area (BSA). BSA was calculated using the following formula:

$$BSA (m^2) = (wt. \text{ in kg})^{0.425} \times (ht. \text{ in cm})^{0.725} \times 0.007184$$

GFR and ERPF were both adjusted for the BSA by the following formula: Measurement $\times 1.73/BSA$

In order to detect a 33% change from baseline in total 24-hour urinary protein excretion (a change of 0.40 on the log scale) with 80% power, 14 patients needed to be enrolled

Results**Demographics/Disposition:**

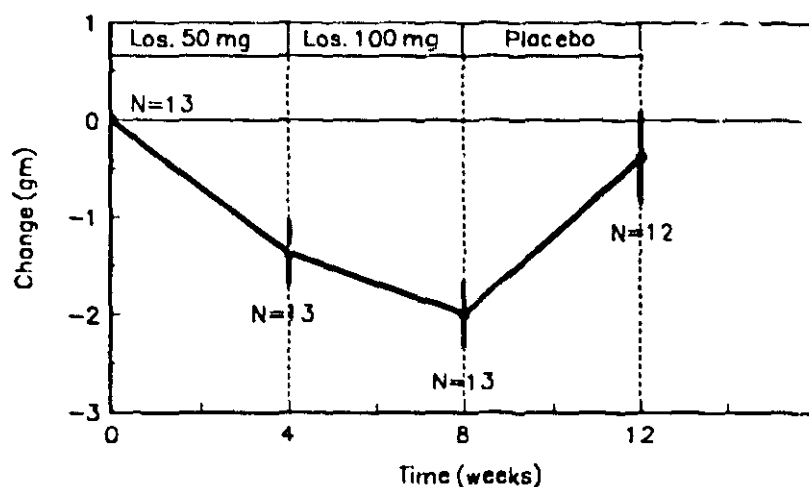
Thirteen patients (11 male, 2 female) were enrolled. One patient (# 0001) discontinued following the completion of Week 8 due to a clinical adverse experience. The average age of subjects was 43.3 years (range: 20 - 62). All subjects were caucasian.

Efficacy Results:**Table 14.4. Mean 24-Hour Urine Protein (gm) Changes from Baseline.**

Week	N	Baseline			Weekly Response			Change from Baseline			WITHIN GRP COMPARISON
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	
4	13	5.82	4.40	4.23	4.45	3.30	4.27	-1.37	-1.10	1.11	0.000
8	13	5.82	4.40	4.23	3.83	2.80	4.14	-1.99	-1.70	1.18	0.000
12	12	5.99	4.55	4.37	5.61	4.00	4.86	-0.38	-0.80	1.59	0.424

ANALYSIS SPECS: WITHIN GROUP = SIGN RANK, BASED ON RANKS

Figure 14.1.

Average ($\pm$ Standard Error) Changes from Baseline of Mean 24 Hr. Urine Protein by Time(Weeks)

Note: All Patients Received Losartan 50 mg for 4 Weeks and 100 mg through Week 8

Table 14.5. Mean Creatinine Clearance (ml/min) Changes from Baseline

Week	N	Baseline			Weekly Response			Change from Baseline			WITHIN GRP COMPARISON
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	
4	13	94.95	90.30	24.76	89.54	90.00	21.22	-5.41	-5.00	13.05	0.174
8	13	94.95	90.30	24.76	90.15	93.00	20.51	-4.79	-7.00	15.70	0.251
12	12	98.44	94.65	22.25	90.58	91.50	19.71	-7.86	-1.00	21.76	0.377

ANALYSIS SPECS: WITHIN GROUP = SIGN RANK, BASED ON RANKS

Table 14.6. ERPF (ml/1.73m²) Change from Baseline

Week	N	Baseline			Weekly Response			Change from Baseline			WITHIN GRP COMPARISON
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	
4	13	271.47	280.84	70.19	296.66	278.43	72.54	25.19	12.00	71.80	0.340
8	13	271.47	280.84	70.19	307.99	287.22	62.33	36.52	22.98	106.11	0.127
12	12	276.50	292.85	70.83	291.96	296.48	40.17	15.46	-0.45	94.44	0.850

ANALYSIS SPECS: WITHIN GROUP = SIGN RANK, BASED ON RANKS

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Table 14.7. Filtration Fraction (%) Changes from Baseline

Week	N	Baseline			Weekly Response			Change from Baseline			WITHIN GRP COMPARISON
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	
4	13	21.321	23.707	4.774	19.119	19.641	3.570	-2.201	-2.443	1.927	0.005
8	13	21.321	23.707	4.774	18.584	19.304	3.214	-2.736	-2.775	2.365	0.003
12	12	21.470	23.831	4.955	21.632	23.496	4.605	0.162	-0.037	1.631	0.970

ANALYSIS SPECS: WITHIN GROUP = SIGN RANK, BASED ON RANKS

Table 14.8. Blood Pressure Diastolic, Supine (mmHg) Changes from Baseline

Week	N	Baseline			Weekly Response			Change from Baseline			WITHIN GRP COMPARISON
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	
4	13	94.31	96.00	6.73	81.08	80.00	7.40	-13.23	-13.00	6.30	0.000
8	13	94.31	96.00	6.73	78.00	77.00	8.35	-16.31	-15.00	7.16	0.000
12	12	94.67	96.00	6.89	77.08	90.50	7.88	-4.58	-4.50	4.78	0.016

ANALYSIS SPECS: WITHIN GROUP = SIGN RANK, BASED ON RANKS

Table 14.9. Blood Pressure Systolic, Supine (mmHg) Changes from Baseline

Week	N	Baseline			Weekly Response			Change from Baseline			WITHIN GRP COMPARISON
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	
4	13	152.77	154.00	13.41	135.69	133.00	15.31	-17.08	-18.00	13.51	0.001
8	13	152.77	154.00	13.41	133.62	129.00	13.81	-19.15	-17.00	12.19	0.001
12	12	154.00	155.50	13.22	155.00	154.00	17.76	1.00	1.00	13.26	0.984

ANALYSIS SPECS: WITHIN GROUP = SIGN RANK, BASED ON RANKS

Table 14.10. PRA (nmol/L/hr) Changes from Baseline

Week	N	Baseline			Weekly Response			Change from Baseline			WITHIN GRP COMPARISON
		Mean	Median	S.D.	Mean	Median	S.D.	Mean	Median	S.D.	
4	13	1.71	1.10	1.59	5.59	4.70	4.21	3.88	3.50	3.20	0.001
8	13	1.71	1.10	1.59	9.02	5.90	7.39	7.32	5.10	7.02	0.002
12	12	1.78	1.15	1.64	2.17	2.10	1.72	0.38	0.75	1.62	0.258

ANALYSIS SPECS: WITHIN GROUP = SIGN RANK, BASED ON RANKS

Safety Results

Patient #0001 withdrew after eight weeks of therapy due to adverse experience. It is not clear what adverse events caused patient #0001 to withdraw.

Six patients experienced clinical adverse events. Patient #0005 experienced a syncopal episode on day 38 which lasted for 10 minutes. Two patients (#0003 and #0008) had edema/swelling while receiving losartan which apparently resolved after approximately 1 week despite continued losartan therapy. Seven patients had laboratory values outside of pre-defined parameters. Only one patient (#0003) had lab abnormalities of clinical relevance. Patient #0003 had decreases in hemoglobin/hematocrit and increases in transaminases while receiving losartan. On day 54, ALT = 112 U/L (baseline ALT = 38 U/L), AST = 105 U/L (baseline AST = 50 U/L) and hemoglobin 10.8 Gm/dl (baseline hgb. = 13.8 Gm/dl). ALT and AST returned to baseline on placebo. Hemoglobin remained stable (10.3 Gm/dl) on placebo.

Study 059. A Multicenter Study to Investigate the Safety and Antihypertensive Efficacy of Losartan (MK-954, DuP 753) in Patients with Severe Hypertension

This is an open label, uncontrolled, multi-center, international (U.S., Europe and S. America) trial in patients with a history of severe hypertension (defined as DBP $\geq$ 115 mmHg). For enrollment, patients had to have either an untreated siDBP 115 - 125 mmHg or a documented history of severe hypertension (SiDBP $\geq$ 115 mmHg) with a currently treated SiDBP of 96-125 mmHg (measured at the trough of the dosing interval) while receiving at least one antihypertensive agent. After discontinuing medications for at least 48 hours, the SiDBP must have remained 96-125 mmHg and not have increased by more than 15 mmHg from the SiDBP on therapy. Fifty percent (50%) of the patients enrolled must have SiDBP 115-125 mmHg

immediately prior to the first dose of losartan. Patients qualified for the study based on medical history, the results of a complete physical examination, routine laboratory evaluation, electrocardiogram (ECG), chest x-ray, and blood-pressure measurement (Visit 1). Patients were seen in the clinic after 1 week of treatment with losartan 50 mg once-daily (Visit 2) for a safety evaluation. Dosage adjustment was not planned at Visit 2 unless the patient's SiDBP was ≥ 105 mmHg and it was clinically indicated. At Visit 3, after 2 weeks of losartan therapy, the dose of losartan was increased to 100 mg once daily, if SiDBP ≥ 95 mmHg. At Visit 4, after 4 weeks of losartan therapy, hydrochlorothiazide (HCTZ) 12.5 mg once daily was added, if SiDBP ≥ 95 mmHg. At Visit 5 (Week 6), HCTZ was increased to 25 mg once daily, if SiDBP ≥ 95 mmHg. Atenolol 50 mg or a calcium channel blocker (felodipine ER 5 mg at U.S. study sites) once daily was added at Visit 6 (Week 8), if SiDBP ≥ 95 mmHg. The final dosage adjustment was made at Visit 7 (Week 10) at which time atenolol was increased to 100 mg (or the calcium channel blocker was increased to the next higher dose, felodipine ER was 10 mg) once daily, if SiDBP ≥ 95 mmHg. Patients were treated for a total of 12 weeks. Table 59.1 lists the procedures performed during the study.

Table 59.1. Clinical and Laboratory Measurements

Visit Week	Screening ¹	Treatment							
		2 1	3 2	4 4	5 6	6 8	7 10	8 12	
Medical History	X								
Physical Examination	X								X
Sign Informed Consent	X								
Medication:									
Withdrawal ²	X								
Losartan		X	X	X	X	X	X	X	X
Clinical Evaluation ³	X ^{3a}	X	X	X	X	X	X	X	X
Laboratory Evaluation ⁴	X		*	*	*	*	*	*	X
ECG	X								X
Chest X-ray ⁵	X								
Dose Titration*			X	X	X	X	X	X	
AE Evaluation		X	X	X	X	X	X	X	X

1 Visit 1 - Treated patients may have required more than one actual visit to the clinic to complete all of the evaluations.
 Visit 8 - If the patient discontinued prior to completion of this visit, all evaluations were performed
 2 Medication Withdrawal - patients were instructed to stop all existing antihypertensive therapy for at least 48 hours prior to the first dose of losartan
 3 Clinical Evaluation - included measurement of blood pressure, heart rate, and body weight at trough (22 to 26 hours after the previous dose of losartan)
 3a At Visit 1, blood pressure was measured at one-hour intervals until 2 consecutive measurements of SiDBP at one-hour intervals were within 7 mmHg. The patient then entered the treatment period and received the first dose of losartan. The baseline blood-pressure margins measurement was obtained immediately prior to the first dose of losartan.
 4 Laboratory Evaluation - included hematology, blood chemistry and urinalysis. A laboratory evaluation was performed at the end of the losartan monotherapy period (*). An additional laboratory evaluation was required at the next visit after addition of HCTZ(*), after an increase in dose of HCTZ(*), at the end of the study (Visit 8), or at the time of premature discontinuation
 5 Chest X-ray - was performed if one was not available from within the previous 6-month period
 * if SiDBP ≥ 95 mmHg, Visit 3 = losartan 100 mg, Visit 4 = add HCTZ 12.5 mg, Visit 5 = increase to HCTZ 25 mg, Visit 6 = add atenolol 50 mg or calcium channel blocker, Visit 7 = Double-Dose of atenolol or calcium channel blocker

There was no primary endpoint listed in the protocol of this trial. The primary objective of the study was to determine whether losartan is safe and effective in controlling blood pressure either alone or in combination with other agents. Blood pressure changes after 4 and 12 weeks treatment were used to assess efficacy.

Results

Demographics and Disposition

One hundred eighty (180) patients entered at 21 centers. The number of patient entered per center ranged from 0 - 29 with a median of 10. Table 59.2 lists the demographic characteristics of the enrolled patients.

Table 59.2. Demographic Data

		N	%
TOTAL PATIENTS		180	
SEX	MALE	96	-53%
	FEMALE	84	-47%
AGE (YRS.)	MEAN +/- (STD)	51.3 +/- (10.122)	
	RANGE	23.0 - 72.0	
ORIGIN	CAUCASIAN	122	-68%
	BLACK	34	-19%
	ASIAN	3	-2%
	HISPANIC	13	-7%
	SPANISH	1	-1%
	MESTIZO	7	-4%

The number of patients on multi-drug therapy for hypertension is not readily accessible. Table 59.3 lists the disposition of patients in the trial. Nine patients withdrew prematurely from therapy. The majority of patients completed the study and continued into an extension period

Table 59.3. Patient Disposition.

TOTAL PATIENTS ENTERED	180
PATIENTS COMPLETED ACUTE PHASE CONTINUING INTO EXTENSION	159
PATIENTS COMPLETED ACUTE PHASE NOT CONTINUING INTO EXTENSION	12
TOTAL DISCONTINUED	9
CLINICAL ADVERSE EXPERIENCE	5
LOST TO FOLLOW-UP	1
THERAPY INEFFECTIVE	1
CLINICAL AE & ECG AE	1
PATIENT WITHDREW	1

Table 59.4 lists the patients withdrawn and the reason for withdrawal.

Table 59.4. Patient Withdrawals

Number	Reason Discontinued	Day Discontinued
5675	Clinical AE	8
5729	Clinical AE	12
5501	Clinical AE	29
5708	Clinical AE	42
5525	Clinical AE	75
5528	Lost To Follow-up	21
5680	Therapy Ineffective	9
5725	Clinical AE & ECG AE	50
5517	Patient Withdrew	3

Efficacy

Table 59.5 shows the mean change in siDBP and siSBP over the treatment period.

Table 59.5. Trough siDBP and siSBP. (All Patients Treated Analysis)

Trough siDBP	WEEK	N	Baseline		Treatment		Change	
			Mean	S.D.	Mean	S.D.	Mean	S.D.
	2	177	112	7.7	104.8	19	-7.3	8.7
	4	172	111.9	7.7	102.6	11.1	-9.3	10.2
	8	170	111.8	7.7	95.9	9	-15.9	9.7
	Final Visit	179	112	7.7	93.1	9.4	-18.9	10.3
Trough siSBP								
	2	177	171.4	16.6	164.5	21.9	-6.9	16.4
	4	172	171.6	16.7	160.3	20.9	-11.3	17.5
	8	170	171.6	16.6	149.1	18	-22.5	17.4
	Final Visit	179	171.5	16.6	145.8	20.1	-25.7	20.2

Table 59.6 lists the number of patients at each visit by the treatment received at that visit. Since titration was not required unless siDBP was ≥ 95 mmHg, the number of patients requiring triple drug therapy at the end of 12 weeks may be underestimated if a "normal blood pressure" (siDBP < 90 mmHg) had been the goal.

Table 59.6. Number of patients on each treatment by week.

Week	L	L/H	L/H/A	L/H/F	L/H/A/F	other	Total
2	174	3	0	0	0	0	177
4	135	37	0	1	0	0	173
8	42	100	4	22	0	L/F = 2	170
Final	39	54	19	56	8	H = 1 H/F = 1 L/F = 1	179

L = losartan, H = hydrochlorothiazide, A = atenolol, F = felodipine

Subgroup analysis were performed by the sponsor based demographic variables. It is difficult to interpret this data due to the open label design of this trial.

Safety

Fifty-eight percent of the patients experienced an event; but less than 2% were considered serious. Table 59.7 compares the possible treatment regimens with regard to the incidence of adverse events.

Table 59.7. Incidence of Adverse Events Based on Treatment Regimen

	Losartan	Losartan/HCTZ	Losartan/HCTZ/ Other	Other	Combined
Number of Patients (%)	N=180	N=142	N=85	N=24	N=180
With One or More Adverse Experiences	79 (43.9%)	46 (32.4%)	27 (31.8%)	4 (16.7%)	105 (58.3%)
With Serious Adverse Experiences	1 (0.6%)	1 (0.7%)	0	1 (4.2%)	3 (1.7%)
Withdrawn Due to Adverse Experiences	3 (1.7%)	2 (1.4%)	0	1 (4.2%)	6 (3.3%)
Who Died	0	0	0	0	0
With Drug-Related Adverse Experiences	28 (15.6%)	17 (12.0%)	11 (12.9%)	2 (8.3%)	45 (25.0%)
Note: The number of adverse experiences in the treatment groups does not sum up to the number in all patients combined because the same patient may have received different treatments at different times and thus could be counted more than once.					
Other: The "Other" group includes all reports of adverse experiences when the patient was not on a regimen defined in the protocol.					

The most common adverse experiences for these treatment regimens are outlined in table 59.8.

Table 59.8. Adverse Experiences Based on Treatment Regimen

	Losartan	Losartan/HCTZ	Losartan/HCTZ/ Other	Other	Combined
	N=180 (%)	N=142 (%)	N=85 (%)	N=24 (%)	N=180 (%)
Nervous System					
Headache	37 (20.6)	13 (9.2)	6 (7.1)	0	47 (26.1)
Dizziness	7 (3.9)	8 (5.6)	5 (5.9)	1 (4.2)	18 (10.0)
Body as a Whole					
Asthenia/Fatigue	5 (2.8)	5 (3.5)	2 (2.4)	0	12 (6.7)
Septicemia	0	0	0	1 (4.2)	1 (0.6)
Syncope	0	0	0	1 (4.2)	1 (0.6)
Respiratory System					
Cough	4 (2.2)	4 (2.8)	0	0	8 (4.4)
Hemoptysis	0	0	0	1 (4.2)	1 (0.6)
Infection, Upper Respiratory	6 (3.3)	2 (1.4)	2 (2.4)	0	10 (5.6)
Digestive System					
Diarrhea	5 (2.8)	3 (2.1)	2 (2.4)	0	9 (5.0)
Musculoskeletal System					
Pain, Knee	2 (1.1)	1 (0.7)	1 (1.2)	1 (4.2)	3 (1.7)
Arthralgia	0	0	0	1 (4.2)	1 (0.6)
Cardiovascular System					
Palpitation	2 (1.1)	2 (1.4)	1 (1.2)	1 (4.2)	6 (3.3)
Premature Beat	0	0	0	1 (4.2)	1 (0.6)
Pulse Abnormality	0	0	0	1 (4.2)	1 (0.6)

Note: The number of adverse experiences in the treatment groups does not add up to the number in all patients combined because the same patient received different treatments at different times and thus could be counted more than once.

Other: The "Other" group includes all reports of adverse experiences when the patient was not on a regimen defined in the protocol.

Six patients were withdrawn from therapy for adverse events. Table 59.9 lists the patients and the adverse events that they experienced during therapy.

Table 59.9. Patients Withdrawn due to Adverse Events

Number	Adverse Experience	Therapy	Start Day	Stop Day
5501	SEIZURE DISORDER	losartan	29	29
5525	DIARRHEA	losartan	11	12
	ACNE		11	16
	DIARRHEA	Los/H	60	64
	PNEUMONIA		70	76
	ACNE		71	76
	RASH		74	76
	HYPOTENSION		75	76
	HYPOCALCEMIA		76	
	HYPOKALEMIA		76	
	HYPONATREMIA		76	
	HYPOPHOSPHATEMIA		76	
	HYPOPROTEINEMIA		76	
	LEUKOCYTE COUNT INCREASED		76	
	SERUM CREATININE INCREASED		76	
	SINUS TACHYCARDIA		76	
	TOTAL SERUM BILIRUBIN INCREASED		76	
5675	DIZZINESS	losartan	1	8
	HEADACHE		1	8
	ANXIETY		8	9
	VERTIGO		8	9
5708	PROTEINURIA	Los/H	29	
	PARESTHESIA		32	43
	WEAKNESS, MUSCLE		32	43
	FASTING BLOOD GLUCOSE INCREASED		43	
	GLYCOSURIA		43	
5725	HEADACHE	losartan	1	2
	GLYCOSURIA		29	
	HEMATURIA		29	
	PREMATURE VENTRICULAR CONTRACTION	Los/H	48	
	PALPITATION		48	48
	SYNCOPE		48	48
	PREMATURE BEAT		48	55
	PULSE ABNORMALITY		48	55
	PALPITATION		49	55
5729	DEPRESSION	losartan	10	15
	PAIN, ABDOMINAL		12	12
	PAIN, BACK		12	12

Patient 5501 is a 38-year-old male patient with severe hypertension, hypothyroidism and a history of epilepsy and recent weight loss (350 lbs to 336 lbs) was treated with losartan 50 to 100 mg for 29 days during the acute phase of the study when he experienced a grand mal seizure while at home upon rising from the dinner table. The patient reported that he had epilepsy in the past and that he had not had any grand mal seizures for the last 20 years although he had not taken any antiepileptic medications for the past 20 years. The patient recovered completely within 3 minutes, sustained no injury and did not seek medical help. He was seen in the clinic the day after the event at which time he reported feeling well and was observed to be neurological intact. The patient was discontinued at this time. The patient stated that he was on an aggressive weight-reduction diet which led to 14 pound weight loss in the previous 2 weeks.

Patient 5725 is a 57-year-old female patient with severe hypertension had been treated with losartan 50 to 100 mg alone for 28 days and then concurrently with HCTZ 12.5 mg for an additional 20 days (study Day 48) when she experienced palpitations and syncope; blood pressure was 187/115 mmHg. Pulse abnormality (irregular pulse) and premature beats were noted on physical examination. An ECG revealed left ventricular hypertrophy with ventricular extrasystoles (PVCs). The patient was hospitalized. Routine blood chemistry showed serum chloride and potassium to be normal. Therapy with losartan and HCTZ was continued with atenolol 25 mg once-daily added to treat the pulse abnormality. Two days later, a repeat ECG revealed an increased number of extrasystoles of more than 30/min. Study therapy with losartan and HCTZ was discontinued as was therapy with atenolol. Therapy with verapamil 240 mg daily and amiodarone 600 mg daily was commenced. Three days after discontinuation, a follow-up ECG revealed no arrhythmia.

Patient 5525 is a 44-year-old male patient with severe hypertension and a history of shortness of breath had been treated with losartan 50 to 100 mg alone for 11 days and then concurrently with HCTZ 12.5 to 25 mg for an additional 49 days (study day 60) when he experienced diarrhea. Ten days later, study day 70, he developed pneumonia. On study day 71, he noticed acne around his mouth followed three days later by a red spotty rash around his neck. On study day 75, the patient experienced hypotension, tachycardia, and gross hematuria followed the next day by hemoptysis. The patient was seen in the

clinic on study day 76 at which time he was observed to be short of breath, pale with a blood pressure of 100/68, pulse 110 and rales and rhonchi over the middle lobe of the right lung. An x-ray showed right middle lobe infiltrate. He was diagnosed with pneumonia and possible sepsis and was hospitalized. Therapy with losartan and HCTZ was discontinued. The patient recovered.

Forty-one patients were noted to have experienced laboratory adverse experiences. Table 59.10 lists some patients with clinically relevant lab abnormalities.

Table 59.10.

Patient #	Test	Baseline Test	Abnormal Test	Day of Test	Comment
5525	creatinine	1.1 mg/dl	1.7 mg/dl	76	Patient on L/H. For most labs, returned to normal off drug. Patient septic.
	phosphorus	4.2 mg/dl	1.7 mg/dl	76	
	potassium	4.8 Meq/L	2.8 Meq/L	76	
	sodium	134 Meq/L	127 Meq/L	76	
	WBC	9,200 /mm ³	22,600 /mm ³	76	
	total Bilirubin				Increased, but not in CANDA
5565	creatinine	1.0 mg/dl	1.8 mg/dl	80	On L/H/I, remained elevated on therapy
5561	eosinophils	2%	9%	89	
5604	total bilirubin				Increased, but not in CANDA. Other LFT not abnormal. On L/H.
5605	total bilirubin				Increased, but not in CANDA. ALT and AST mildly elevated
5606	eosinophil	2%	10%	106	WBC = 5,500/mm ³
	total bilirubin				Increased, but not in CANDA
5703	total bilirubin				Increased, but not in CANDA
5607	BUN	29 mg/dl	57 mg/dl	92	
	creatinine	.8 mg/dl	1.2 mg/dl	92	On L/H/A/N
5614	hemoglobin	12.7 g/dl	10.0 g/dl	103	On L/H/AM
5712	potassium	3.8 Meq/L	3.0 Meq/L	87	On L/H
5724	potassium	4.6 Meq/L	3.0 Meq/L	71	On L/H, K up to 3.6 at day 83.

L = losartan, H = HCTZ, F = felodipine, A = atenolol, I = isradipine, N = nifedipine, AM = amlodipine

Long Term Therapy Studies. 1 protocols 011, 021, 049, 050 and 054 Open Label Follow-Up.

The sponsor has summarized the long term open label follow-up studies of protocols 011, 021, 049, 050 and 054 in a single clinical summary report. The data presentation in this report was divided according to duration of treatment with losartan in the following categories: (1) experience in patients treated with losartan for less than 6 months, (2) experience in patients treated with losartan for at least 6 months but less than a year, and (3) experience in patients treated with losartan for a year or more. The double-blind portion of protocols 011, 021 and 050 are summarized separately in the review of NDA 20-386. Protocols 049 and 054 are reviewed separately in Dr. Knudson's review of NDA 20-387.

At the beginning of the open-label extensions, patients were transferred from their double-blind therapy (either losartan, losartan/HCTZ, placebo, or active control agent) to open-label losartan or losartan/HCTZ. Clinical assessments varied between protocol and are outlined in table LTF 1.

Table LTF 1. Clinical and Laboratory Measurements in Extensions

Parameter	Protocol	Frequency
Clinic visit, Vital signs (trough)	011	Monthly
	021	Every 2 months
	049	Every 2 months (every 3 months after first year)
	050	Every 3 months
	054	First month, then every 2 months
Adverse Experience Assessment	011	Monthly
	021	Every 2 months
	049	Every 2 months (every 3 months after the first year)
	050	Every 3 months
	054	First month, then every 2 months
Laboratory Evaluation	011	First month, then every 2 months
	021	Every 6 months
	049	Month 4, then every 6 months (every 6 months after the first year)
	050	Month 4, then every 6 months
	054	Month 4, then every 6 months
Electrocardiogram	011	Every 3 months
	021	Every 6 months
	049	Month 4, then every 6 months (annually after the first year)
	050	Month 12
	054	Month 4, then every 6 months
Physical Examination	All	Annually

The dosage titrations employed in the extension protocols are shown in table LTF 2.

Table LTF 2. Dosage Titration Steps in Study Extensions

Protocol	Titration Steps (All dosages in mg)
011	Los 50 → Los 100 → Los 150 → Los 100/HCTZ 12.5 → Los 150/HCTZ 12.5 → Los 150/HCTZ 25 → Los 150/HCTZ 50
021	Los 50 → Los 50/HCTZ 12.5 → Los 50/HCTZ 25 → Los 50/HCTZ 25 + calcium channel blocker
049	Los 50 → Los 50/HCTZ 6.25 → Los 50/HCTZ 12.5 → Los 50/HCTZ 25 → Los 50/HCTZ 25 + Felodipine 5 → Los 50/HCTZ 25 + Felodipine 10
050	Los 50 → Los 50/HCTZ 6.25 → Los 50/HCTZ 12.5 → Los 50/HCTZ 12.5 + Felodipine 5 → Los 50/HCTZ 12.5 + Felodipine 10
054	Los 50/HCTZ 6.25 → Los 50/HCTZ 12.5 → Los 50/HCTZ 12.5 + Felodipine 5 → Los 50/HCTZ 12.5 + Felodipine 10
Los = losartan	HCTZ = Hydrochlorothiazide

In Protocol 011, all dosage titrations could be made at 2-week intervals. In the other protocols, the initial step was to last 4 weeks, then the remaining steps could be made at 2-week intervals. In Protocols 021, 049, 050, and 054, dosage titrations were to be performed if the trough sitting diastolic blood pressure was ≥ 90 mmHg. In Protocol 011, dosage titrations could be performed if the trough supine diastolic blood pressure was > 90 mmHg.

Results

Demographics and Disposition

Six-hundred and fifty-nine of the original 2071 patients randomized in these trials continued into open label studies. Table LTF 3 lists the number of patients contributed from each study.

Table LTF 3.

Protocol #	# of patients randomized into double blind period	# of patients continuing into open label
011	576	307
021	122	9
049	304	102
050	366	193
054	703	48
Total	2071	659

The demographics of the patients in the long term open label studies is listed in table LTF 4. This table includes all patients receiving any dose of losartan +/- combination therapy. Losartan treatment exposure (< 6 months, 6 - 12 months, >12 months) includes double blind exposure for those randomized to losartan therapy in the double blind portion of the trials. Six hundred and thirteen of the 659 patients received losartan alone at some time point during the open label extension period. Forty-six of 48 patients in study 054 started on losartan/HCTZ at the beginning of the open label period (see table LTF 2 for the titration scheme for study 054).

Table LTF 4. Demographic Data - Patients Treated with Losartan (with or without HCTZ or other therapy) in Extensions.
[Time of Follow-up determined as of 3/31/93]

	Losartan for <6 Months	Losartan for >6 Months but <1 Year	Losartan for 1 Year or More	Total
Total Patients	127	226	306	659
Sex				
Male	88	150	195	433
Female	39	76	111	226
Age (yrs)				
<36	9	11	22	42
36-45	34	42	53	129
46-55	43	71	97	211
56-64	25	66	85	176
65-74	13	35	43	91
≥75	3	1	6	10
Mean (S.D.)	51.0 (10.8)	53.6 (10.8)	53.1 (11.1)	52.9 (11.0)
Median	50	54	53	53
Range	28-77	26-77	25-88	25-88
Race				
Black	13	29	33	75
Non-Black	114	197	273	584
Duration of Disease (yrs)				
<1	1	7	13	21
1 to 5	35	77	89	201
>5 to 10	39	47	80	166
>10	52	95	124	271
Mean (S.D.)	10.9 (8.2)	10.7 (8.9)	10.1 (7.5)	10.4 (8.1)
Median	9	9	9	9
Range	0.5-46.0	0.08-44.0	0.08-38.0	0.08-46.0
Reasons Discontinued*				
Total	81	71	17	169
Clinical AE	20	26	7	53
Laboratory AE	2	2	0	4
Therapy Ineffective	32	23	2	57
Protocol Deviation	2	1	0	3
Lost to Follow-up	8	7	1	16
Patient Withdrew	14	7	6	27
Other/Pt. Uncooperative	3	5	1	9

*Note: Some patients had adverse experiences that began in the double-blind study, continued during the extension, and resulted in the patient being discontinued during the extension. These patients were not counted in this report. The time of exposure included the double blind treatment period in those who were randomized to losartan.

The exposure to losartan therapy in the extension phase either alone or of any combination is presented in table LTF 4a.

LTF 4a.

Patient Exposure to Losartan +/- other anti-hypertensive therapy. N = 659. [Does not include double-blind exposure]

Total Days on losartan in Extension	166,127
Mean # of Days on Losartan	252
Median # of Days on Losartan	272
Range of Days exposed to Losartan	6 - 635

It is of interest to separate those out who were exposed to losartan alone at some time in the open label extension. Six-hundred and thirteen patients were on losartan therapy alone for at least part of the extension period. Table LTF 4b lists the exposure to losartan alone.

LTF 4b.

Patient Exposure to Losartan Alone. N = 613. [Does not include double-blind exposure]

Total Days on losartan Alone in Extension	75,725
Mean # of Days on Losartan Alone	123
Median # of Days on Losartan Alone	Not able to compute in CANDa
Range of Days exposed to Losartan Alone	Not able to compute in CANDa

The WMA CANDa database lists 170 patients (from the Merck clinical summary the number is 169) discontinuing the study prematurely. Table LTF 4c lists the number of withdrawals from each study and the reason for withdrawal. The additional patient in the WMA database (compared to the clinical summary report) was a clinical adverse experience. A complete list of premature withdrawals and the reason for withdrawal can be found in the appendix.

Table LTF 4c. Reason for Withdrawal from Open Label Extensions.

Reason Discontinued	Study 011	Study 021	Study 049	Study 050	Study 054	Total
Clinical AE	28	.	9	16	1	54
Lab AE	2	.	.	2	.	4
Lost to Follow-up	11	1	2	2	.	16
Protocol Deviation	1	.	2	.	.	3
Patient Uncooperative	5	.	.	1	.	6
Therapy Ineffective	29	.	16	12	.	57
PATIENT WITHDREW	13	.	6	7	1	27
OTHER	1	.	1	1	.	3
TOTAL	90	1	36	41	2	170

Efficacy

The mean changes in DBP and the response rates at 6 and 12 months of therapy suggest that losartan +/- combination therapy lowers blood pressure. The sponsor's clinical summary reports the changes in mean DBP from baseline and from the end of the double blind treatment period for each study. The summary tables for changes in DBP from baseline can be found in the appendix.

Safety (from WMA database)

Two patients died during the long term open label portions of the trials. Table LTF 5 lists the patients who died.

Table LTF 5. Serious Fatal Clinical Adverse Experiences (Patients Treated with Losartan in Extensions)

Study #	Patient #	Sex/Age	Treatment	Daily Dose (mg)	Study Day of Onset	Adverse Experience
011-009	0174	M70	L	100	89 85	CVA Coma
050-023	2414	M46	L/H	50/6 25	244	Cerebral aneurysm

Patient #0174 in study 011 was a 70 year old hypertensive male was hospitalized on 4/30/91 for what appeared to be a stroke. A CT scan of the brain showed a hemorrhagic infarct of the mid-brain. The patient did not recover consciousness and was kept alive via life-support (respirator) until 5/1/91. An EEG done on 5/1/91 showed extremely depressed brain function. It was the opinion of the consulting neurologist that the patient was beyond recovery and advised the family accordingly. The family chose to discontinue life-support at that time. No spontaneous respiratory activity was noted, and the patient died at 7:45 PM on 5/1/91. The patient had been treated for moderately severe hypertension since 1975. He had no other known complications from hypertension; his only abnormal findings were an S4 on physical examination and a LAHB and RBBB on EKG. At the time of the adverse event, the patient was taking losartan 100 mg q d. and was last seen in the clinic on 22APR91 (Supine BP = 167/100 mmHg, standing BP = 162/110 mmHg). The patient was taking no other concomitant medication. Patient #2414 in study 050 was a 46-year-old hypertensive male with ankylosing spondylitis, hypercholesterolemia, and back pain, and a history of cigarette smoking, who collapsed at home on 12/7/92. Despite medical intervention, he was pronounced dead. The cause of death was found to be a ruptured cerebral aneurysm. At the time of the event the patient was receiving losartan/HCTZ 50/6.25 mg, and ibuprofen.

Fifty-four patients withdrew from the study due to clinical adverse experiences and four patients for laboratory adverse experiences. Table LTF 6 lists the patients withdrawn due to clinical adverse experience. Table LTF 7 lists the patients withdrawn due to laboratory adverse experiences. Patient # 493 is listed in both tables. Patient #322 (protocol 011, losartan 100 mg) is a 51 year old Caucasian male who experienced sloughing of the skin (eschar) on day 265 which resulted in

withdrawal. In the sponsor's clinical summary (table 87a in CSR), this patient is listed as withdrawing due to impotence. Further clarification is provided by the sponsor. On study day 265, the patient requested withdrawal due to decreased libido. On examination, the patient had "eschar" on the lower extremities. It is unclear whether the eschar was related to losartan therapy. Patient #0493 (study 011; losartan 100 mg/HCTZ 12.5 mg) appears to have withdrawn due to an acute attack of gout. Patient #8815 (study 054; losartan 50 mg/HCTZ 12.5 mg/felodipine 5 mg) experienced flushing in addition to depression. Patient #648 (Study 011; losartan 50 mg/100mg) withdrew due to weight loss of 30 pounds. This patient was not included in table 87a. The evaluation for weight loss was ongoing. Patient #2248 (Study 050; Losartan 50 mg) was discontinued because of muscle aches and joint swelling. This patient was not included in table 87a.

Table LTF 6. Patients Withdrawn Due to Adverse Experiences (from table 87a of sponsor's clinical summary report)

Protocol #	Patient #	Sex/ Age	Treatment	Daily Dose (mg)	Study Day of Onset	Relative Day Discontinued	Adverse Experience	Serious	Resolved
011-004	0068	F62	L	100	114	117	Arthralgia	No	Yes
011-005	0095	M51	L	100	108 108	108	Angina pectoris Supraventricular tachycardia	Yes Yes	Yes Yes
011-005	0097	M67	L	100	269	269	Atrial fibrillation	No	Yes
011-009	0170	F53	L/H	100/12.5	160	164	Rash	No	Yes
011-009	0172	M60	L	50	581	589	Rash	No	No
011-009	0174	M70	L	100	89 89	89	CVA Coma	Yes Yes	Yes Yes
011-013	0260	F71	L	50	108 108	150	Arrhythmia Dyspnea	No No	No No
011-014	0276	F53	L/H	100/12.5	291 291	296	Dizziness Nausea	No No	No No
011-016	0322	M51	L	50	97	265	Libido decreased	No	No
011-017	0339	F53	L	150	111	132	Asthma/fatigue	No	Yes
011-018	0365	M60	L	100	116	90	Depression	No	Yes
011-020	0402	M48	L/H	100/12.5	176	178	Myalgia	No	Yes
011-020	0406	F48	L	150	113	114	Rash	No	No
011-020	0407	M50	L/H	150/25	155	162	Impotence	No	Yes
011-024	0493	M71	L/H	100/12.5	175 175 175	181	Edema/swelling Erythema Toe pain	No No No	Yes Yes Yes
011-025	0510	M40	L	50	534	553	Hearing loss	Yes	No
011-025	0519	M63	L	50	561	563	Rash	No	No
011-028	0579	M70	L/H	150/12.5	350	364	Chest pain	No	No
011-	0648	M44	L	50/100	7	88	Weight loss		No
011-031	0644	M51	L/H	100/12.5	323 323	383	Exertional dyspnea Chest pain	No No	No No
011-031	0646	M34	L/H	150/12.5	128 128	133	Nocturia Urinary frequency	No No	Yes Yes
011-032	0666	F58	L	100	66	72	Neoplasm, skin, malignant	Yes	No
011-036	0740	F39	L	50	70 70	79	Chest pain Dyspnea	No No	Yes Yes
011-037	0764	M44	L	150	206	206	Impotence	No	No
011-037	0766	M53	L	100	206	218	Prostate disorder	No	No
011-038	0783	M61	L/H	100/12.5	218	286	Diarrhea	Yes	Yes
011-039	0818	M53	L	50	419 399	419 419	Dyspnea Atrial fibrillation	Yes Yes	No
011-032	0882	F53	L	50	453	454	Aneurysm	Yes	No
050-003	2042	M62	L	50	217	222	Obstruction, carotid artery	Yes	No
050-011	2187	M52	L/H/F	50/12.5/10	238	245	Edema/swelling	No	Yes
050-012	2212	M70	L/H	50/6.25	184	193	Asthma	No	No
050-013	2217	F52	L/H	50/12.5	317 317 317	317	Dyspnea Chest pain Atrial tachycardia	No No No	Yes Yes Yes
050-013	2226	M32	---	OFF	323	---	Suicide attempt	Yes	Yes
050-014	2241	M46	L/H	50/6.25	119 119	126	Agitation Malaise	No No	Yes Yes
050-014	2246	M54	L/H/F	50/12.5/5	166	228	Edema/swelling	No	No
050-	2248	M53	L	50	1	216	Muscle Aches Joint Swelling		Onk
050-015	2255	M48	L/H/F	50/12.5/10	216	273	Edema/swelling	No	Yes
050-016	2283	M44	L	50	206 206	264	Asthma/fatigue Orthostatic hypotension	No No	No No
050-019	2325	M42	L	50	99	153	Impotence	No	Yes
050-019	2336	M61	L/H/F	50/12.5/10	172	202	Edema/swelling	No	No

Table LTF 6. (continued)

Protocol #	Patient #	Sex/ Age	Treatment	Daily Dose (mg)	Study Day of Onset	Relative Day Discontinued	Adverse Experience	Serious	Resolved
050-021	2365	M61	L	50	59 59	59	Facial edema Rash	No No	No No
050-021	2371	F50	L/H/F	50/12.5/10	304 304 304	332	Tachycardia Muscle weakness Flushing	No No No	No No No
050-021	2373	M59	L/H/F	50/12.5/5	197	197	Myocardial infarction	Yes	Yes
050-023	2414	M46	L/H	50/6.25	244	244	Cerebral aneurysm	Yes	No
049-001	7016	M52	L/H/F	50/25/10	292	326	Impotence	No	No
049-012	7199	M41	L/H/F	50/25/10	307	307	Gastroenteritis	No	Yes
049-014	7236	M48	L/H/F	50/12.5/10	133	139	Edema/swelling	Yes	No
049-016	7264	F68	L L L/F	50 50 50/5	85 203 259	267	Abdominal pain Rash Asthenia/fatigue	No No No	Yes Yes Yes
049-017	7279	M52	L	50	267	338	Neoplasm, tongue, malignant	Yes	No
049-027	7361	M45	L/H/F	50/12.5/5	147	159	Headache	No	Yes
049-023	7411	M61	---	Off	293	286	Neoplasm, kidney, malignant	Yes	Yes
049-023	7414	M56	L	50	98	114	Myalgia	No	No
049-023	7453	M52	L/H/F	50/25/5	168	181	Tachycardia	No	Yes
054-039	8815	F55	L/H/F	50/12.5/5	162	205	Depression	No	No

Treatment: L=losartan, H=HCTZ, F=felodipine

Table LTF 7. Laboratory Adverse Experiences Causing Discontinuation

Protocol #	Patient #	Sex/ Age	Treatment	Study Day of Onset	Relative Day Discontinued	Adverse Experience	Serious
011-004	0064	M47	L/H 100/12.5	97	103	Hematuria	No
011-024	0493	M71	L 100	182	181	Hyperuricemia	No
011-031	0638	M66	L/H 50/50	322 332 352	351	ALT increased ALT increased ALT increased	No No No
050-013	2230	M54	L/H 50/12.5	233 233	232	AST increased ALT increased	No No
050-017	2305	M51	L/H 50/6.25	134 134 134 134	154	Alk. Phos. increased Hemoglobin increased Leukocyte count increased Hematocrit increased	No No No No

Treatment: L=losartan, H=HCTZ

Patient #64 had urine blood reported for the first time on day 90 as 15 RBC/HPF and on day 97 as 100 RBC/HPF. Urine WBC, up to 15 WBC/HPF, were reported throughout treatment.

Patient #493 had a baseline serum uric acid of 9.6 mg/dl. On day 105 and 154, serum uric acid was 10.8 and 10.6 mg/dl respectively.

Patient #638, #473 and #2230 had increases in ALT and AST as outlined in table LTF 7a.

LTF 7a. Transaminases for patients #638, #473 and #2230.

Patient #	Day	ALT (U/L)	AST (U/L)
638	Baseline	39	26
	203	38	31
	266	79	47
	322	138	67
	332	109	55
	352	123	73
473	Baseline	19	23
	410	60	45
	484	175	188
	489	156	68
	533	139	110
	540	101	52
	568	23	25
2230	Baseline	44	44
	107	93	66
	122	81	63
	136	96	62
	211	219	174
	233	152	116

Three additional patients had simultaneous increases in AST and ALT > 100 U/L. Patient # 2097 had an increase in ALT 197 U/L (baseline ALT = 106 U/L.) and AST to 112 U/L (baseline AST = 60 U/L.) on day 203. The next value was obtained on day 408. AST was within normal limits but ALT remained elevated. Patient # 319 had a AST of 151 U/L (baseline = 29 U/L.) and a ALT of 179 (baseline = 26 U/L.) on day 582. AST and ALT on day 590 were normal. Patient # 530 had a ALT of 167 U/L and AST of 109 on day 204. On day 217, AST and ALT were normal.

Several patients had elevations of serum creatinine that were clinically relevant. Patient # 594 had an increase in creatine to a maximum of 2.4 mg/dl (baseline = 1.2 mg/dl) on losartan 150 mg/ HCTZ 25 mg (day 377). The dose of HCTZ was eliminated and the creatinine returned to baseline values. Patient # 646 had an increase in creatinine to 2.4 mg/dl (baseline = 1.2 mg/dl) on losartan 150 mg/HCTZ 25 mg (day 134). Patient #834 had an increase in creatinine to 1.8 mg/dl (baseline = .7 mg/dl) on losartan 150 mg/HCTZ 25 mg (day 405). Patient #2212 (study 50) had an increase in creatinine to 2.8 mg/dl (baseline = 1.2 mg/dl) and BUN to 35 mg/dl (baseline = 13 mg/dl) on losartan/HCTZ (day 198; it appears that therapy was stopped on day 194 for reasons that are unclear). Creatinine on day 209 (off drug) was 1.4 mg/dl.

Patient #2305 had elevations of hemoglobin values to a maximum of 19.9 Gm/dl (baseline = 17.9 Gm/dl) and WBC of 13.9 THS/MM³.

Thirteen of the patients withdrawn due to adverse experience had adverse experiences described as serious. Twenty patients had serious adverse events that did not result in withdrawal. Table LTF 8 list the patients who experienced serious adverse events in the open label extension.

Table LTF 8. Serious Non-Fatal Clinical Adverse Experiences (Patients Treated with Losartan in Extensions)

Protocol #	Patient #	Sex/Age	Treatment	Daily Dose (mg)	Day of Onset	Adverse Experience	Outcome
011-002	0027	M57	L/H	150/25	403	Neoplasm, skin, malignant (melanoma)	Still Present
011-003	0048	M36	L/H	100/12.5	185	Pneumonia	Recovered
011-004	0070	M53	L	50	289	Bone pain	Recovered
011-004	0071	M49	L L/H	50 150/12.5	237 362	Neoplasm, skin, malignant (melanoma) Bursitis	Recovered Recovered
021-004	0072	F63	L	50	363 363	Pneumonia Sinusitis	Recovered Recovered
011-005	0095	M51	L	100	108 108	Angina pectoris* Supraventricular tachycardia*	Recovered Recovered
011-022	0442	F64	L L L L	100 50 50 50	293 399 452 467	Depression Depression Depression Depression	Recovered Recovered Recovered Recovered
011-022	0444	F73	L	150	357 357	CVA Parosia	Recovered Still Present
011-025	0508	M66	L/H	150/12.5	498	Melanoma	Still Present
011-025	0510	M40	L	50	534	Hearing loss* (Sensory Neural)	Still Present
011-025	0517	M57	L	100	333	Traumatic arthropathy	Recovered
011-026	0527	M53	---	OFF	322	Pericardial effusion	Recovered
011-026	0530	F52	L/H	100/25	247	Cholelithiasis	Recovered
011-032	0652	M33	L	100	101	Tear, ligament	Recovered
011-032	0655	M29	L	50	101 102	Chest pain T-wave abnormality (ECG)	Recovered
011-032	0656	M51	L/H	150/25	369	Atrial fibrillation	Recovered
011-032	0660	F58	L	100	66	Neoplasm, skin, malignant* (melanoma)	Still Present
011-032	0668	M49	L/H	150/12.5	338	Retinal detachment	Recovered
011-038	0783	M61	L/H	100/12.5	218	Diarrhea* (rectal bleeding, rectal cancer)	Recovered
011-039	0818	M53	L	50	419 399	Dyspnea* Atrial Fibrillation*	Still Present
011-040	0828	M65	---	OFF	133	Neoplasm, skin, malignant (melanoma)	Recovered
011-040	0842	F59	L/H	100/12.5	274	Leg pain	Still Present
011-032	0882	F53	L	50	453	Aneurysm* (ruptured cerebral)	Still Present
050-002	2022	M66	L/H/F	50/12.5/5	336	Neoplasm, prostate, malignant	Still Present
050-003	2042	M62	L	50	217	Obstruction, carotid artery*	Still Present
050-013	2226	M32	---	OFF	323	Suicide attempt*	Recovered
050-014	2246	M54	L	50	127	Urolithiasis	Recovered
050-021	2373	M59	L/H/F	50/12.5/5	197	Myocardial infarction*	Recovered
049-010	7172	M58	---	OFF	209	Hemiplegia	Still Present
049-014	7236	M48	L	50	59	Urolithiasis	Recovered
049-017	7279	M52	L	50	267	Neoplasm, tongue, malignant*	Still Present
049-023	7411	M61	---	OFF	294	Neoplasm, kidney, malignant*	Recovered
054-039	8804	M68	L/H	50/6.25	85	Strain (muscle)	Recovered

Treatment L=losartan, H=HCTZ, F=felodipine. *Caused Discontinuation from Study, 1 = withdrew on day 189, 2 = discontinued med on day 280

The following narrative summaries describe the serious adverse experiences which occurred in the study extensions.

Study 011-002/AN 0027: This 57-year-old hypertensive male had a biopsy which identified a melanoma on the right shoulder. In addition to losartan 150 mg, the patient was receiving HCTZ 25 mg and a potassium supplement at the time of this experience.

Study 011-003/AN 0048: This 36-year-old hypertensive male reported having "flu-like" symptoms. He was admitted to the hospital with a diagnosis of pneumonia. In addition to losartan 100 mg, at the time of this experience the patient was receiving HCTZ 12.5 mg. At the time of the hospitalization, he was also taking a variety of over-the-counter products for his flu-like symptoms.

Study 011-004/AN 0070: This 53-year-old male was hospitalized for an elective coccygectomy. The patient had a history of coccyx pain which worsened during the time he participated in the study. At the time of the incident, the patient was taking losartan 50 mg once daily. Study drug was not interrupted. The patient recovered.

Study 011-004/AN 0071: This 49-year-old hypertensive male presented at the study site with an irregular looking mole on his back. This mole had been present prior to the patient's participation in the double-blind and open-label extension phases of the study. The study investigator biopsied the mole and the pathological examination classified the specimen as a melanoma. Study drug (losartan 50 mg once daily) was continued. The investigator considered this event to be definitely not study drug related. This same patient was hospitalized for surgical removal of the bursa sack in his elbow. He had injured the elbow at work, and it subsequently became infected. The patient was discharged, and fully recovered. At the time of the event the patient was receiving losartan 150 mg and HCTZ 12.5 mg.

Study 021-004/AN 0072: This 63-year-old hypertensive female was admitted to the hospital with a severe sinus infection. While in the hospital, a chest x-ray indicated that the patient also had pneumonia. She was discharged four days

later. Losartan therapy was interrupted while the patient was hospitalized. At the time of the hospitalization she was receiving losartan 50 mg once daily.

Study 011-005/AN 0095: This 51-year-old hypertensive male was admitted to the hospital with angina and supraventricular tachycardia. Study medication (losartan 100 mg) was discontinued, and the patient was started on verapamil and digoxin.

Study 011-022/AN 0442: This 64-year-old hypertensive female reported feeling depressed. She went to the emergency room and was subsequently admitted to the psychiatric ward. Therapy with losartan 100 mg was continued. She is considered to have chronic intermittent depression, which is considered to be a permanent/substantial disability.

Study 011-022/AN 0444: This 73-year-old hypertensive female presented at the clinic for a regularly scheduled visit with symptoms of a TIA. The patient was subsequently scheduled for outpatient diagnostic testing at the local hospital. It was discovered during the testing that there had been a rapid change in her vascular lab study and ultrasound of her carotid, and she was hospitalized. She underwent angiograms which showed a 90% occlusion of the right carotid which was surgically corrected. About 24 hours after surgery, she developed a weakness of the right leg and her brain scan at that time showed a lesion in the left side which was opposite the side of the surgery. She continued to take her medications (losartan 150 mg) throughout the hospitalization.

Study 011-025/AN 0508: This 66-year-old hypertensive male had a melanoma removed from his right arm. At the time of this event he was receiving losartan/HCTZ 150/12.5 mg, which was continued.

Study 011-025/AN 0510: This 40-year-old hypertensive male noted right-sided deafness. The patient requested that the study drug (losartan 50 mg) be discontinued. An otologic exam revealed sensory neural hearing loss in the right ear. This was considered to be a permanent disability.

Study 011-025/AN 0517: This 57-year-old hypertensive male was hospitalized for repair of a torn rotator cuff. At the time of the incident, the patient was taking losartan 100 mg once daily. Study drug was not interrupted. The patient recovered and continued in the study.

Study 011-026/AN 0527: This 53-year-old hypertensive male was admitted to the hospital with pericardial effusion, without signs of myocardial infarction or congestive heart failure. Study drug (100 mg losartan) was interrupted.

Study 011-026/AN 0530: This 52-year-old hypertensive female was admitted to the hospital for an elective cholecystectomy. The patient had a history of abdominal pain prior to entry into the acute phase of the study, but it increased in intensity. The pain was diagnosed to be cholelithiasis, and the patient then elected to have the surgery. At the time of the cholecystectomy, the patient was controlled on losartan 100 mg and HCTZ 25 mg, and she was also receiving estrogen replacement, antacid, and potassium chloride.

Study 011-032/AN 0652: This 33-year-old hypertensive male was hospitalized for repair of a cruciate ligament tear. At the time of the incident, the patient was taking losartan 100 mg once daily. Study drug was not interrupted. The patient recovered and continued with the study.

Study 011-032/AN 0655: This 29-year-old hypertensive male was admitted to the hospital with chest pressure and left arm numbness; a T-wave abnormality was also noted. A cardiac catheterization suggested the pain was due to angina; myocardial infarction was ruled out. Losartan therapy was interrupted during the hospitalization. In addition to losartan 50 mg, the patient was receiving antacid at the time of the experience.

Study 011-032/AN 0656: This 51-year-old hypertensive male experienced palpitations. The patient was hospitalized and found to have atrial fibrillation and hypokalemia. Laboratory analysis revealed serum potassium 3.2 and serum CPK 192. The patient was treated with heparin, digoxin, and intravenous potassium. In addition to losartan 150 mg, at the time of this experience the patient was receiving hydrochlorothiazide 25 mg daily, simvastatin, and aspirin. Therapy with hydrochlorothiazide was discontinued and therapy with losartan continued.

Study 011-032/AN 0666: This 58-year-old non-black hypertensive female (with a history of prior melanoma which was surgically removed) noted a lump on her left groin (original melanoma on right side). A biopsy was positive for malignant melanoma. At the time of the experience she was receiving losartan 100 mg which was discontinued.

Study 011-032/AN 0668: This 49-year-old hypertensive male presented at his ophthalmologist's office complaining of blurred vision and irritation to his left eye. Upon examination, it was discovered that the patient had suffered a retinal detachment. He was admitted to the hospital and the retina was surgically reattached; the patient was subsequently discharged. At the time of the incident, the patient was taking losartan 150 mg and HCTZ 12.5 mg. Drug was continued.

Study 011-038/AN 0783: This 61-year-old hypertensive male developed diarrhea and hemorrhoid bleeding. He was found to have a "large, fungating mass in the rectal vault". He was admitted to the hospital and underwent resection of an adenocarcinoma of the rectum, and a small liver nodule was also resected. At the time of the event, the patient was receiving losartan 100 mg and HCTZ 12.5 mg.

Study 011-039/AN 0818: This 53-year-old hypertensive male was admitted to the hospital for atrial fibrillation and shortness of breath. He was treated with digoxin and procainamide HCl. At the time of the adverse experience, the patient was receiving losartan 50 mg which was discontinued.

Study 011-040/AN 0828: This 65-year-old hypertensive male had a mole removed from his left arm by his private physician. The mole was biopsied and diagnosed as malignant melanoma. The patient was admitted to the hospital and underwent radical dissection of left upper arm with complete lymph node removal of left axilla. According to the patient, all nodes and surrounding tissues were biopsied, none were found to be cancerous.

Study 011-040/AN 0832: This 59-year-old hypertensive female suffered a fractured patella in a car accident. The patient was hospitalized for surgery; the patella was repaired with a pin. At the time of the accident, the patient was taking losartan 100 mg/HCTZ 12.5 once daily.

Study 011-032/AN 0882: This 53-year-old black hypertensive female patient was hospitalized for what was diagnosed as a rupture of a posterior communicating artery aneurysm. The patient remains hospitalized on a ventilator, is responsive to some verbal stimuli and exhibits small amounts of leg and eye movement. At the time of the incident, the patient was taking losartan 50 mg. The patient was discontinued from the clinical trial.

Study 050-002/AN 2022: This 66-year-old male was diagnosed with prostate cancer. He was receiving losartan 50 mg, HCTZ 12.5 mg, and felodipine 5 mg, which were continued.

Study 050-003/AN 2042: This is a 62-year-old Caucasian male with diabetes mellitus, hypothyroidism and arthritis and who had a history of right leg claudication, portacaval shunt and splenorenal shunt. An ultrasound and subsequent arteriography revealed occlusion of the right internal carotid artery and bilateral stenosis. Therapy with losartan was discontinued. The patient underwent right carotid endarterectomy with saphenous vein patch angioplasty. At the time of this event the patient was receiving losartan 50 mg daily, glipizide, sodium levothyroxine, acetaminophen, zinc, multivitamin, vitamin E, potassium, vitamin B and beta-carotene. Aspirin was added to his treatment regimen.

Study 050-013/AN 2225: This 32-year-old black male with a history of untreated depression and alcohol abuse had been treated with losartan 50 mg. Concomitant medication included hydrochlorothiazide 6.25 mg daily and captopril. After drinking heavily, the patient reportedly had an altercation with his ex-wife and then took overdoses of his medications including approximately 150 mg of hydrochlorothiazide, 3750 mg of losartan and approximately 750 mg of captopril. He was hospitalized and placed in intensive care. He was treated with intravenous fluids to prevent hypotension and monitored overnight. All medications were discontinued. It was reported that the patient did not develop hypotension.

Study 050-014/AN 2246: This 54-year-old hypertensive male, with a prior history of kidney stone, reported low back pain and abdominal pain, and was hospitalized. Laboratory evaluation revealed urine RBC and bacteria. An intravenous pyelogram confirmed the diagnosis of nephrolithiasis. The patient improved with treatment and was discharged. At the time of the event, the patient was receiving losartan 50 mg daily.

Study 050-021/AN 2373: This 59-year-old male with diabetes mellitus, psoriasis and rosacea, and a history of pneumococcal pneumonia, began to experience arm, upper back and chest pain. The chest pain continued and the patient was hospitalized with an anterolateral myocardial infarction. Therapy with study drug and felodipine ER was discontinued, and the patient was placed on therapy with an ACE inhibitor and hydrochlorothiazide. At the time of the event, the patient was receiving losartan 50 mg daily, glyburide, tetracycline, anthralin ointment and flucronide, hydrochlorothiazide 12.5 mg, and felodipine ER 5 mg.

Study 049-010/AN 7172: This 58-year-old hypertensive male did not return to the clinic and several attempts were made to contact him. The patient reportedly had a stroke while in Argentina. The exact dose, if any, at the time of the experience was unknown.

Study 049-014/AN 7236: This 48-year-old male with diabetes mellitus developed severe lower back pain. An intravenous pyelogram revealed a large kidney stone and the patient was hospitalized. Study drug therapy (losartan 50 mg) was continued. The calculus was of calcium oxalate composition. The patient subsequently recovered.

Study 049-017/AN 7279: This 52-year-old hypertensive male noticed a lump on the left side of his tongue. He was diagnosed as having a malignant tumor. The patient was sent for surgical resection and radiation. Study drug therapy was discontinued. At the time of the event, the patient was receiving losartan 50 mg daily.

Study 049-023/AN 7411: This 61-year-old male, with an existing left kidney cyst (evaluated previously for renal carcinoma, but not surgically excised), was hospitalized for removal of his left kidney. The final pathology report revealed multifocal papillary renal cell carcinoma. All nodes were negative. The patient developed pneumonia and hepatitis after surgery, but was subsequently discharged. The patient had a negative prostate biopsy. Losartan was discontinued.

Study 054-039/AN 8804: This 68-year-old hypertensive male suffered a fall and was hospitalized with gluteal pain. He was diagnosed as having strained his gluteal muscle; he subsequently recovered. The patient continued study drug throughout the hospitalization. At the time of this event, he was taking losartan 50 mg and HCTZ 6.25 mg daily.

Clinical Adverse Events

Table LTF 9 lists the incidence of adverse events in patients on any combination of losartan or losartan alone. Of the 659 patients exposed to losartan with or without combination therapy, 477 (72%) experienced at least one adverse event during the open label extension. There was no difference in incidence rates within subgroups.

LTF 9. Incidence of Patients with at Least One Adverse Event on Losartan +/- combination therapy.

	total	male	female	caucasian	black	other	> 65	≤ 65
exposed to losartan:	659	433	226	548	75	36	101	558
at least 1 ae on losartan	477 (72%)	308 (69%)	177 (78%)	394 (72%)	57 (76%)	26 (72%)	70 (69%)	417 (73%)

Table LTF 10 lists incidences of clinical adverse events in patient on losartan. The list is not comprehensive in that it includes adverse events that occurred in > 1% of patients, have potential serious clinical implications, are characteristic with ACE Inhibitors or have clinical relevance based on the mechanism of action of losartan. There were 226 females and 433 males. Myalgia, decreased hematocrit, gout, hyperuricemia, dental pain and trauma occurred at greater than double the incidence in males verses females. Urinary tract infections and abdominal pain occurred at greater than double the incidence in females verses males. Impotence was reported in 13 males. Subgroup comparisons based on race and age are difficult to interpret since the open label extension only included 11.3 % black and 15.3 % ≥ 65 years of age.

Table LTF 10. Listing of Adverse Events Based on Gender on Losartan +/- Combination Therapy. [Includes adverse events that have a total incidence > 1%, have potential serious clinical implications, are characteristic in ACE Inhibitors or may have clinical relevance based on the mechanism of action of losartan.]

Adverse Experience	Female N=226	Male N=433	Total N=659	Adverse Experience	Female N=226	Male N=433	Total N=659
ALKALINE PHOSPHATASE INCREASED	2	6	8	HYPONATREMIA		1	1
ALT INCREASED	5	18	23	IMPOTENCE		13	13
ANXIETY	4	5	9	INFECTION, DENTAL PROCESS	2	6	8
AST INCREASED	2	11	13	URI	42	73	115
BRONCHITIS	7	8	15	INFLUENZA	3	8	11
CONGESTION, NASAL	7	15	22	INSOMNIA	5	9	14
CONGESTION, RESPIRATORY	3	4	7	MYALGIA	1	8	9
COUGH	15	18	33	NAUSEA	13	9	22
CRAMP, MUSCLE	5	5	10	ORTHOSTATIC EFFECTS	2	8	10
DIARRHEA	15	13	28	PAIN, ABDOMINAL	19	9	28
DIZZINESS	16	31	47	PAIN, BACK	15	13	28
DYSPEPSIA	5	9	14	PAIN, CHEST	12	20	32
DYSPNEA	6	6	12	PAIN, DENTAL	1	7	8
EDEMA, FACIAL		1	1	PAIN, FLANK	2	6	8
EDEMA, ORBITAL		1	1	PAIN, KNEE	4	5	9
EDEMA/SWELLING	13	13	26	PAIN, LEG	4	3	7
EFFUSION, PERICARDIAL		1	1	PAIN, SHOULDER	5	8	13
FALLING	1		1	PAIN, TOE		6	6
FECAL OCCULT BLOOD		3	3	PAIN, WRIST	1	2	3
FLU LIKE ILLNESS	4	7	11	PALPITATION	1	2	3
FLUID OVERLOAD		1	1	PARESIS	1		1
GOUT	1	7	8	PARESTHESIA	5	8	13
HEADACHE	39	53	92	PHARYNGITIS	13	14	27
HEARING LOSS	1	1	2	PYURIA	12	7	19
HEMATOCRIT DECREASED	1	6	7	RASH	12	11	23
HEMATURIA	8	15	23	SERUM CREATININE INCREASED	1	4	5
HEMOGLOBIN DECREASED	3	6	9	SINUS DISORDER	7	7	14
HYPERGLYCEMIA	7	11	18	SINUSITIS	9	10	19
HYPERKALEMIA		1	1	SLOUGHING SKIN		1	1
HYPERNATREMIA		1	1	STRAIN	2	8	10
HYPERURICEMIA	1	7	8	INCREASED TOTAL BILIRUBIN	1	1	2
HYPESTHESIA	4	7	11	TRAUMA	2	9	11
HYPOKALEMIA	6	11	17	UROLITHIASIS		4	4

Table LTF 11 lists the incidence of adverse events in patients while on losartan alone. Of the 613 patients who were on losartan alone for some period during the extension phase, 315 (51%) had an adverse experience while on losartan alone. In subgroups, the percentage of patients with at least one adverse event is similar. Subgroup comparisons was only reviewed based on gender. Subgroup comparisons based on race and age are difficult to interpret since the open label extension only included 12% black and 14.5% ≥ 65 years of age.

LTF 11. Incidence of Patients with at Least One Adverse Event on Losartan Alone

	total	male	female	caucasian	black	other	≥ 65	< 65
exposed to losartan alone*	613	402	211	504	73	36	89	524
at least 1 ae on losartan alone	315 (51%)	200 (50%)	115 (55%)	270 (54%)	32 (44%)	13 (36%)	44 (49%)	271 (52%)
at least 1 ae on any losartan combination	488 (79%)							

*may have received additional therapy at some time in extension

Table LTF 12 lists incidences of clinical adverse events in patients on losartan alone. The list is not comprehensive in that it includes adverse events that occurred in > 1% of patients, have potential serious clinical implications, are characteristic with ACE Inhibitors or have clinical relevance based on the mechanism of action of losartan. The time of exposure to losartan alone in this database is approximately 50% the time of exposure to losartan +/- combination. The most common adverse experiences (occurring in greater than 3% of patients) are asthenia/fatigue, diarrhea, dizziness, headache and upper respiratory infection. Cough was reported in 2.7% of patients. Gout was reported in four patients. [Reviewer's Note: This is important to know since the sponsor has touted losartan for lowering uric acid levels. Although that observation may be true it is unclear whether it is clinically relevant.] Patient #2365 (protocol 011; losartan 50 mg) was a 61 year old male who developed facial edema on day 59 of the extension which resulted in withdrawal from the study.

Table LTF 12. Listing of Adverse Events Based on Gender on Losartan Alone. [Includes adverse events that have a total incidence > 1%, have potential serious clinical implications, are characteristic in ACE Inhibitors or may have clinical relevance based on the mechanism of action of losartan.]

Adverse Experience	Female	Male	Total
ALT INCREASED	3	11	14
AST INCREASED	.	5	5
ASTHENIA/FATIGUE	10	13	23
COMA	.	1	1
CONGESTION, NASAL	1	7	8
COUGH	6	11	17
CVA	1	1	2
CVA, HEMORRHAGIC	.	1	1
DIARRHEA	11	9	20
DIZZINESS	5	15	20
EDEMA, FACIAL	.	1	1
EDEMA, ORBITAL	.	1	1
EDEMA/SWELLING	8	4	12
FALLING	1	.	1
GOUT	1	3	4
HEADACHE	27	30	57
HEMATURIA	4	5	9
HEMOGLOBIN DECREASED	1	1	2
HYPERURICEMIA	.	3	3
HYPOTENSION	1	.	1
URI	25	45	70
UTI	9	2	11
INSOMNIA	3	7	10
NAUSEA	7	7	14
ORTHOSTATIC EFFECTS	2	3	5
PAIN, ABDOMINAL	9	7	16
PAIN, BACK	8	6	14
PAIN, CHEST	8	8	16
PHARYNGITIS	6	9	15
PYURIA	5	2	7
RASH	9	8	17
SINUS DISORDER	5	4	9
SINUSITIS	8	6	14
SLOUGHING SKIN	.	1	1
STRAIN	2	5	7
SWELLING, EYE	.	1	1
SWELLING, JOINT	4	1	5
SYNCOPE	.	1	1
UROLITHIASIS	.	4	4
URTICARIA	.	1	1
VERTIGO	.	3	3

Heart Failure Trials						
Study #	Design/ Patient Population	Treatment Groups	N	Primary Endpoint	Other Measures	Page
016	- r, db, pc, single dose - Heart Failure patients	- placebo	12	Intracardiac Hemodynamics		190
		- losartan 5, 10, 25, 75, 150 mg	54			
047	- r, db, pc, 12 wk Rx period - CHF patients	- placebo	29	Intracardiac hemodynamics	- neurohormones - plasma losartan and E-3174	190
		- losartan 2.5 mg	31			
		- losartan 10 mg	33			
		- losartan 25 mg	34			
		- losartan 50 mg	27			

wk = week, db = double-blind, ol = open label, od = once a day, bid = twice a day, r = randomized, ac = active control, pc = placebo control, nc = no control, p = parallel, co = crossover, bx = history, HTN = hypertension, ACEI = angiotensin converting enzyme inhibitor, NE = norepinephrine, Epi = epinephrine, PRA = plasma renin activity

Study 016. Randomized, Double-blind, Placebo-controlled, Multicenter Study of the Hemodynamic Responses to a Single Oral Dose of MK-954 (DuP 753) in Patients with Heart Failure.

This was a randomized, double blind, placebo controlled trial designed to measure changes in intracardiac hemodynamics after a single dose of placebo or losartan (5, 10, 25, 75, 150 mg) in patients with congestive heart failure. Since the efficacy information collected in this study is not pertinent to the proposed indication of this NDA, only safety data will be reviewed. Patients with a history of CHF (NYHA Class II - IV), off of vasodilators and ejection fractions less than 40% were enrolled. Sixty-six patients, 10 - 12 per treatment group, received double-blind therapy. Eighty-four percent were men.

Two deaths occurred (#154, #512) seven and twelve days after the single oral dose of losartan and another two patients (#107 cholelithiasis, #256 pulmonary edema) had non-fatal serious adverse events 9 and 12 days after the single oral dose of losartan. Patient #154 was a 66 year-old Caucasian male with an ejection fraction of 29%, NYHA Class II heart failure and a history of myocardial infarction. He was randomized and received a single oral dose of losartan 5 mg on 4/7/91. On April 11, 1991, he had a myocardial infarction and suffered cardiogenic shock with bradycardia. He was admitted to the hospital and treated with atropine, dopamine, and streptokinase and his heart rate was maintained with a pacemaker. The patient was stable for 48 hours then subsequently had episodes of ventricular tachycardia which were followed by ventricular fibrillation. On April 13, 1991 the patient died. Autopsy demonstrated left ventricular myocardial infarction and extensive sclerosis of the coronary arteries. A thrombus was found in the circumflex artery. The investigator felt the myocardial infarction and ventricular fibrillation were not related to study drug. Patient #512 was a 62 year-old Caucasian male with an ejection fraction of 16% and NYHA Class III heart failure. The etiology of heart failure in this patient was ischemic cardiomyopathy. The patient had a myocardial infarction in 1977. The patient was randomized and received a single oral dose of losartan 150 mg on 6/19/91. On 6/20/91, prestudy therapy of furosemide, quinidine, isosorbide dinitrate, diltiazem, aspirin, and enalapril was reinstated. On 6/30/91, the patient was found dead in bed.

There was no significant difference in non-serious adverse events between treatments.

Study 047. Multicenter, Double-blind, Randomized, Parallel, Multiple-dose, Placebo-controlled Study of the Hemodynamic and Clinical Effects of Losartan in Patients with Heart Failure (U.S. and International Centers)

Protocol

This was a randomized, double-blind, placebo controlled trial designed to test the hypothesis that oral administration of losartan for 12 weeks would produce sustained hemodynamic and clinical improvement in patients with heart failure. The primary endpoint of the trial was the change in hemodynamics after the initial dose and after 12 weeks of therapy. Patients of either sex with evidence of left ventricular failure were eligible for inclusion if they:

- were New York Heart Association (NYHA) Functional Class II, III, or IV.
- had a resting left ventricular ejection fraction $\leq 40\%$ as measured by radionuclide ventriculography or contrast angiography within 6 weeks prior to the study.
- were ≥ 18 years of age.
- had not received vasodilators (including angiotensin-converting enzyme [ACE] inhibitors) and antihypertensive agents (excluding diuretics) for at least 14 days prior to randomization and inotropic agents (except digitalis) for at least 7 days prior to randomization.
- if the patient was receiving digitalis and/or diuretics, had received doses stable for 14 and 7 days, respectively, prior to randomization.

Patients were excluded if they experienced CABG surgery, coronary angioplasty, CVA or TIA in the previous 3 months, had uncontrolled angina pectoris or had uncontrolled cardiac arrhythmia or required anti-arrhythmic therapy. Patients with severe pulmonary disease or with a history of clinically important renal, hepatic, hematological, or neurological disorders were excluded.

Patients entered a baseline period of unspecified duration during which they underwent a history and physical exam, symptom review, laboratory evaluation and radionuclide ventriculogram (if not performed within the previous 6 weeks). On day -1, patients were hospitalized to undergo insertion of a swan ganz catheter. In order to be randomized into the trial, the mean pulmonary capillary wedge pressure was ≥ 13 mmHg. Patients were randomized to either placebo, losartan 2.5 mg, losartan 10 mg, losartan 25 mg or losartan 50 mg on day 1 for 12 weeks of double blind treatment. Hemodynamic measurements were measured repeatedly after the first and last doses of randomized therapy. The procedures performed during the study are outlined in table 47.1 and 47.2.

Table 47.1. Clinical Observations and Laboratory Measurements

	Baseline		Double-Blind							
	Day -1	Day 1	Week 1	Week 2	Week 4	Week 8	Week 12 Pre-HD ^a	Week 12 Post-HD ^a		
Complete Physical Exam	X							X		
Abbreviated Physical Exam ^b		X	X	X	X	X	X			
Laboratory Screens ^c	X	X		X		X	X			
Chest Roentgenogram including CT Ratio ^d	X						X			
Electrocardiogram (12-Lead)	X	X		X		X	X			
Hospitalization		X	X				X	X		
Resting Radionuclide Left Ventricular Ejection Fractione	X									
Dyspnea-Fatigue Index	X	X				X	X	X		
Invasive Hemodynamics			X				X ^f			
Neurohormonal Blood Samples			X				X ^f			
Drug Level Blood Samples			X				X ^f			

^a Pre-hemodynamic and post-hemodynamic (HD) study

^b Includes evaluation of the signs and symptoms of heart failure (presence of third heart sound, jugular venous pulsation at 45°, pulmonary rales, peripheral edema, orthopnea, paroxysmal nocturnal dyspnea, exertional dyspnea, and New York Heart Association Functional Class)

^c Laboratory evaluation included standard urinalysis (specific gravity, pH, protein, glucose, and microscopic exam), hematology (hemoglobin, hematocrit, WBC differential count, platelet count), serum chemistry (BUN, creatinine, total bilirubin, AST, ALT, glucose, LDH, uric acid, sodium, potassium, magnesium, chloride, alkaline phosphatase, carbon dioxide content, total protein, albumin, calcium, phosphorus, total cholesterol, triglycerides), and trough digoxin or digitoxin level at Day -1 and Week 12 for those patients receiving these agents

^d The cardiothoracic (CT) ratio is the ratio of the widest transverse diameter of the cardiac silhouette to the widest thoracic diameter

^e If not performed within 6 weeks prior to the hemodynamic study.

^f During the second hemodynamic study.

Table 47.2. Schedule of Acute and Chronic Hemodynamic Periods

	Baseline	Hour(s) After Oral Dose of Losartan									
		0.5	1	2	3	4	5	6	10	12	24
Hemodynamics	X	X	X	X	X	X	X	X	X	X	X
Plasma Angiotensin II	X						X				X
Serum Aldosterone	X						X				X
Plasma Norepinephrine	X						X				X
Plasma Renin Activity	X						X				X
Drug Levels ^a	X						X			X	X
Light Meal ^b								X		X	

^a Plasma drug samples were collected from all patients but concentrations (losartan and its metabolite E-3174) were determined for the 25 mg dose only.

^b Fluid intake of 200 mL was allowed with each meal.

Results

The hemodynamic data will not be reviewed. Only safety data will be presented. One hundred and fifty-four patients were randomized and given double-blind therapy. The numbers of patients entered into the study by investigator are shown in Table 47.3. Most patients were white males with ischemic heart disease or cardiomyopathy as the etiology of heart failure. The mean age was 61 years, the mean duration of the diagnosis was 4 years, the mean ejection fraction 25% and 68% of the patients were NYHA class II. Demographic and heart failure characteristics are summarized in Table 47.3.

Table 47.3. Demographics

	Placebo (N=29)	2.5 mg (N=31)	10 mg (N=33)	25 mg (N=34)	50 mg (N=27)	Total (N=154)
Sex						
Female	1 (3%)	8 (26%) ^a	3 (9%)	8 (24%)	3 (11%)	23 (15%)
Male	28 (97%)	23 (74%)	30 (91%)	26 (76%)	24 (89%)	131 (85%)
Age (years)						
Mean	60.5	61.2	60.6	60.1	59.9	60.5
S.D.	11.4	11.7	11.1	10.3	10.6	10.9
Range	34-80	28-77	40-76	36-77	28-74	26-80
Racial Origin						
Caucasian	25 (86%)	22 (71%)	28 (85%)	26 (76%)	25 (93%) ^b	126 (82%)
Black	2 (7%)	3 (10%)	3 (9%)	3 (9%)	0	11 (7%)
Other	2 (7%)	6 (19%)	2 (6%)	5 (15%)	2 (8%)	17 (11%)

a. Statistically significant difference against the placebo group, $p < 0.05$

b. Statistically significant difference against the 2.5 mg group, $p < 0.05$

c. Statistically significant difference against the 10 mg group, $p < 0.05$

d. Statistically significant difference against the 25 mg group, $p < 0.05$

Baseline intracardiac pressure measurements were similar between treatment groups except for baseline pulmonary capillary wedge pressures (PCWP). Table 47.4 lists the baseline PCWP. The minimum value for all losartan groups is < 13 mmHg. Thus, some patients in all losartan treatment groups do not fulfill the criteria for enrollment that the mean PCWP be > 13 mmHg.

Table 47.4. Pulmonary Capillary Wedge Pressure (mmHg)

	N	Baseline					Comparison			
		Mean	S.D.	Median	Min	Max	vs. B	vs. c	vs. D	vs. E
PBO	29	21.6	7.9	19	10.5	38.5	NS	NS	*	*
losartan 2.5 mg	30	18.4	5.3	17	12.5	33	--	NS	NS	NS
losartan 10 mg	32	21.5	8.1	19.5	7.5	37	--	--	*	*
losartan 25 mg	34	17.7	6.3	16.3	8.5	41.5	--	--	--	NS
losartan 50 mg	27	17.6	6.2	16.5	9	39.5	--	--	--	--

NS -- NOT STATISTICALLY SIGNIFICANT

* -- TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, $P < 0.05$

** -- TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, $P < 0.01$

Nineteen patients did not complete the double blind portion of the study. Table 47.5 list the reasons for discontinuation. The majority were discontinued due to adverse events. Only one patient (#1067) discontinued due to ineffective therapy. Three patients receiving losartan therapy died. Three deaths were reported for the double-blind period of the study. Two deaths (# 1128, 1133) were in the losartan 2.5 mg group, and one (# 1139) was in the losartan 10 mg group. Additionally, one death (# 1195) occurred 30 days following the completion of the double-blind period and discontinuation of losartan in a patient that received losartan 10 mg during the double-blind period. A summary of the events surrounding the deaths is presented in table 47.5a.

Table 47.5. Patient Disposition

	PBO (N=29)	2.5 mg (N=31)	10 mg (N=33)	25 mg (N=34)	50 mg (N=27)
Completed Double-Blind/ Not Continuing Into Extension	7	5	8	9	7
Completed Double-Blind/ Continuing Into Extension	18	24	20	20	17
Discontinued Double-blind Phase	4	2	5	5	3
Clinical Adverse Experience	4	2	4	5	3
Therapy Ineffective	0	0	1	0	0

Table 47.4a. Deaths

Patient Number	Summary
1128	This 68-year-old Caucasian male with an ejection fraction of 29%, NYHA functional class IIa heart failure, angina, peripheral vascular disease and a history of 2 myocardial infarctions and coronary artery bypass graft was randomized to receive single daily doses of losartan 2.5 mg. The etiology of heart failure in this patient was ischemic heart disease. His last dose of study drug was on Day 84. He was concomitantly treated with dipyridamole. On Day 85, he experienced a cardiac arrest and was hospitalized. On admission, the patient was found to be in ventricular fibrillation and died that day.
1133	This 71-year-old Caucasian male with an ejection fraction of 14%, NYHA Class IIb heart failure, atrial fibrillation, diabetes, and a history of 3 myocardial infarctions was randomized to receive single daily doses of losartan 2.5 mg. The etiology of heart failure in this patient was ischemic heart disease. Concomitant medications included digitoxin, furosemide, spironolactone, glyburide, and warfarin. On Day 21, the patient died suddenly - attempts at resuscitation failed. The investigator identified the cause of death as ventricular fibrillation.
1139	This 65-year-old Caucasian male with an ejection fraction of 23%, NYHA Class IIb heart failure, atrial fibrillation and a history of myocardial infarction and coronary artery bypass graft surgery was randomized to receive single daily doses of losartan 10 mg. The etiology of heart failure in this patient was ischemic heart disease. Concomitant medications included digoxin, furosemide, spironolactone, dipyridamole, and aspirin. On Day 10, the patient suffered ventricular fibrillation and cardiac arrest. He was resuscitated and was hospitalized, but remained unconscious. On Day 15, the patient developed pneumonia. On Day 17 life-sustaining measures were withdrawn. On Day 18, the patient died. Autopsy confirmed pneumonia as the cause of death.
1195	This 67-year-old Caucasian male with an ejection fraction of 22%, NYHA Class IIb heart failure, angina, and a history of myocardial infarction, and ventricular tachycardia was randomized to receive single daily doses of losartan 10 mg. The etiology of heart failure in this patient was ischemic heart disease. The patient completed the study and losartan was discontinued on Day 85. Twelve days following completion of the study, the patient suffered cardiac arrest and was resuscitated. He was hospitalized and was found to have suffered a myocardial infarction. These episodes caused serious cerebral degeneration which led to the patient's death thirty days after completion of the study.

Table 47.6 lists the patients withdrawn from therapy prematurely. Eighteen patients withdrew due to adverse events.

Table 47.6. Patients Withdrawn from Therapy

Patient Number	Treatment	Age	Gender	Race	Reason Discontinued	Stop Day	Adverse Event	AE start day	AE stop day
1005	Losartan 25 mg	73	M	Caucasian	Clinical AE	2	HYPOTENSION, ORTHOSTATIC	2	2
							VOMITING	2	2
1020	Losartan 10 mg	54	F	Caucasian	Clinical AE	58	DIZZINESS	4	4
							DIZZINESS	7	7
							DIZZINESS	9	9
							INSOMNIA	13	18
							DYSPNEA	17	58
							HEART FAILURE	30	35
							WEAKNESS, MUSCLE	30	35
							HEART FAILURE	53	54
1060	Losartan 50 mg	69	M	Caucasian	Clinical AE	2	HYPOTENSION	1	3
1070	Losartan 25 mg	47	M	Caucasian	Clinical AE	16	BRONCHITIS	3	9
							DIARRHEA	14	18
							HEADACHE	14	18
							NAUSEA	14	18
							PRURITUS	14	18
							SWEATING	14	18
							ALT INCREASED	17	
							AST INCREASED	17	
							LDH INCREASED	17	
							PLATELET COUNT INCREASED	17	
1072	Losartan 25 mg	67	M	Caucasian	Clinical AE	73	HYPOTENSION	11	11
							DIARRHEA	11	17
							NAUSEA	11	17
							ASTHENIA/FATIGUE	43	73
							MEMORY IMPAIRMENT	43	73
							DYSPNEA	59	73
1073	Placebo	67	M	Caucasian	Clinical AE	74	ATRIAL FIBRILLATION	2	2
							HEART FAILURE	74	80

Table 47.6. Patients Withdrawn from Therapy (continued)

Patient Number	Treatment	Age	Gender	Race	Reason Discontinued	Stop Day	Adverse Event	AE start day	AE stop day
1082	Losartan 25 mg	77	M	Caucasian	Clinical AE	2	HYPOENSION	2	2
1090	Losartan 10 mg	73	M	Caucasian	Clinical AE	23	EDEMA, PULMONARY	23	24
							HEART FAILURE	23	24
1101	Losartan 50 mg	67	M	Caucasian	Clinical AE	9	BLURRED VISION	4	4
							ASTHENIA/FATIGUE	4	13
							DIZZINESS	4	13
							BLURRED VISION	5	5
							BLURRED VISION	6	6
							BLURRED VISION	8	8
							HYPOENSION, ORTHOSTATIC	9	9
1112	Placebo	65	M	Negro	Clinical AE	43	FEVER	1	1
							PAIN, CATHETER, CARDIAC	1	1
							HEART FAILURE	9	56
1123	Placebo	71	M	Negro	Clinical AE	61	SEPTICEMIA	1	1
							EDEMA/SWELLING	16	70
							OBSTRUCTION, URINARY TRACT	30	84
							HEPATOMEGALY	60	61
1128	Losartan 25 mg	68	M	Caucasian	Clinical AE	85	DYSPPNEA	8	21
							WHEEZING	8	21
							CARDIAC ARREST	85	85
							DEATH	85	85
							VENTRICULAR FIBRILLATION	85	85
1133	Losartan 25 mg	71	M	Caucasian	Clinical AE	21	CONSTIPATION	1	1
							MYALGIA	1	1
							DEATH	21	21
							VENTRICULAR FIBRILLATION	21	21
1139	Losartan 10 mg	65	M	Caucasian	Clinical AE	10	CARDIAC ARREST	10	10
							VENTRICULAR FIBRILLATION	10	10
1174	Losartan 50 mg	28	F	Caucasian	Clinical AE/Continuing	1	HYPOENSION	1	1
1176	Losartan 25 mg	73	M	Caucasian	Clinical AE	2	RASH	1	5
							DIARRHEA	2	2
							HYPOENSION, ORTHOSTATIC	2	2
1188	Losartan 10 mg	70	M	MEXICAN	Clinical AE	45	DEPRESSION	2	45
							PHLEBITIS/THROMBOPHLEBITIS	6	16
							ABSCESS	13	16
							AV BLOCK, SECOND DEGREE	30	37
							EDEMA, PULMONARY	44	47
1206	Placebo	69	M	Caucasian	Clinical AE	71	DYSPPNEA	32	72
							HEART FAILURE	71	72

As table 47.7 illustrates, there was no difference in the number of patients with at least one adverse event.

Table 47.7. Incidence of Patients With At Least One Adverse Experience

	PBO (N=29)	2.5 MG (N=31)	10 MG (N=33)	25 MG (N=34)	50 MG (N=27)
Number (%) of Patients	n (%)	n (%)	n (%)	n (%)	n (%)
With One Or More Adverse Experiences	19 (65.5)	18 (58.1)	18 (54.5)	19 (55.9)	16 (59.3)

Table 47.8 lists the patients who experienced a serious adverse event.

Table 47.8. Listing of Information for Serious Clinical Adverse Experiences

Patient Number	Sex/Age/NYHA	Total Daily Dosage	Onset Day	Adverse Experience	Duration	Intensity
PLACEBO GROUP						
1054	M/76/IV	OFFDRUG	44	Ventricular Tachycardia	5 days	Severe
1211	M/34/IIa	PBO	82	Ventricular Tachycardia	1 min	Severe
1206	M/69/IIa	PBO	71	Heart Failure	2 days	Severe
1235	M/57/IIb	PBO	69	Dyspnea	12 hrs	Severe
1123	M/71/IIa	PBO	1	Septicemia	1 day	Mild
			30	Obstruction, Urinary Tract	55 days	Moderate
1136	M/68/IIb	PBO	71	Pneumonia	5 days	Moderate
1192	M/45/III	PBO	58	Heart Failure	28 days	Severe
		OFFDRUG	88	Pneumonia	6 days	
1186	M/59/III	PBO	2	Embolism/Pulmonary Infarction	14 days	Moderate
			43	Dyspnea	18 days	Severe
LOSARTAN 2.5 mg GROUP						
1004	F/64/III	2.5 mg	14	Chest Pain	2 hrs	Moderate
1051	M/69/IIa	OFFDRUG	8	Cardiac Arrest	1 hr	Severe
		2.5 mg	14	Ventricular Tachycardia	1 hr	Severe
1071	F/73/III	2.5 mg	58	Atrial Fibrillation	35 days	Severe
1194	M/72/IIb	2.5 mg	9	Pneumonia	20 days	Severe
1189	F/69/IIb	2.5 mg	59	CVA	26 days	Moderate
LOSARTAN 10 mg GROUP						
1020	F/54/III	10 mg	30	Heart Failure	6 days	Severe
			53	Heart Failure	2 days	Severe
1047	M/58/III	10 mg	77	Heart Failure	60 days	Severe
1185	M/71/III	10 mg	55	Hepatobiliary Pain	12 days	Moderate
1188	M/70/III	10 mg	44	Pulmonary Edema	4 days	Severe
1195 [†]	M/67/IIb	OFFDRUG	97	Cardiac Arrest	1 day	
			97	Myocardial Infarction	1 day	
			97	Cerebral Degeneration	19 days	
			115	Death		
LOSARTAN 25 mg GROUP						
1025	M/62/III	25 mg	8	Pneumonia	7 days	Severe
1072	M/67/IIa	25 mg	59	Dyspnea	15 days	Severe
1080	M/60/III	25 mg	92	Bacteremia	1 day ^{††}	Moderate
LOSARTAN 50 mg GROUP						
1174	F/28/III	50 mg	1	Hypotension	9 hrs	Severe

[†] This patient died 30 days following completion of the double-blind period and discontinuation of losartan therapy

^{††} This adverse experience occurred on the last day of double-blind therapy and continued into the open-label extension period.

Patient #1031 (losartan 2.5 mg) who was on warfarin 5.0 mg daily had an elevated prothrombin time on day 33. Additional information was presented in the submission of 10/7/94. This patient experienced gingival bleeding with a prothrombin time of 29.4 seconds.

For both supine and standing heart rate, the placebo levels at the end of the study had increased by 7 to 8 beats/min above baseline levels, while the 25 mg and 50 mg groups maintained baseline levels. There was not a consistent pattern of change in blood pressure compared to placebo.

Neurohormone levels (aldosterone, renin activity, angiotensin II, norepinephrine, epinephrine and dopamine) were measured during both hemodynamic periods at Hours 0, 5 and 24 postdose. The neurohormone concentrations were provided as log transformed means. Significant differences between treatment groups are discussed as fold changes from baseline, that is, the geometric mean of the original measurements, which translates to the geometric mean of ratios (posttreatment value/pre-treatment value). The geometric mean is calculated from the logarithmic mean (Table 95) after exponentiation (geometric mean = exp(mean of logarithmic values)). In this form, this data is uninterpretable from a clinical perspective. The sponsor will need to supply the means and range of values for the various neurohormones.

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Patients Discontinued in Study 011.

Patient #	Treatment	Reason Discontinued	Day Discontinued
33	Losartan 150 mg	Clinical AE	17
488	Losartan 150 mg	Clinical AE	20
489	Losartan 10 mg	Clinical AE	24
85	Losartan 50 mg	Clinical AE	34
294	Losartan 100 mg	Clinical AE	36
399	Losartan 10 mg	Clinical AE	36
684	Losartan 25 mg	Clinical AE	41
649	Placebo	Lab AE	28
115	Losartan 25 mg	Lab AE	32
321	Enalapril	Lab AE	41
802	Placebo	Lab AE	43
376	Losartan 50 mg	Lost to Followup	1
698	Placebo	Lost to Followup	16
496	Losartan 100 mg	Lost to Followup	29
808	Placebo	Lost to Followup	31
192	Losartan 25 mg	Lost to Followup	42
466	Enalapril	Lost to Followup	62
190	Losartan 100 mg	Protocol Deviation	1
743	Losartan 50 mg	Protocol Deviation	8
210	Losartan 25 mg	Protocol Deviation	10
475	Placebo	Patient Uncooperative	56
480	Placebo	Patient Uncooperative	56
469	Losartan 100 mg	Patient Uncooperative	57
359	Placebo	Therapy Ineffective	6
761	Losartan 150 mg	Therapy Ineffective	12
680	Placebo	Therapy Ineffective	13
419	Losartan 150 mg	Therapy Ineffective	14
706	Losartan 25 mg	Therapy Ineffective	14
447	Losartan 10 mg	Therapy Ineffective	22
837	Losartan 25 mg	Therapy Ineffective	28
632	Losartan 150 mg	Therapy Ineffective	39
613	Placebo	Therapy Ineffective	51
799	Losartan 10 mg	Therapy Ineffective	54
505	Losartan 10 mg	Therapy Ineffective	56
699	Losartan 10 mg	Therapy Ineffective	64
548	Losartan 150 mg	Clinical and Lab AE	34
119	Losartan 100 mg	Patient Withdrew	6
124	Enalapril	Patient Withdrew	10
498	Losartan 100 mg	Patient Withdrew	12
552	Losartan 100 mg	Patient Withdrew	14
805	Losartan 100 mg	Patient Withdrew	55
651	Losartan 100 mg	Patient Withdrew	49
452	Placebo	Patient Withdrew	50
49	Placebo	Patient Withdrew	52
485	Losartan 25 mg	Patient Withdrew	55
494	Losartan 10 mg	Patient Withdrew	56
490	Losartan 100 mg	Patient Withdrew	59
617	Losartan 150 mg	Clinical AE/Cont.	28
667	Enalapril	Clinical AE/Cont.	47
659	Losartan 10 mg	Therapy Ineffective/Cont.	49

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Patients Discontinued from Double-Blind Phase of Study 050.

Patient Number	Treatment Regimen	Reason Discontinued	Day Discontinued
2170	Losartan 50mg/100mg	Clinical Adverse Experience	1
2397	Losartan 50mg/100mg	Clinical Adverse Experience	9
2160	Losartan 50mg/100mg	Clinical Adverse Experience	11
2386	Losartan 50mg/100mg	Clinical Adverse Experience	21
2028	Placebo	Clinical Adverse Experience	23
2266	Losartan 50mg/100mg	Clinical Adverse Experience	32
2020	Losartan 50mg/100mg	Clinical Adverse Experience	36
2149	Placebo	Clinical Adverse Experience	39
2271	Losartan 50mg/100mg	Clinical Adverse Experience	47
2292	Placebo	Clinical Adverse Experience	72
2394	Losartan 50mg/100mg	Lost To Followup	6
2282	Losartan 50 mg	Lost To Followup	9
2291	Losartan 50 mg	Lost To Followup	29
2314	Placebo	Lost To Followup	54
2110	Losartan 50 mg	Lost To Followup	64
2396	Placebo	Lost To Followup	68
2385	Placebo	Protocol Deviation	5
2436	Losartan 50 mg	Protocol Deviation	13
2383	Losartan 50 mg	Protocol Deviation	35
2278	Losartan 50mg/100mg	Protocol Deviation	84
2285	Placebo	Protocol Deviation	87
2243	Losartan 50mg/100mg	Patient Uncooperative	89
2228	Losartan 50 mg	Therapy Ineffective	10
2378	Placebo	Therapy Ineffective	21
2232	Placebo	Therapy Ineffective	22
2227	Placebo	Therapy Ineffective	35
2072	Losartan 50 mg	Therapy Ineffective	48
2158	Placebo	Therapy Ineffective	51
2063	Placebo	Therapy Ineffective	62
2284	Losartan 50 mg	Patient Withdrew	3
2235	Placebo	Patient Withdrew	14
2328	Losartan 50mg/100mg	Patient Withdrew	42
2205	Placebo	Patient Withdrew	64
2119	Losartan 50mg/100mg	Patient Withdrew	84
2247	Losartan 50mg/100mg	Therapy Ineffective*	5
2376	Losartan 50mg/100mg	Therapy Ineffective*	15
2412	Placebo	Therapy Ineffective*	19
2372	Losartan 50 mg	Therapy Ineffective*	24
2423	Losartan 50 mg	Therapy Ineffective*	29
2365	Placebo	Therapy Ineffective*	48
2209	Losartan 50 mg	Therapy Ineffective*	65
2253	Placebo	Therapy Ineffective*	71
2408	Placebo	Protocol Violator*	18
2313	Losartan 50 mg	Protocol Violator*	43

* continued in open label phase

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*Investigators were shipped drug but enrolled no patients

Study 065. Patients Discontinued from Double-Blind Phase

Patient #	Treatment	Reason Discontinued	Day Discontinued
1301	Losartan 50 mg	Clinical AE	4
1373	Placebo	Clinical AE	4
1308	Placebo	Clinical AE	5
1145	Placebo	Clinical AE	10
1415	Losartan 25mg BID	Clinical AE	16
1607	Losartan 25mg BID	Clinical AE	16
1623	Placebo	Clinical AE	27
1272	Placebo	Clinical AE	33
1153	Placebo	Clinical AE	39
1596	Losartan 25mg BID	Clinical AE	41
1421	Placebo	Clinical AE	43
1560	Placebo	Clinical AE	52
1246	Placebo	Clinical AE	84
1330	Placebo	Clinical AE	85
1599	Losartan 50 mg	Lab AE	84
1750	Losartan 50 mg	Lab AE	90
1628	Losartan 50 mg	Lost to Followup	1
1685	Losartan 25 mg	Lost to Followup	1
1407	Losartan 50 mg	Lost to Followup	30
1676	Losartan 25 mg	Lost to Followup	57
1655	Placebo	Protocol Deviation	12
1417	Placebo	Protocol Deviation	18
1692	Losartan 25 mg	Protocol Deviation	27
1290	Losartan 50 mg	Protocol Deviation	36
1631	Losartan 25mg BID	Protocol Deviation	60
1674	Losartan 25mg BID	Protocol Deviation	60
1668	Losartan 25 mg	Protocol Deviation	85
1669	Placebo	Protocol Deviation	85
1219	Placebo	Therapy Ineffective	7
1161	Losartan 50 mg	Therapy Ineffective	13
1288	Losartan 25mg BID	Therapy Ineffective	15
1273	Losartan 25 mg	Therapy Ineffective	16
1280	Placebo	Therapy Ineffective	21
1164	Placebo	Therapy Ineffective	27
1168	Losartan 50 mg	Therapy Ineffective	28
1170	Placebo	Therapy Ineffective	28
1175	Losartan 25 mg	Therapy Ineffective	28
1464	Placebo	Therapy Ineffective	28
1174	Losartan 50 mg	Therapy Ineffective	35
1691	Placebo	Therapy Ineffective	35
1768	Placebo	Therapy Ineffective	55
1228	Losartan 25mg BID	Therapy Ineffective	58
1249	Losartan 50 mg	Therapy Ineffective	58
1603	Placebo	Therapy Ineffective	60
1126	Placebo	Therapy Ineffective	61
1411	Losartan 50 mg	Therapy Ineffective	62
1310	Losartan 25mg BID	Patient Withdrew	7
1267	Losartan 25mg BID	Patient Withdrew	27
1420	Losartan 25 mg	Patient Withdrew	28
1386	Losartan 25 mg	Patient Withdrew	29
1127	Losartan 25 mg	Patient Withdrew	50
1418	Losartan 25mg BID	Patient Withdrew	51
1351	Losartan 50 mg	Patient Withdrew	56

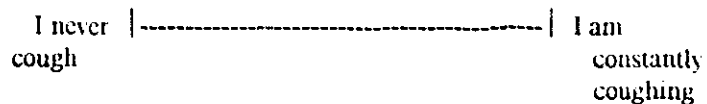
Study 56. Questionnaire and Visual Analog scale.

On this page is a list of words that describe symptoms people have. Please read each one carefully, then mark the box under the answer which describes whether you have experienced the symptom in the last week, and, if so, the extent to which it has bothered you.

	Not at All	A Little	Moderately	Quite a Bit	Extremely
Dry mouth					
Cramps in legs					
Dry cough					
Racing Heart					
Heartburn					
Headache					
Sore throat					
Getting up at night to pass urine					
Flushing of face					

Visual Analog Scale

Please make a vertical line to show how often you cough.



Study L11. Open Label Mean Change in suDBP
Mean Reduction at Months 6 and 12 in Supine Blood Pressure (Trough, mmHg) From Baseline

MEASUREMENT	MONTH	LOS-HCTZ-CCB-OTHER	N	BASE		FINAL		CHANGE	
				Mean	S.D.	Mean	S.D.	Mean	S.D.
Supine Diast	6	50- 0 -NO -NO	75	101.4	2.0	84.2	5.3	-17.3	5.7
		50-12.5-NO -NO	4	105.0	5.7	91.5	11.1	-13.5	5.7
		50-25 -NO -NO							
		100- 0 -NO -NO	47	102.0	2.6	85.3	4.9	-15.7	4.9
		100-12.5-NO -NO	48	103.3	3.2	87.4	5.4	-15.9	5.9
		100-25 -NO -NO	4	103.8	2.5	83.3	2.9	-20.5	2.6
		100-50 -NO -NO							
		150- 0 -NO -NO	17	102.2	3.8	88.2	6.3	-14.0	6.2
		150-12.5-NO -NO	15	105.0	3.8	88.5	5.1	-16.5	6.8
		150-25 -NO -NO	33	103.9	3.8	88.4	5.1	-15.5	5.7
	150-50 -NO -NO	33	105.1	4.5	91.6	7.7	-13.5	8.2	
	12	50- 0 -NO -NO	48	101.6	2.4	83.7	4.4	-17.9	4.5
		50-12.5-NO -NO	3	101.0	0.0	87.0	8.7	-14.0	8.7
		50-25 -NO -NO							
		100- 0 -NO -NO	36	101.5	1.5	86.9	7.8	-14.6	7.7
		100-12.5-NO -NO	27	103.7	3.3	87.3	4.0	-16.4	4.8
		100-25 -NO -NO	8	103.3	2.9	88.3	3.0	-15.0	4.1
		150- 0 -NO -NO	12	102.9	3.7	88.3	4.7	-14.6	5.8
		150-12.5-NO -NO	12	103.8	4.0	88.3	4.7	-15.6	4.2
		150-25 -NO -NO	25	103.6	3.1	87.8	5.5	-15.8	5.5
150-50 -NO -NO		27	105.8	4.8	87.6	4.8	-18.2	6.8	
Supine Syst	6	50- 0 -NO -NO	75	152.8	14.7	136.5	15.3	-16.3	14.6
		50-12.5-NO -NO	4	152.3	7.4	132.8	8.4	-19.5	11.0
		50-25 -NO -NO							
		100- 0 -NO -NO	47	152.3	14.9	137.3	14.1	-15.0	13.4
		100-12.5-NO -NO	48	163.0	14.8	141.4	16.6	-21.6	15.8
		100-25 -NO -NO	4	162.8	14.1	132.5	3.7	-30.3	13.8
		100-50 -NO -NO							
		150- 0 -NO -NO	17	160.1	18.6	144.8	15.9	-15.4	13.8
		150-12.5-NO -NO	15	154.7	10.4	134.4	13.0	-20.3	17.6
		150-25 -NO -NO	33	158.4	14.5	139.4	15.7	-19.0	16.5
	150-50 -NO -NO	33	169.3	14.5	144.0	15.5	-25.3	13.2	
	12	50- 0 -NO -NO	48	150.3	14.2	133.9	14.1	-16.4	13.7
		50-12.5-NO -NO	3	151.0	8.7	128.7	8.7	-22.3	10.0
		50-25 -NO -NO							
		100- 0 -NO -NO	36	154.6	14.5	137.7	12.4	-16.9	14.2
		100-12.5-NO -NO	27	163.7	15.2	138.4	16.3	-25.3	17.5
		100-25 -NO -NO	8	150.0	11.6	133.0	9.7	-17.0	16.5
		150- 0 -NO -NO	12	157.4	10.2	135.9	9.4	-21.5	14.3
		150-12.5-NO -NO	12	162.8	12.6	145.7	11.3	-17.1	12.6
		150-25 -NO -NO	25	160.8	13.6	138.4	15.2	-22.4	16.0
150-50 -NO -NO		27	166.1	15.1	136.6	14.1	-29.4	13.6	

Study L21. Open Label Mean Change in siDBP.

Mean Reduction at Months 6 and 12 in Sitting Blood Pressure (Trough, mmHg) From Baseline

MEASUREMENT	MONTH	LOS-HCTZ-CCB-OTHER	N	BASE		FINAL		CHANGE	
				Mean	S.D.	Mean	S.D.	Mean	S.D.
Sitting Diast	6	50- 0 -NO -NO	5	99.6	2.9	82.8	5.5	-16.8	8.0
		50-12.5-NO -NO	3	99.7	1.2	84.7	4.0	-15.0	5.0
		50-25 -NO -NO							
	12	50- 0 -NO -NO	5	99.6	2.9	81.6	6.3	-18.0	8.1
		50-12.5-NO -NO							
		50-25 -NO -NO							
Sitting Syst	6	50- 0 -NO -NO	5	144.4	15.7	128.8	14.6	-15.6	11.0
		50-12.5-NO -NO	3	158.3	23.0	134.7	3.8	-23.7	23.0
		50-25 -NO -NO							
	12	50- 0 -NO -NO	5	144.4	15.7	129.2	14.7	-15.2	16.1
		50-12.5-NO -NO	1						
		50-25 -NO -NO	1						

Study L49. Open Label Mean Change in siDBP.

Mean Reduction at Months 6 and 12 in Sitting Blood Pressure (Trough, mmHg) From Baseline

MEASUREMENT	MONTH	LOS-HCTZ-CCB-OTHER	N	BASE		FINAL		CHANGE	
				Mean	S.D.	Mean	S.D.	Mean	S.D.
Sitting Diast	6	0-6.25-NO -NO	1						
		50- 0 -NO -NO	19	100.1	4.7	86.8	6.7	-13.3	7.1
		50- 0 -YES-NO	1						
		50-6.25-NO -NO	12	104.9	7.3	87.5	5.4	-17.4	8.7
		50-12.5-NO -NO	13	104.2	4.7	89.4	7.0	-14.8	8.1
		50-12.5-YES-NO	22	107.8	7.2	92.3	8.0	-15.5	7.5
		50-25 -NO -NO	2	101.0	0.0	93.0	8.5	-8.0	8.5
		50-25 -YES-NO	7	107.1	8.7	93.4	4.4	-13.7	8.6
		12	50- 0 -NO -NO	5	99.0	3.9	85.4	9.1	-13.6
	50- 0 -YES-NO		1						
	50-6.25-NO -NO		4	101.0	8.2	85.3	3.1	-15.8	7.2
	50-12.5-NO -NO		5	100.8	1.8	87.2	3.9	-13.6	4.4
	50-12.5-YES-NO		3	110.0	3.5	91.0	2.0	-19.0	5.3
	50-25 -NO -NO		2	109.5	2.1	97.0	2.8	-12.5	4.9
	Sitting Syst	6	0-6.25-NO -NO						
50- 0 -NO -NO			10	151.8	14.6	137.1	12.8	-14.7	15.3
50- 0 -YES-NO									
50-6.25-NO -NO			12	159.4	14.7	142.3	14.2	-17.2	11.8
50-12.5-NO -NO			13	152.2	16.9	134.6	14.9	-17.5	12.2
50-12.5-YES-NO			22	166.4	17.3	139.5	13.7	-27.0	18.6
50-25 -NO -NO			2	159.0	9.0	123.0	1.4	-36.0	8.5
50-25 -YES-NO			7	166.3	21.8	143.4	13.7	-22.9	14.7
12			50- 0 -NO -NO	5	154.6	11.5	135.8	11.9	-18.8
		50- 0 -YES-NO							
		50-6.25-NO -NO	4	158.5	12.7	131.3	8.4	-27.3	10.6
		50-12.5-NO -NO	5	153.4	19.6	136.4	19.3	-17.0	7.6
		50-12.5-YES-NO	3	165.0	17.3	137.3	3.5	-27.7	13.9
		50-25 -NO -NO	2	153.0	2.8	135.0	2.8	-18.0	0.0
50-25 -YES-NO		7	163.9	21.1	141.4	18.4	-22.4	14.7	

Study L50. Open Label Mean Change in siDBP.

Mean Reduction at Months 6 and 12 in Sitting Blood Pressure (Trough, mmHg) From Baseline

MEASUREMENT	MONTH	LOS-HCTZ-CCB-OTHER	N	BASE		FINAL		CHANGE		
				Mean	S.D.	Mean	S.D.	Mean	S.D.	
Sitting Diast	6	50- 0 -NO -NO	47	99.2	3.9	84.8	5.2	-14.4	5.4	
		50- 0 -YES-NO								
		50-6.25-NO -NO	23	101.2	4.3	88.3	4.0	-12.8	5.7	
		50-12.5-NO -NO	42	102.5	4.6	88.7	4.6	-13.8	6.1	
		50-12.5-YES-NO	46	104.5	5.0	89.6	5.7	-14.9	7.4	
		50-25 -YES-NO	4	109.0	2.2	93.0	5.9	-16.0	5.0	
	12	50- 0 -NO -NO	23	99.3	4.0	85.7	6.0	-13.7	4.5	
		50-6.25-NO -NO	8	101.1	2.9	89.1	6.2	-12.0	5.2	
		50-12.5-NO -NO	18	102.7	4.2	88.6	5.2	-14.1	7.4	
		50-12.5-YES-NO	21	103.9	5.0	86.9	6.2	-17.0	7.4	
		50-25 -NO -NO								
		50-25 -YES-NO								
	Sitting Syst	6	50- 0 -NO -NO	47	144.4	11.5	129.4	12.1	-15.0	9.1
			50- 0 -YES-NO							
50-6.25-NO -NO			23	151.3	12.6	136.4	13.9	-14.8	15.5	
50-12.5-NO -NO			42	156.0	15.2	136.5	12.6	-19.5	15.9	
50-12.5-YES-NO			46	161.5	20.4	141.3	14.8	-20.2	14.9	
50-25 -YES-NO			4	170.8	12.4	143.5	8.4	-27.3	19.2	
12		50- 0 -NO -NO	23	142.3	12.7	130.6	13.2	-11.7	11.3	
		50-6.25-NO -NO	8	153.9	13.0	140.3	10.5	-13.6	13.2	
		50-12.5-NO -NO	18	160.7	15.7	140.7	11.4	-20.1	15.5	
		50-12.5-YES-NO	21	165.9	22.0	143.6	15.1	-22.3	17.3	
		50-25 -NO -NO	1							
		50-25 -YES-NO	1							

Study L54. Open Label Mean Change in siDBP.

Mean Reduction at Month 6 in Sitting Blood Pressure (Trough, mmHg) From Baseline

MEASUREMENT	MONTH	LOS-HCTZ-CCB-OTHER	N	BASE		FINAL		CHANGE	
				Mean	S.D.	Mean	S.D.	Mean	S.D.
Sitting Diast	6	50-6.25-NO -NO	14	99.6	2.6	85.4	3.1	-14.1	3.4
		50-12.5-NO -NO	5	102.2	5.3	88.2	8.7	-14.0	4.4
		50-12.5-YES-NO	7	105.1	6.3	89.0	3.5	-16.1	4.7
Sitting Syst	6	50-6.25-NO -NO	14	150.7	14.5	134.5	13.7	-16.2	16.4
		50-12.5-NO -NO	5	149.4	7.3	131.4	7.9	-18.0	6.1
		50-12.5-YES-NO	7	159.7	27.2	141.6	15.1	-18.1	16.9

Patients Withdrawn from Open Label Extension of Protocols 011, 021, 049, 050 and 054.

Study	Patient #	Reason Discontinued	Day Discontinued
L11	68	Clinical AE	117
L11	95	Clinical AE	108
L11	97	Clinical AE	269
L11	170	Clinical AE	164
L11	172	Clinical AE	589
L11	174	Clinical AE	89
L11	260	Clinical AE	150
L11	276	Clinical AE	296
L11	322	Clinical AE	265
L11	339	Clinical AE	132
L11	365	Clinical AE	90
L11	402	Clinical AE	178
L11	406	Clinical AE	114
L11	407	Clinical AE	162
L11	493	Clinical AE	181
L11	510	Clinical AE	553
L11	519	Clinical AE	563
L11	579	Clinical AE	364
L11	644	Clinical AE	383
L11	646	Clinical AE	133
L11	648	Clinical AE	88
L11	666	Clinical AE	72
L11	740	Clinical AE	79
L11	764	Clinical AE	266
L11	766	Clinical AE	218
L11	783	Clinical AE	286
L11	818	Clinical AE	419
L11	882	Clinical AE	454
L11	64	Lab AE	103
L11	638	Lab AE	351
L11	178	Lost to Followup	92
L11	179	Lost to Followup	195
L11	186	Lost to Followup	137
L11	188	Lost to Followup	280
L11	378	Lost to Followup	301
L11	474	Lost to Followup	292
L11	596	Lost to Followup	513
L11	770	Lost to Followup	159
L11	809	Lost to Followup	92
L11	816	Lost to Followup	115
L11	817	Lost to Followup	216
L11	677	Protocol Deviation	163
L11	46	Patient Uncooperative	269
L11	355	Patient Uncooperative	217
L11	652	Patient Uncooperative	306
L11	682	Patient Uncooperative	133
L11	801	Patient Uncooperative	345
L11	52	Therapy Ineffective	294
L11	69	Therapy Ineffective	152
L11	91	Therapy Ineffective	300
L11	180	Therapy Ineffective	182
L11	211	Therapy Ineffective	197
L11	229	Therapy Ineffective	62
L11	231	Therapy Ineffective	195
L11	338	Therapy Ineffective	185
L11	364	Therapy Ineffective	252
L11	416	Therapy Ineffective	246
L11	417	Therapy Ineffective	132
L11	444	Therapy Ineffective	634

Patients Withdrawn from Open Label Extension of Protocols 011, 021, 049, 050 and 054. (con't)

Study	Patient #	Reason Discontinued	Day Discontinued
L11	467	Therapy Ineffective	669
L11	484	Therapy Ineffective	179
L11	486	Therapy Ineffective	167
L11	504	Therapy Ineffective	185
L11	568	Therapy Ineffective	183
L11	616	Therapy Ineffective	172
L11	647	Therapy Ineffective	216
L11	654	Therapy Ineffective	238
L11	659	Therapy Ineffective	144
L11	672	Therapy Ineffective	153
L11	674	Therapy Ineffective	167
L11	675	Therapy Ineffective	166
L11	756	Therapy Ineffective	185
L11	758	Therapy Ineffective	98
L11	760	Therapy Ineffective	140
L11	800	Therapy Ineffective	167
L11	875	Therapy Ineffective	186
L11	280	Patient Withdrew	218
L11	401	Patient Withdrew	222
L11	503	Patient Withdrew	342
L11	526	Patient Withdrew	565
L11	527	Patient Withdrew	515
L11	530	Patient Withdrew	472
L11	612	Patient Withdrew	137
L11	645	Patient Withdrew	149
L11	739	Patient Withdrew	133
L11	807	Patient Withdrew	504
L11	819	Patient Withdrew	570
L11	824	Patient Withdrew	118
L11	829	Patient Withdrew	314
L11	413	Other	96
L21	90	Lost to Followup	306
L49	7016	Clinical AE	326
L49	7199	Clinical AE	307
L49	7236	Clinical AE	139
L49	7264	Clinical AE	267
L49	7279	Clinical AE	338
L49	7361	Clinical AE	159
L49	7411	Clinical AE	286
L49	7414	Clinical AE	114
L49	7453	Clinical AE	181
L49	7146	Lost to Followup	113
L49	7172	Lost to Followup	186
L49	7004	Protocol Deviation	129
L49	7170	Protocol Deviation	211
L49	7173	Therapy Ineffective	254
L49	7217	Therapy Ineffective	161
L49	7230	Therapy Ineffective	166
L49	7232	Therapy Ineffective	190
L49	7233	Therapy Ineffective	203
L49	7234	Therapy Ineffective	149
L49	7235	Therapy Ineffective	172
L49	7237	Therapy Ineffective	108
L49	7238	Therapy Ineffective	140
L49	7239	Therapy Ineffective	110
L49	7270	Therapy Ineffective	191
L49	7304	Therapy Ineffective	188
L49	7410	Therapy Ineffective	179
L49	7436	Therapy Ineffective	134

Patients Withdrawn from Open Label Extension of Protocols 011, 021, 049, 050 and 054. (con't)

Study	Patient #	Reason Discontinued	Day Discontinued
L49	7449	Therapy Ineffective	81
L49	7451	Therapy Ineffective	134
L49	7156	Patient Withdrew	102
L49	7227	Patient Withdrew	143
L49	7240	Patient Withdrew	155
L49	7267	Patient Withdrew	109
L49	7433	Patient Withdrew	149
L49	7450	Patient Withdrew	124
L49	7011	Other	260
L50	2042	Clinical AE	222
L50	2187	Clinical AE	245
L50	2212	Clinical AE	193
L50	2217	Clinical AE	317
L50	2226	Clinical AE	323
L50	2241	Clinical AE	126
L50	2246	Clinical AE	228
L50	2248	Clinical AE	216
L50	2255	Clinical AE	273
L50	2283	Clinical AE	264
L50	2325	Clinical AE	153
L50	2336	Clinical AE	202
L50	2365	Clinical AE	59
L50	2371	Clinical AE	332
L50	2373	Clinical AE	197
L50	2414	Clinical AE	244
L50	2230	Lab AE	232
L50	2305	Lab AE	154
L50	2127	Lost to Followup	161
L50	2377	Lost to Followup	167
L50	2067	Patient Uncooperative	118
L50	2062	Therapy Ineffective	127
L50	2074	Therapy Ineffective	171
L50	2143	Therapy Ineffective	203
L50	2155	Therapy Ineffective	204
L50	2161	Therapy Ineffective	159
L50	2199	Therapy Ineffective	225
L50	2222	Therapy Ineffective	207
L50	2247	Therapy Ineffective	20
L50	2268	Therapy Ineffective	252
L50	2324	Therapy Ineffective	153
L50	2329	Therapy Ineffective	174
L50	2398	Therapy Ineffective	163
L50	2165	Patient Withdrew	161
L50	2169	Patient Withdrew	189
L50	2174	Patient Withdrew	189
L50	2188	Patient Withdrew	149
L50	2231	Patient Withdrew	209
L50	2281	Patient Withdrew	218
L50	2405	Patient Withdrew	304
L50	2404	Other	307
L54	8815	Clinical AE	205
L54	8263	Patient Withdrew	101

Listing of Losartan and Placebo Adverse Event Incidence Rates for Studies 011, 050 and 065 Combined.

	Losartan	Placebo	Total
Number Randomized	985	302	1287
Adverse Experience			
ABRASION, CORNEAL	0.1%	0.3%	0.2%
ACCOMMODATION DISORDER	0.1%	0.0%	0.1%
ACID REGURGITATION	0.1%	0.3%	0.2%
ACNE	0.1%	0.0%	0.1%
ALK PHOS. INCREASED	0.3%	0.7%	0.4%
ALLERGY	0.2%	0.0%	0.2%
ALOPECIA	0.3%	0.0%	0.2%
ALT INCREASED	2.8%	1.7%	2.6%
ALTERATION, RETINAL PIGMENT	0.1%	0.0%	0.1%
ANGINA PECTORIS	0.3%	0.0%	0.2%
ANOREXIA	0.5%	0.3%	0.5%
ANOSMIA	0.1%	0.0%	0.1%
ANXIETY	0.6%	0.7%	0.6%
ANXIETY DISORDER	0.1%	0.0%	0.1%
APPETITE CHANGE	0.1%	0.0%	0.1%
APETITE INCREASE	0.2%	0.0%	0.2%
ARCUS SENILIS	0.1%	0.0%	0.1%
ARRHYTHMIA	0.1%	0.0%	0.1%
ARTERIOLAR NARROWING	0.0%	0.3%	0.1%
ARTHRALGIA	0.1%	0.7%	0.2%
ARTHRITIS	0.1%	0.0%	0.1%
AST INCREASED	1.5%	0.7%	1.3%
ASTHENIA/FATIGUE	3.4%	5.0%	3.7%
ASTHMA	0.3%	0.0%	0.2%
ATAXIA	0.0%	0.7%	0.2%
AV BLOCK, FIRST DEGREE	0.2%	0.3%	0.2%
AV BLOCK, SECOND DEGREE	0.1%	0.0%	0.1%
AXIS DISTURBANCE	0.3%	0.0%	0.2%
BACTERIURIA	0.3%	0.0%	0.2%
BENIGN PROSTATIC HYPERTROPHY	0.1%	0.0%	0.1%
BICARBONATE DECREASED	0.1%	0.0%	0.1%
BLURRED VISION	0.3%	1.0%	0.5%
BONE FIXATION DEVICE	0.1%	0.0%	0.1%
BOWEL PATTERN CHANGE	0.1%	0.0%	0.1%
BRADYCARDIA	0.1%	0.0%	0.1%
BROMHYDROSIS	0.0%	0.3%	0.1%
BRONCHITIS	0.8%	0.7%	0.8%
BROWACHE	0.1%	0.0%	0.1%
BURN	0.1%	0.7%	0.2%
BURNING/STINGING, EYE	0.3%	0.0%	0.2%
BURSITIS	0.0%	0.3%	0.1%
CARDIOMEGALY	0.1%	0.0%	0.1%
CARPAL TUNNEL SYNDROME	0.1%	0.0%	0.1%
CELLULITIS	0.1%	0.0%	0.1%
CHILLS	0.4%	0.3%	0.4%
CHOLELITHIASIS	0.1%	0.0%	0.1%
CONFUSION	0.1%	0.3%	0.2%
CONGESTION, NASAL	2.0%	1.3%	1.9%
CONGESTION, PULMONARY	0.2%	0.0%	0.2%
CONGESTION, RESPIRATORY	0.6%	0.7%	0.6%
CONJUNCTIVITIS	0.1%	0.0%	0.1%
CONSTIPATION	0.5%	0.3%	0.5%
CONTUSION	0.2%	0.3%	0.2%
COSTOCHONDRITIS	0.1%	0.0%	0.1%
COUGH	3.6%	3.0%	3.4%
CRAMP, MUSCLE	1.0%	0.3%	0.9%

Listing of Losartan and Placebo Adverse Event Incidence Rates for Studies 011, 050 and 065 Combined.

	Losartan	Placebo	Total
Number Randomized	985	302	1287
CVA	0.1%	0.3%	0.2%
DEATH	0.0%	0.3%	0.1%
DEFECT, RETINAL	0.1%	0.0%	0.1%
DENTAL CARIES	0.1%	0.3%	0.2%
DEPRESSION	0.5%	0.7%	0.5%
DERMATITIS	0.1%	0.0%	0.1%
DERMATITIS, CONTACT	0.2%	0.0%	0.2%
DERMATOMYCOSIS	0.2%	0.0%	0.2%
DIARRHEA	2.3%	2.0%	2.3%
DIPLOPIA	0.1%	0.0%	0.1%
DISCOMFORT, PHARYNGEAL	0.5%	0.3%	0.5%
DISCOMFORT, VISUAL	0.2%	0.0%	0.2%
DISTENTION, ABDOMINAL	0.1%	0.7%	0.2%
DIZZINESS	3.2%	2.0%	3.0%
DRUSEN, MACULAR	0.0%	0.3%	0.1%
DRY EYES	0.1%	0.0%	0.1%
DRY MOUTH	0.2%	0.7%	0.3%
DYSARTHRIA	0.0%	0.3%	0.1%
DYSCHIZIA	0.1%	0.0%	0.1%
DYSPEPSIA	1.1%	1.0%	1.1%
DYSPHASIA	0.1%	0.0%	0.1%
DYSPNEA	0.6%	1.7%	0.9%
DYSPNEA, EXERTIONAL	0.2%	0.0%	0.2%
ECCHYMOSIS	0.0%	0.3%	0.1%
ECZEMA	0.0%	0.3%	0.1%
EDEMA, EYELID	0.1%	0.0%	0.1%
EDEMA, FACIAL	0.1%	0.0%	0.1%
EDEMA/SWELLING	1.8%	2.0%	1.9%
EMOTIONAL CHANGES	0.2%	0.0%	0.2%
ENTRAPMENT, NERVE	0.1%	0.0%	0.1%
EPISTAXIS	0.7%	0.0%	0.5%
ERYTHEMA	0.1%	0.0%	0.1%
ESOPHAGITIS	0.1%	0.3%	0.2%
EUSTACHIAN TUBE DISORDER	0.1%	0.0%	0.1%
EXCORIATION	0.1%	0.0%	0.1%
EXTRAOCULAR MUSCLE IMBALANCE	0.1%	0.0%	0.1%
EYE MOVEMENT DISORDER	0.1%	0.0%	0.1%
FALLING	0.1%	0.0%	0.1%
FASCICULATION	0.1%	0.0%	0.1%
FECAL ABNORMALITY	0.2%	0.0%	0.2%
FEVER	0.8%	1.0%	0.9%
FLATULENCE	0.0%	0.7%	0.2%
FLU LIKE ILLNESS	0.2%	1.7%	0.5%
FLUID OVERLOAD	0.4%	0.3%	0.4%
FLUSHING	0.8%	1.0%	0.9%
FOLLICULITIS	0.1%	0.0%	0.1%
FRACTURE, ANKLE	0.1%	0.0%	0.1%
FRACTURE, CLAVICLE, RT	0.1%	0.0%	0.1%
FULLNESS IN EARS	0.1%	0.3%	0.2%
GALLOP RHYTHM	0.0%	0.7%	0.2%
GASTROENTERITIS	0.1%	0.3%	0.2%
GASTROENTERITIS, INFECTIOUS	0.3%	1.0%	0.5%
GGT INCREASED	0.1%	0.3%	0.2%
GLAUCOMA	0.0%	0.3%	0.1%
GLOSSODYNIA	0.1%	0.0%	0.1%
GLYCOSURIA	0.2%	0.0%	0.2%
GOUT	0.5%	0.3%	0.5%
RETINOPATHY, KIIH WAGENER, (II)	0.1%	0.0%	0.1%

Listing of Losartan and Placebo Adverse Event Incidence Rates for Studies 011, 050 and 065 Combined.

	Losartan	Placebo	Total
Number Randomized	985	302	1287
HDL DECREASED	0.1%	0.0%	0.1%
HEADACHE	14.2%	15.9%	14.6%
HEADACHE, VASCULAR	0.0%	0.3%	0.1%
HEARING LOSS	0.1%	0.0%	0.1%
HEART FAILURE	0.2%	0.7%	0.3%
HEMATOCRIT DECREASED	0.2%	0.0%	0.2%
HEMATOCRIT INCREASED	0.0%	0.3%	0.1%
HEMATURIA	0.7%	0.3%	0.6%
HEMIPARESIS	0.1%	0.0%	0.1%
HEMOGLOBIN DECREASED	0.1%	0.0%	0.1%
HEMOGLOBIN INCREASED	0.0%	0.3%	0.1%
HEMOGLOBINURIA	0.3%	0.0%	0.2%
HEMOPHTHALMOS	0.1%	0.0%	0.1%
HEMORRHAGE, RETINAL	0.0%	0.3%	0.1%
HEMORRHAGE, SUBCONJUNCTIVAL	0.1%	0.0%	0.1%
HEPATITIS A AB POSITIVE	0.1%	0.0%	0.1%
HEPATITIS, VIRAL	0.1%	0.0%	0.1%
HERNIA, INGUINAL	0.1%	0.0%	0.1%
HERPES SIMPLEX	0.2%	0.0%	0.2%
HERPES ZOSTER	0.2%	0.0%	0.2%
HOARSENESS	0.0%	0.7%	0.2%
HYPERCHOLESTEROLEMIA	0.2%	0.0%	0.2%
HYPERESTHESIA	0.0%	0.3%	0.1%
HYPERGLYCEMIA	0.8%	0.3%	0.7%
HYPERKALEMIA	0.1%	0.0%	0.1%
HYPERPIGMENTATION	0.1%	0.0%	0.1%
HYPERTENSION	0.1%	0.0%	0.1%
HYPERTENSION INCREASED	0.1%	0.0%	0.1%
HYPERTRIGLYCERIDES	0.2%	0.3%	0.2%
HYPERURICEMIA	0.5%	0.3%	0.5%
HYPERVENTILATION	0.1%	0.0%	0.1%
HYPESTHESIA	0.2%	0.0%	0.2%
HYPOCALCEMIA	0.1%	0.0%	0.1%
HYPOGLYCEMIA	0.1%	0.0%	0.1%
HYPOKALEMIA	0.2%	0.3%	0.2%
HYPOTENSION, ORTHOSTATIC	0.1%	0.0%	0.1%
IMPETIGO	0.1%	0.0%	0.1%
IMPOTENCE	0.7%	0.3%	0.6%
INFECTION, DENTAL PROCESS	0.2%	0.7%	0.3%
INFECTION, EYE	0.1%	0.0%	0.1%
INFECTION, HERPES	0.1%	0.0%	0.1%
INFECTION, RESPIRATORY	0.1%	0.0%	0.1%
INFECTION, SKIN	0.1%	0.0%	0.1%
INFECTION, ULCER, SKIN	0.1%	0.0%	0.1%
INFECTION, URINARY TRACT	0.7%	1.0%	0.8%
INFECTION, VIRAL	0.1%	0.0%	0.1%
INFLAMMATION, EYELID	0.2%	0.3%	0.2%
INFLUENZA	0.3%	0.3%	0.3%
INSOMNIA	1.2%	0.3%	1.0%
INTRACULAR PRES. INCREASE	0.1%	0.0%	0.1%
IRRITABILITY	0.2%	0.3%	0.2%
IRRITABLE BOWEL SYNDROME	0.3%	0.0%	0.2%
IRRITATION, NASAL	0.1%	0.0%	0.1%
ISCHEMIA, MYOCARDIAL	0.1%	0.3%	0.2%
ITCHING, EYE	0.3%	0.3%	0.3%
KERATOSIS, SEBORRHEIC	0.2%	0.0%	0.2%
LACERATION	0.1%	0.3%	0.2%
LARYNGITIS	0.2%	0.3%	0.2%

Listing of Losartan and Placebo Adverse Event Incidence Rates for Studies 011, 050 and 065 Combined.

	Losartan	Placebo	Total
Number Randomized	985	302	1287
LDH INCREASED	0.1%	0.3%	0.2%
LEFT ANTERIOR HEMIBLOCK	0.1%	0.0%	0.1%
LEFT ATRIAL HYPERTROPHY	0.1%	0.3%	0.2%
LEFT BUNDLE BRANCH BLOCK	0.1%	0.3%	0.2%
LEFT VENTRICULAR HYPERTROPHY	0.0%	0.3%	0.1%
LESION, SKIN	0.1%	0.0%	0.1%
LEUKOCYTE COUNT INCREASED	0.1%	0.0%	0.1%
LEUKOCYTES DECREASED	0.4%	1.0%	0.5%
LIBIDO DECREASED	0.6%	0.0%	0.5%
LYMPHADENOPATHY	0.2%	0.7%	0.3%
LYMPHOCYTES DECREASED	0.1%	0.0%	0.1%
LYMPHOCYTES INCREASED	0.0%	0.3%	0.1%
MALAISE	0.2%	0.0%	0.2%
MASS, BREAST	0.1%	0.0%	0.1%
MELENA	0.0%	0.3%	0.1%
MEMORY IMPAIRMENT	0.2%	0.3%	0.2%
MENSTRUATION DISORDER	0.2%	0.0%	0.2%
MIGRAINE	0.0%	0.7%	0.2%
MONOCYTES INCREASED	0.0%	0.3%	0.1%
MYALGIA	0.9%	1.0%	0.9%
MYOCARDIAL INFARCTION	0.1%	0.3%	0.2%
MYOPIA	0.1%	0.0%	0.1%
NAIL DISORDER	0.0%	0.3%	0.1%
NAUSEA	1.7%	3.6%	2.2%
NEOPLASM, INTESTINAL, METASTATIC	0.0%	0.3%	0.1%
NEOPLASM, MALIGNANT	0.1%	0.0%	0.1%
NEOPLASM, SKIN, BENIGN	0.2%	0.0%	0.2%
NERVOUSNESS	0.0%	1.3%	0.3%
NEUTROPHILS DECREASED	0.0%	0.7%	0.2%
NEUTROPHILS INCREASED	0.2%	0.0%	0.2%
NOCTURIA	0.0%	0.3%	0.1%
NODULE, CUTANEOUS	0.0%	0.3%	0.1%
NONSPECIFIC ST T CHANGE	0.1%	0.0%	0.1%
OBSTRUCTION, AIRWAY, UPPER	0.1%	0.0%	0.1%
OPACITY, LENS	0.1%	0.0%	0.1%
OPACITY, VITREOUS	0.1%	0.0%	0.1%
ORTHOSTATIC EFFECTS	0.8%	0.0%	0.6%
OSTEOARTHRITIS	0.1%	0.0%	0.1%
OTITIS	0.2%	0.3%	0.2%
OTITIS EXTERNA	0.0%	0.3%	0.1%
OTITIS MEDIA	0.0%	0.3%	0.1%
PAIN	0.2%	0.0%	0.2%
PAIN, ABDOMINAL	1.5%	2.3%	1.7%
PAIN, ANKLE	0.2%	0.0%	0.2%
PAIN, ARM	0.5%	0.3%	0.5%
PAIN, BACK	1.8%	1.3%	1.7%
PAIN, BONE	0.2%	0.0%	0.2%
PAIN, BREAST	0.2%	0.0%	0.2%
PAIN, CHEST	1.3%	1.7%	1.4%
PAIN, DENTAL	0.7%	0.7%	0.7%
PAIN, EAR	0.3%	0.7%	0.4%
PAIN, EYE	0.0%	1.0%	0.2%
PAIN, FINGER	0.2%	0.0%	0.2%
PAIN, FLANK	0.3%	0.0%	0.2%
PAIN, FOOT	0.4%	0.7%	0.5%
PAIN, HAND	0.2%	0.0%	0.2%
PAIN, HIP	0.5%	0.0%	0.4%
PAIN, JAW	0.1%	0.0%	0.1%
PAIN, KNEE	0.6%	0.3%	0.5%

Listing of Losartan and Placebo Adverse Event Incidence Rates for Studies 011, 050 and 065 Combined.

	Losartan	Placebo	Total
Number Randomized	985	302	1287
PAIN, LEG	1.0%	0.0%	0.8%
PAIN, MUSCULOSKELETAL	0.5%	0.0%	0.4%
PAIN, NECK	0.4%	0.7%	0.5%
PAIN, POSTOPERATIVE	0.3%	0.3%	0.3%
PAIN, SHOULDER	0.9%	0.3%	0.8%
PAIN, TOE	0.2%	0.0%	0.2%
PAIN, WRIST	0.2%	0.0%	0.2%
PALPITATION	0.7%	0.3%	0.6%
PARESTHESIA	0.8%	0.3%	0.7%
PIT INCREASE	0.1%	0.3%	0.2%
PERVERSION, TASTE	0.1%	0.3%	0.2%
PHARYNGITIS	1.8%	3.0%	2.1%
PHLEBITIS/THROMBOPHLEBITIS	0.0%	0.3%	0.1%
PHOTOPHOBIA	0.0%	0.3%	0.1%
PHOTOPSIA	0.1%	0.0%	0.1%
PHOTOSENSITIVITY	0.1%	0.0%	0.1%
PLATELET COUNT DECREASED	0.1%	0.0%	0.1%
PLATELET COUNT INCREASED	0.2%	0.0%	0.2%
PNEUMONIA	0.2%	0.0%	0.2%
PNEUMONIA, VIRAL	0.1%	0.0%	0.1%
POLYURIA	0.2%	0.0%	0.2%
PVC	0.2%	0.7%	0.3%
PROLONGED QT INTERVAL	0.2%	0.0%	0.2%
PROTEINURIA	0.8%	1.3%	0.9%
PROTHROMBIN TIME INCREASED	0.1%	0.3%	0.2%
PRURITUS	0.6%	0.3%	0.5%
PRURITUS ANI	0.1%	0.0%	0.1%
PRURITUS VULVAE	0.1%	0.0%	0.1%
PYURIA	0.7%	0.7%	0.7%
RADICULOPATHY, LUMBAR	0.1%	0.0%	0.1%
RASH	0.5%	1.3%	0.7%
RAYNAUD'S PHENOMENON	0.1%	0.3%	0.2%
REDNESS, EYE	0.1%	0.0%	0.1%
RETINOPATHY	0.1%	0.0%	0.1%
RHINITIS	0.5%	0.7%	0.5%
RHINITIS, ALLERGIC	0.2%	0.3%	0.2%
RHINORRHEA	0.1%	1.0%	0.3%
RIGHT BUNDLE BRANCH BLOCK	0.1%	0.0%	0.1%
SALIVATION INCREASE	0.1%	0.0%	0.1%
SCIATICA	0.0%	0.3%	0.1%
SCLEROSIS, NUCLEAR	0.2%	0.0%	0.2%
SCOTOMA	0.1%	0.0%	0.1%
SERUM CREATININE INCREASED	0.1%	0.0%	0.1%
SINUS BRADYCARDIA	0.3%	0.0%	0.2%
SINUS DISORDER	1.6%	1.3%	1.6%
SINUS DISORDER, CHRONIC	0.0%	0.3%	0.1%
SINUSITIS	0.9%	0.3%	0.8%
SLEEP DISORDER	0.1%	0.0%	0.1%
SNEEZING	0.4%	0.0%	0.3%
SOMNOLENCE	0.2%	0.3%	0.2%
SPASM	0.1%	0.0%	0.1%
SPRAIN, ARM	0.1%	0.0%	0.1%
SPRAIN, KNEE	0.1%	0.0%	0.1%
SPRAIN, NECK	0.1%	0.0%	0.1%
STIFFNESS	0.5%	0.0%	0.4%
STRAIN	0.2%	0.3%	0.2%
STRAIN, BACK	0.3%	0.7%	0.4%
SWEATING	0.4%	0.3%	0.4%

Listing of Losartan and Placebo Adverse Event Incidence Rates for Studies 011, 050 and 065 Combined.

	Losartan	Placebo	Total
Number Randomized	985	302	1287
SWELLING, JOINT	0.5%	1.0%	0.6%
SYNCOPE	0.2%	0.0%	0.2%
T WAVE INVERSION	0.0%	0.3%	0.1%
TACHYCARDIA	0.5%	0.3%	0.5%
TASTE LOSS	0.1%	0.0%	0.1%
TEARING	0.2%	0.7%	0.3%
TENDINITIS	0.0%	0.7%	0.2%
THIRST	0.2%	0.3%	0.2%
TIC	0.1%	0.3%	0.2%
TINEA CRURIS	0.1%	0.0%	0.1%
TINNITUS	0.5%	0.0%	0.4%
TM JOINT DYSFUNCTION	0.1%	0.0%	0.1%
TONSILLITIS	0.1%	0.0%	0.1%
TOOTH DISORDER	0.1%	0.0%	0.1%
TOOTH ERUPTION DISTURBANCE	0.1%	0.0%	0.1%
TOTAL BILIRUBIN INCREASED	0.3%	0.0%	0.2%
TRAUMA	0.0%	0.7%	0.2%
TRAUMA, CARTILAGE	0.0%	0.3%	0.1%
TYMPANOSCLEROSIS	0.1%	0.0%	0.1%
ULCER, MOUTH	0.1%	0.0%	0.1%
URI	7.8%	6.3%	7.5%
URINARY FREQUENCY	0.5%	0.7%	0.5%
URINARY URGENCY	0.0%	0.3%	0.1%
URINE SEDIMENT ABNORMALITY	0.1%	0.0%	0.1%
URTICARIA	0.2%	0.7%	0.3%
VAGINITIS	0.1%	0.0%	0.1%
VERTIGO	0.6%	0.0%	0.5%
VISUAL ACUITY DECREASED	0.1%	0.0%	0.1%
VOMITING	0.6%	0.3%	0.5%
WARM SENSATION	0.1%	0.7%	0.2%
WEAKNESS, MUSCLE	0.1%	0.3%	0.2%
WEIGHT LOSS	0.1%	0.0%	0.1%
WHEEZING	0.1%	0.0%	0.1%
TOTAL			

Complete Listing of Losartan Adverse Event Incidence by Dose in Nine Trials.

	10 mg	25 mg	50 mg	100 mg	150 mg	variable	25 mg bid	50/100 mg	50 mg bid	Total
Patients Randomized	80	201	341	134	84	382	106	123	31	1482
Patients with at Least 1 AE	41	112	184	53	47	201	60	69	14	786
Percent with at least 1 AE	51%	56%	61%	43%	56%	53%	57%	56%	45%	53%
Adverse Experience										
ABNORMAL SENSATION	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0	0.0%	0	0.1%
ABRASION, CORNEAL	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
ACCOMMODATION DISORDER	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
ACID REGURGITATION	0.0%	0.0%	0.3%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
ACNE	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
ALK. PHOS. INCREASED	0.0%	0.5%	0.3%	0.0%	0.0%	1.0%	0.9%	0.0%	0.0%	0.5%
ALLERGY	0.0%	0.0%	0.6%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%	0.2%
ALOPECIA	1.3%	0.0%	0.3%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%
ALT INCREASED	3.8%	3.0%	1.5%	3.7%	3.6%	1.0%	0.0%	4.9%	6.5%	2.3%
ALTERATION, RETINAL PIGMENT	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
ANGINA PECTORIS	1.3%	0.0%	0.0%	0.0%	0.0%	1.3%	0.0%	1.6%	0.0%	0.5%
ANOREXIA	0.0%	0.5%	0.9%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.3%
ANOSMIA	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.9%	0.0%	0.0%	0.1%
ANXIETY	1.3%	0.5%	0.9%	0.7%	0.0%	0.3%	0.0%	0.0%	0.0%	0.5%
ANXIETY DISORDER	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
APPETITE CHANGE	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
APPETITE INCREASE	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.9%	0.0%	0.0%	0.1%
ARCUS SENILIS	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
ARRHYTHMIA	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.9%	0.0%	0.0%	0.1%
ARTHRALGIA	0.0%	0.0%	0.3%	0.0%	0.0%	0.8%	0.0%	0.0%	0.0%	0.3%
ARTHRITIS	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%	0.9%	0.0%	0.0%	0.2%
AST INCREASED	2.5%	2.0%	1.2%	0.7%	1.2%	0.5%	0.0%	2.4%	6.5%	1.3%
ASTHENIA/FATIGUE	3.8%	2.5%	3.5%	3.0%	4.8%	6.0%	5.7%	1.6%	3.2%	4.0%
ASTHMA	0.0%	0.5%	0.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%
ATAXIA	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%	0.0%	0.0%	0.0%	0.1%
ATRIAL FIBRILLATION	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
AV BLOCK, FIRST DEGREE	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.6%	0.0%	0.1%
AV BLOCK, SECOND DEGREE	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
AXIS DISTURBANCE	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.9%	0.8%	0.0%	0.2%
BACTERIURIA	0.0%	0.5%	0.0%	1.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%
BENIGN PROSTATIC HYPERTROPHY	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.9%	0.0%	0.0%	0.1%
BICARBONATE DECREASED	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	3.2%	0.1%
BLURRED VISION	0.0%	0.5%	0.3%	0.0%	0.0%	0.3%	0.0%	0.8%	0.0%	0.3%
BONE FIXATION DEVICE	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
BOWEL PATTERN CHANGE	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
BRADYCARDIA	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
BRONCHITIS	0.0%	1.5%	0.0%	0.0%	1.2%	0.8%	1.9%	1.6%	3.2%	0.8%
BROWACHE	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
BUN INCREASED	0.0%	0.0%	0.0%	0.0%	0.0%	1.0%	0.0%	0.0%	0.0%	0.3%
BURN	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
BURNING STINGING, EYE	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.4%	0.0%	0.2%
CARBON DIOXIDE INCREASED	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%	0.0%	0.0%	0.0%	0.1%
CARDIOMEGALY	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
CARPAL TUNNEL SYNDROME	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.9%	0.0%	0.0%	0.1%
CELLULITIS	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
CHILLS	0.0%	0.5%	0.6%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%	0.3%
CHOLECYSTITIS	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
CHOLELITHIASIS	1.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
COLD EXTREMITIES	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
COLD SENSATION	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
CONFUSION	0.0%	0.0%	0.0%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%	0.1%
CONGESTION, NASAL	0.0%	1.5%	2.6%	2.2%	3.6%	0.3%	2.8%	1.6%	6.5%	1.8%

Complete Listing of Losartan Adverse Event Incidence by Dose in Nine Trials.

	10 mg	25 mg	50 mg	100 mg	150 mg	variable	25 mg bid	50/100 mg	50 mg bid	Total
CONGESTION, PULMONARY	0.0%	1.0%	0.0%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%
CONGESTION, RESPIRATORY	1.3%	1.0%	0.6%	1.5%	0.0%	0.3%	0.0%	0.8%	0.0%	0.6%
CONJUNCTIVITIS	0.0%	0.0%	0.3%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
CONSTIPATION	1.3%	1.0%	0.3%	0.0%	1.2%	0.5%	0.0%	0.0%	3.2%	0.5%
CONTUSION	1.3%	0.0%	0.0%	0.0%	1.2%	0.3%	0.0%	0.0%	0.0%	0.2%
COSTOCHONDRITIS	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.9%	0.0%	0.0%	0.1%
COUGH	6.3%	4.0%	2.6%	3.0%	3.6%	3.1%	2.8%	4.9%	3.2%	3.4%
CRAMP, MUSCLE	0.0%	1.5%	0.9%	0.0%	0.0%	0.5%	0.9%	2.4%	0.0%	0.8%
CVA	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.9%	0.0%	0.0%	0.1%
DEFECT, RETINAL	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
DEFORMITY, LOWER EXTREMITY	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
DENTAL CARIES	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
DEPRESSION	0.0%	0.0%	0.9%	0.0%	1.2%	0.3%	0.0%	0.8%	0.0%	0.4%
DERMATITIS	0.0%	0.0%	0.3%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
DERMATITIS, CONTACT	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
DERMATOMYCOSIS	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.9%	0.0%	0.0%	0.1%
DIARRHEA	3.8%	2.0%	2.9%	1.5%	2.4%	1.3%	1.9%	1.6%	3.2%	2.1%
DIPLOPIA	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
DISCOMFORT, PHARYNGEAL	0.0%	1.5%	0.3%	0.7%	0.0%	0.3%	0.9%	0.0%	0.0%	0.5%
DISCOMFORT, VISUAL	0.0%	0.5%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
DISORIENTATION	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
DISTENTION, ABDOMINAL	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
DIZZINESS	2.5%	4.5%	4.1%	0.7%	2.4%	6.5%	3.8%	3.3%	3.2%	4.2%
DREAM ABNORMALITY	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.0%	3.2%	0.3%
DRY EYES	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
DRY MOUTH	0.0%	0.0%	0.6%	0.0%	0.0%	0.3%	0.9%	0.0%	0.0%	0.3%
DYSCHYZIA	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
DYSPEPSIA	1.3%	1.0%	0.9%	0.7%	3.6%	1.6%	1.9%	0.8%	0.0%	1.3%
DYSPHASIA	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
DYSPNEA	0.0%	0.0%	0.9%	0.0%	0.0%	0.3%	0.0%	2.4%	0.0%	0.5%
DYSPNEA, EXERTIONAL	1.3%	0.0%	0.0%	0.0%	1.2%	0.3%	0.0%	0.0%	0.0%	0.2%
DYSURIA	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
ECZEMA	0.0%	0.0%	0.0%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
EDEMA, EYELID	0.0%	0.0%	0.0%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%	0.1%
EDEMA, FACIAL	0.0%	0.0%	0.0%	0.0%	1.2%	0.3%	0.0%	0.0%	6.0%	0.1%
EDEMA/SWELLING	1.3%	1.5%	2.9%	0.7%	0.0%	2.6%	0.0%	2.4%	0.0%	1.9%
EMBOLISM/INFARCTION, PULMONARY	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
EMOTIONAL CHANGES	0.0%	0.0%	0.0%	0.7%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
ENTRAPMENT, NERVE	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
EOSINOPHILS INCREASED	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.0%	0.0%	0.2%
EPISTAXIS	1.3%	0.5%	1.2%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.5%
ERYTHEMA	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
ESOPHAGITIS	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
EUSTACHIAN TUBE DISORDER	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
EXCORIATION	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
EXTRAOCULAR MUSCLE IMBALANCE	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
EYE MOVEMENT DISORDER	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
FALLING	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.9%	0.0%	0.0%	0.1%
FASCICULATION	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
FASTING GLUCOSE INCREASED	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%	0.0%	0.0%	0.0%	0.1%
FECAL ABNORMALITY	0.0%	0.5%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
FEVER	0.0%	0.5%	0.6%	0.7%	2.4%	0.0%	0.9%	1.6%	0.0%	0.6%
FLATULENCE	0.0%	0.0%	0.0%	0.0%	0.0%	1.0%	0.0%	0.0%	0.0%	0.3%
FLU LIKE ILLNESS	0.0%	0.0%	0.6%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.2%
FLUID OVERLOAD	0.0%	0.5%	0.9%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%
FLUSHING	0.0%	0.0%	1.2%	0.7%	3.6%	0.3%	0.0%	0.8%	0.0%	0.7%
FOLLICULITIS	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%

Complete Listing of Losartan Adverse Event Incidence by Dose in Nine Trials.

	10 mg	25 mg	50 mg	100 mg	150 mg	variable	25 mg bid	50/100 mg	50 mg bid	Total
INFECTION, RESPIRATORY	0.0%	0.0%	0.3%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
INFECTION, SKIN	1.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
INFECTION, ULCER, SKIN	0.0%	0.0%	0.0%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%	0.1%
INFECTION, URINARY TRACT	0.0%	0.5%	0.6%	2.2%	0.0%	0.8%	0.9%	0.0%	0.0%	0.7%
INFECTION, VIRAL	0.0%	0.0%	0.3%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
INFLAMMATION, EYELID	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
INFLUENZA	0.0%	0.0%	0.0%	0.0%	1.2%	2.4%	0.9%	0.8%	3.2%	0.9%
INFUSED VEIN COMPLICATION	0.0%	0.0%	0.0%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
INSOMNIA	1.3%	1.5%	1.8%	0.7%	0.0%	1.3%	0.9%	0.0%	0.0%	1.1%
INTRAOCULAR PRES. INCREASE	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
IRRITABILITY	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
IRRITABLE BOWEL SYNDROME	1.3%	0.5%	0.0%	0.0%	0.0%	0.0%	0.9%	0.0%	0.0%	0.2%
IRRITATION, NASAL	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
ISCHEMIA, MYOCARDIAL	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
ITCHING, EYE	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	1.6%	0.0%	0.2%
KERATOSIS, SEBORRHEIC	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.6%	0.0%	0.1%
LACERATION	1.3%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
LARYNGITIS	0.0%	0.0%	0.3%	0.0%	1.2%	0.0%	0.0%	0.8%	0.0%	0.2%
LDH INCREASED	0.0%	0.0%	0.0%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%	0.1%
LEFT ANTERIOR HEMIBLOCK	1.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
LEFT ATRIAL HYPERTROPHY	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
LEFT BUNDLE BRANCH BLOCK	1.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
LEFT VENTRICULAR HYPERTROPHY	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
LESION, SKIN	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
LEUKOCYTE COUNT INCREASED	0.0%	0.0%	0.3%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
LEUKOCYTES DECREASED	0.0%	1.0%	0.0%	0.7%	1.2%	0.0%	0.0%	0.0%	0.0%	0.3%
LIBIDO DECREASED	1.3%	0.5%	0.6%	0.0%	0.0%	0.0%	1.9%	0.0%	0.0%	0.4%
LIVER PALPABLE	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
LYMPHADENOPATHY	0.0%	0.0%	0.0%	1.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
LYMPHOCYTES DECREASED	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
LYMPHOCYTES INCREASED	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
MALAISE	0.0%	0.5%	0.0%	0.0%	1.2%	0.3%	0.0%	0.0%	0.0%	0.2%
MASS, BREAST	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
MEMORY IMPAIRMENT	0.0%	0.0%	0.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
MENSTRUATION DISORDER	0.0%	1.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%
MURMUR, HEART	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
MYALGIA	1.3%	0.5%	0.6%	0.7%	1.2%	0.5%	1.9%	0.8%	3.2%	0.8%
MYOCARDIAL INFARCTION	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
MYOPIA	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
NAUSEA	1.3%	2.0%	2.6%	0.7%	0.0%	2.9%	0.0%	2.4%	3.2%	2.0%
NEOPLASM, MALIGNANT	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.9%	0.0%	0.0%	0.1%
NEOPLASM, SKIN, BENIGN	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
NEUTROPHILS INCREASED	0.0%	0.0%	0.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
NONSPECIFIC ST-T CHANGE	1.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
OBSTRUCTION, AIRWAY, UPPER	0.0%	0.0%	0.0%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
OCCLUSION, ARTERIAL	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
OPACITY, LENS	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
OPACITY, VITREOUS	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
ORTHOSTATIC EFFECTS	0.0%	0.0%	0.6%	2.2%	3.6%	1.0%	0.0%	0.0%	0.0%	0.8%
OSTEOARTHRITIS	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
OSTEOARTHRITIS, ELBOW	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
OTITIS	0.0%	0.5%	0.0%	0.0%	0.0%	0.3%	0.9%	0.0%	0.0%	0.2%
OTITIS MEDIA	0.0%	0.0%	0.0%	0.7%	0.0%	0.3%	0.0%	0.0%	3.2%	0.2%
PAIN	0.0%	0.0%	0.6%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.2%
PAIN, ABDOMINAL	3.8%	1.0%	2.1%	1.5%	1.2%	2.4%	0.0%	0.8%	0.0%	1.7%
PAIN, ANKLE	0.0%	0.5%	0.3%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.2%
PAIN, ARM	0.0%	0.5%	0.3%	0.0%	0.0%	0.8%	0.9%	1.6%	0.0%	0.5%
PAIN, BACK	3.8%	2.0%	2.1%	1.5%	2.4%	2.1%	0.9%	0.8%	0.0%	1.9%

Complete Listing of Losartan Adverse Event Incidence by Dose in Nine Trials.

	10 mg	25 mg	50 mg	100 mg	150 mg	variable	25 mg bid	50/100 mg	50 mg bid	Total
PAIN, BONE	0.0%	0.0%	0.0%	0.7%	0.0%	0.3%	0.0%	0.8%	0.0%	0.2%
PAIN, BREAST	1.3%	0.5%	0.0%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%
PAIN, CHEST	1.3%	2.0%	1.2%	0.7%	1.2%	1.6%	1.9%	0.0%	0.0%	1.3%
PAIN, DENTAL	0.0%	0.0%	0.9%	1.5%	0.0%	0.3%	0.9%	0.8%	0.0%	0.5%
PAIN, EAR	0.0%	0.5%	0.3%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%	0.2%
PAIN, FINGER	0.0%	0.0%	0.0%	0.7%	0.0%	0.3%	0.9%	0.0%	0.0%	0.2%
PAIN, FLANK	0.0%	0.0%	0.3%	1.5%	1.2%	0.0%	0.0%	0.0%	0.0%	0.3%
PAIN, FOOT	0.0%	0.0%	0.6%	0.7%	0.0%	0.3%	0.0%	0.8%	0.0%	0.3%
PAIN, HAND	0.0%	0.0%	0.0%	0.0%	1.2%	0.0%	0.9%	0.0%	0.0%	0.1%
PAIN, HIP	2.5%	0.0%	0.6%	0.0%	0.0%	0.5%	0.0%	0.8%	0.0%	0.5%
PAIN, JAW	0.0%	0.0%	0.0%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%	0.1%
PAIN, KNEE	0.0%	2.5%	0.6%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%
PAIN, LEG	2.5%	1.0%	1.5%	0.7%	0.0%	0.5%	0.0%	1.6%	0.0%	0.9%
PAIN, MUSCULOSKELETAL	0.0%	0.5%	0.6%	1.5%	0.0%	0.3%	0.9%	0.8%	0.0%	0.5%
PAIN, NECK	0.0%	0.5%	0.6%	0.7%	0.0%	0.5%	0.0%	0.0%	0.0%	0.4%
PAIN, PLEURITIC	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
PAIN, POSTOPERATIVE	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.9%	0.8%	0.0%	0.2%
PAIN, SHOULDER	1.3%	1.0%	1.2%	0.0%	2.4%	0.3%	0.0%	0.0%	0.0%	0.7%
PAIN, TOE	0.0%	0.5%	0.3%	0.0%	0.0%	0.3%	0.0%	0.8%	0.0%	0.3%
PAIN, WRIST	0.0%	0.5%	0.3%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.2%
PALLOR	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
PALPITATION	0.0%	1.0%	0.9%	0.0%	0.0%	0.3%	1.9%	0.8%	3.2%	0.7%
PANIC DISORDER	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
PARANOID DISORDER	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
PARESTHESIA	0.0%	1.5%	0.9%	0.0%	1.2%	0.3%	0.0%	0.8%	0.0%	0.6%
PERCUSSION ABNORMAL, LUNG	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
PERVERSION, TASTE	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.9%	0.0%	0.0%	0.1%
PHARYNGITIS	1.3%	2.0%	4.1%	0.7%	0.0%	1.6%	0.0%	0.0%	3.2%	1.8%
PHOTOPSIA	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
PHOTOSENSITIVITY	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
PLATELET COUNT DECREASED	0.0%	0.5%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
PLATELET COUNT INCREASED	1.3%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
PNEUMONIA	0.0%	0.5%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
PNEUMONIA, VIRAL	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
POLYURIA	0.0%	0.0%	0.3%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%	0.1%
PROLONGED QT INTERVAL	0.0%	0.0%	0.3%	0.0%	0.0%	0.3%	0.0%	0.8%	0.0%	0.2%
PROTEINURIA	1.3%	0.5%	1.2%	0.7%	0.0%	0.8%	0.0%	0.8%	0.0%	0.7%
PROTHROMBIN TIME INCREASED	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
PRURITUS	1.3%	1.0%	0.3%	0.0%	0.0%	0.8%	0.9%	0.8%	0.0%	0.6%
PRURITUS ANI	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
PRURITUS VULVAE	0.0%	0.0%	0.0%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
PSORIASIS	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
PTT INCREASED	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
PVC	1.3%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
PYURIA	1.3%	0.5%	0.3%	0.7%	2.4%	0.0%	0.0%	0.8%	0.0%	0.5%
RADICULOPATHY, LUMBAR	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
RASH	0.0%	0.5%	0.6%	0.0%	0.0%	0.8%	0.9%	0.8%	0.0%	0.5%
RAYNAUD'S PHENOMENON	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
REDNESS, EYE	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
REFLUX ESOPHAGITIS	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
RETINOPATHY	1.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
RETINOPATHY, HYPERTENSIVE	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
RETINOPATHY, KEITH WAGENER, (II)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
RHINITIS	1.3%	0.5%	0.6%	0.0%	0.0%	0.8%	0.9%	0.0%	0.0%	0.5%
RHINITIS, ALLERGIC	0.0%	0.0%	0.3%	0.0%	0.0%	0.8%	0.0%	0.8%	0.0%	0.3%
RHINORRHEA	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%	0.9%	0.0%	0.0%	0.2%
RIGHT BUNDLE BRANCH BLOCK	0.0%	0.0%	0.0%	0.7%	0.0%	0.5%	0.0%	0.0%	0.0%	0.2%

Complete Listing of Losartan Adverse Event Incidence by Dose in Nine Trials.

	10 mg	25 mg	50 mg	100 mg	150 mg	variable	25 mg bid	50/100 mg	50 mg bid	Total
SALIVATION INCREASE	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
SALPINGO OOPHORITIS	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
SCLEROSIS, NUCLEAR	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
SCOTOMA	0.0%	0.0%	0.0%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
SERUM CREATININE INCREASED	0.0%	0.0%	0.3%	0.0%	0.0%	1.3%	0.0%	0.0%	0.0%	0.4%
SINUS ARRHYTHMIA	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	3.2%	0.1%
SINUS BRADYCARDIA	0.0%	0.0%	0.3%	0.7%	0.0%	0.3%	0.0%	0.8%	0.0%	0.3%
SINUS DISORDER	2.5%	1.0%	1.5%	1.5%	2.4%	0.3%	0.9%	2.4%	0.0%	1.2%
SINUS TACHYCARDIA	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
SINUSITIS	0.0%	1.0%	1.5%	0.7%	0.0%	0.5%	0.9%	0.8%	0.0%	0.8%
SLEEP DISORDER	0.0%	0.5%	0.0%	0.0%	0.0%	1.0%	0.0%	0.0%	0.0%	0.3%
SNEEZING	1.3%	0.5%	0.3%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%	0.3%
SOMNOLENCE	0.0%	0.0%	0.0%	0.7%	0.6%	1.8%	0.0%	0.8%	0.0%	0.6%
SPASM	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.9%	0.0%	0.0%	0.1%
SPRAIN, ARM	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
SPRAIN, KNEE	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
SPRAIN, NECK	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
STIFFNESS	0.0%	0.5%	0.3%	0.0%	0.0%	0.8%	1.9%	0.8%	0.0%	0.5%
STOMATITIS, APHTHOUS	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
STRAIN	1.3%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
STRAIN, BACK	0.0%	0.0%	0.3%	0.0%	0.0%	0.3%	1.9%	0.0%	0.0%	0.3%
SWEATING	0.0%	0.0%	0.9%	0.0%	0.0%	0.5%	0.9%	0.0%	0.0%	0.4%
SWELLING, JOINT	0.0%	1.5%	0.3%	0.0%	0.0%	0.3%	0.0%	0.8%	0.0%	0.4%
SYNCOPE	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	1.6%	0.0%	0.2%
T WAVE INVERSION	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%	0.0%	0.0%	0.0%	0.1%
TACHYCARDIA	0.0%	0.0%	0.9%	0.0%	1.2%	0.5%	0.0%	0.8%	0.0%	0.5%
TASTE LOSS	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.9%	0.0%	0.0%	0.1%
TEARING	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
TENDINITIS	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%	0.0%	0.0%	0.0%	0.1%
THIRST	0.0%	0.0%	0.0%	0.0%	1.2%	0.5%	0.9%	0.0%	0.0%	0.3%
TIC	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	0.1%
TINEA CRURIS	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
TINNITUS	0.0%	0.0%	1.2%	0.7%	0.0%	0.5%	0.0%	0.8%	0.0%	0.5%
TM JOINT DYSFUNCTION	1.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
TONSILLITIS	0.0%	0.0%	0.3%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
TOOTH DISORDER	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.9%	0.0%	0.0%	0.1%
TOOTH ERUPTION DISTURBANCE	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
TOTAL BILIRUBIN INCREASED	1.3%	0.0%	0.0%	0.0%	2.4%	0.0%	0.0%	0.0%	0.0%	0.2%
TRAUMA	0.0%	0.5%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
TYMPANOSCLEROSIS	0.0%	0.0%	0.0%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%	0.1%
ULCER, DUODENAL	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
ULCER, MOUTH	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
ULCER, PEPTIC	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
URI	1.3%	9.5%	7.0%	6.0%	8.3%	7.1%	10.4%	8.1%	9.7%	7.4%
URINARY FREQUENCY	1.3%	0.0%	0.3%	0.0%	1.2%	0.0%	1.9%	0.0%	0.0%	0.3%
URINARY INCONTINENCE	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
URINE SEDIMENT ABNORMALITY	0.0%	0.0%	0.0%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
URTICARIA	0.0%	0.0%	0.3%	0.0%	0.0%	0.3%	0.9%	0.0%	0.0%	0.2%
VAGINITIS	1.3%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.1%
VERTIGO	1.3%	0.5%	0.0%	2.2%	2.4%	1.3%	0.0%	0.0%	0.0%	0.8%
VISUAL ACUITY DECREASED	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
VOMITING	0.0%	0.5%	0.6%	0.7%	0.0%	0.8%	0.0%	1.6%	0.0%	0.6%
WARM SENSATION	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.9%	0.0%	0.0%	0.1%
WEAKNESS, MUSCLE	0.0%	0.0%	0.3%	0.0%	0.0%	0.5%	0.0%	0.0%	0.0%	0.2%
WEIGHT LOSS	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
WHEEZING	0.0%	0.0%	0.0%	0.0%	1.2%	0.0%	0.0%	0.0%	0.0%	0.1%
TOTAL (Number of Events)	86	232	409	116	100	450	124	164	29	1710

Serious Nonfatal Adverse Experiences in Hypertensive Patients From All Sources

Protocol # / Study #	Patient #	Age/Sex	Treatment	Dose (mg)	Relative Day of Onset	Adverse Experience	Discontinued	Outcome
011-002	0033	56/M	Los	150	1	Pain, Chest	Yes	Recovered
011-004	0070	53/M	Los	50	289	Pain, Bone	No	Recovered
011-019	0381	52/M	Los	50	542*	Myocardial Infarction	No	Present
011-022	0442	64/F	Los	100	293	Depression	No	Recovered
			Los	50	399	Depression	No	Recovered
			Los	50	452	Depression	No	Recovered
			Los	50	467	Depression	No	Recovered
011-022	0450	56/M	Los	50	525*	Hemorrhage, Gastrointestine	No	Recovered
011-032	0882	53/F	Los	50	453	Aneurysm	Yes	Present
011-038	0783	61/M	Los/HCTZ	100/12.5	218	Diarrhea	Yes	Recovered
021-001	0006	69/F	Off-drug	--	62	Allergy	No	Recovered
011-002	0027	57/M	Los/HCTZ	150/25	403	Neoplasm, Skin, Malignant	No	Present
011-002	0027	58/M	Los/HCTZ	150/25	458*	Bacteremia	No	Present
011-003	0048	36/M	Los/HCTZ	100/12.5	185	Pneumonia	No	Recovered
021-004	0072	63/F	Los	50	363	Pneumonia	No	Recovered
			Los	50	363	Sinusitis	No	Recovered
011-004	0071	49/M	Los	50	237	Neoplasm, Skin, Malignant	No	Recovered
011-004	0071	50/M	Los/HCTZ	150/12.5	362	Bursitis	No	Recovered
011-005	0095	51/M	Los	100	108	Angina Pectoris	Yes	Recovered
			Los	100	108	Supraventricular Tachycard.	Yes	Recovered
011-019	0399	64/M	Los	10	15	Edema Swelling	Yes	Present
					32	Angina Pectoris	Yes	Present
					32	Dyspnea, Exertional	Yes	Present
011-022	0444	73/F	Los	150	357	CVA	No	Recovered
			Los	150	357	Paresis	No	Present
011-024	0495	48/F	Los/HCTZ	100/12.5	409*	Neoplasm, Uterine, Benign	No	Recovered
011-02*	0508	66/M	Los/HCTZ	150/12.5	498	Melanoma	No	Present
011-025	0508	67/M	Los/HCTZ	50/12.5	594*	Neoplasm, Intestinal, Malig	No	Present
011-025	0510	40/M	Los	50	534	Hearing Loss	Yes	Present
011-025	0517	57/M	Los	100	333	Arthropathy, Traumatic	No	Recovered
011-026	0527	53/M	Off-drug	--	322	Effusion, Pericardial	No	Recovered
011-026	0530	52/F	Los/HCTZ	100/25	247	Cholelithiasis	No	Recovered
011-027	0548	52/M	Los	150	28	Hepatitis, Viral	Yes	Recovered
			Los	150	28	Serum Bilirubin Increased	Yes	N/A
			Los	150	28	AST Increased	Yes	N/A
			Los	150	28	ALT Increased	Yes	N/A
			Los	150	30	Asthemia Fatigue	Yes	Recovered
			Los	150	30	Malaise	Yes	Recovered
			Los	150	30	Fever	Yes	Recovered
			Los	150	34	Serum Bilirubin Increased	Yes	N/A
			Los	150	34	AST Increased	Yes	N/A
			Los	150	34	ALT Increased	Yes	N/A
			Los	150	34	GGT Increased	Yes	N/A
			Los	150	34	LDH Increased	Yes	N/A
			Los	150	34	Hep. A Antibody Positive	Yes	N/A
			Los	150	35	Serum Bilirubin Increased	Yes	N/A
			Los	150	35	AST Increased	Yes	N/A
			Los	150	35	ALT Increased	Yes	N/A
			Los	150	35	GGT Increased	Yes	N/A
Off-drug	--	39	Serum Bilirubin Increased	Yes	N/A			
Off-drug	--	39	AST Increased	Yes	N/A			
Off-drug	--	39	ALT Increased	Yes	N/A			
Off-drug	--	42	Serum Bilirubin Increased	Yes	N/A			
Off-drug	--	42	AST Increased	Yes	N/A			
Off-drug	--	42	ALT Increased	Yes	N/A			
011-028	0577	/F	Los	50	396*	Neoplasm, Breast, Malig	No	Recovered
011-028	0578	60/F	Los	50	648*	Atrial Fibrillation	No	Present
011-030	0615	54/M	Los/HCTZ/El	100/25/5	644*	Pain, Chest	No	Recovered
011-032	0652	33/M	Los	100	101	Tear, Ligament	No	Recovered
011-032	0655	29/M	Los	50	101	Pain, Chest	No	Recovered
			Los	50	102	T-Wave Abnormality	No	--

Serious Nonfatal Adverse Experiences in Hypertensive Patients From All Sources

Protocol # / Study #	Patient #	Age/Sex	Treatment	Dose (mg)	Relative Day of Onset	Adverse Experience	Discontinued	Outcome
011-032	0656	51/M	Los/HCTZ	100/25	369	Atrial Fibrillation	No	Recovered
011-032	0666	58/F	Los	100	66	Neoplasm, Skin, Malignant	Yes	Present
011-032	0668	49/M	Los/HCTZ	150/12.5	338	Detachment, Retinal	No	Recovered
011-032	0668	51/M	Los/HCTZ	50/12.5	576*	Detachment, Retinal	No	Recovered
011-034	0705	47/M	Los/HCTZ	150/25	403*	Intervertebral Disc Disorder	No	Recovered
011-039	0818	53/M	Los	50	399	Atrial Fibrillation	Yes	--
			Los	50	419	Dyspnea	Yes	Present
011-040	0828	65/M	Off-drug	--	133	Neoplasm, Skin, Malignant	No	Recovered
011-040	0832	59/F	Los/HCTZ	100/12.5	274*	Pain, Leg	No	Present
011-040	0832	61/F	Los/HCTZ	100/12.5	381*	Hematuria	Yes	Present
			Los/HCTZ	100/12.5	464*	Neoplasm, Bladder, Malignant	Yes	Present
011-040	0833	70/M	Los/HCTZ/Fel	150/25/5	493*	Neoplasm, Prostate, Malignant	No	Present
044-001	3021	60/M	Los/HCTZ	50/6.25	194	Syncope	No	Recovered
044-001	3026	63/M	Los/HCTZ/Fel	50/12.5/12.5	200*	Neoplasm, Prostate, Benign	No	Present
			Los/HCTZ/Fel	50/12.5/12.5	215*	Premature Ventric. Contract.	No	Recovered
044-001	3240	41/F	Los/HCTZ/Fel	50/12.5/10	91*	Myocardial Infarction	Yes	Recovered
044-006	3083	61/F	Los	50	34*	Syncope	No	Recovered
044-006	3095	57/F	Los	50	107*	Myocardial Infarction	Yes	Recovered
044-007	3125	59/F	Los	100	66	Salpingo-Oophoritis	Yes	Present
044-008	3142	37/M	Off-drug	--	97	Gout	Yes	Present
045-006	4189	57/M	Los	100	78	Embolism Infarction, Pulm.	No	Recovered
			Los	100	78	Pain, Pleuritic	No	Recovered
045-009	4129	70/F	Los	50	2	Pain, Abdom. Lat.	Yes	Present
045-012	4203	59/M	Los	50	183*	Myocardial Infarction	Yes	Recovered
048-010	0363	41/F	Los	50	24*	Hypoglycemia	Yes	Recovered
048-011	6064	57/M	Los/HCTZ	50/6.25	67	Hemophthalmos	Yes	Present
			Los/HCTZ	50/6.25	67	Edema, Macular	Yes	Present
048-012	6343	49/F	Los	50	70	Syncope	No	Recovered
			Los	50	70	Paresthesia	No	Recovered
048-013	0535	53/M	Los/HCTZ	50/12.5	148*	Lymphoma	Yes	Present
048-014	6281	71/F	Los/HCTZ	50/6.25	7*	Atrial Fibrillation	No	Recovered
			Los/HCTZ	50/6.25	7*	Congestion, Pulmonary	No	Recovered
			Los/HCTZ	50/6.25	7*	Pain, Chest	No	Recovered
			Los/HCTZ	50/6.25	7*	Tachycardia	No	Recovered
048-014	0782	61/F	Los	50	151*	Cholecystitis	No	Recovered
048-015	6231	49/M	Los/HCTZ	50/12.5	89	Atrial Fibrillation	No	Recovered
			Los/HCTZ	50/12.5	101	Heart Disorder, Ischemic	No	Present
048-016	6291	63/M	Los/HCTZ	50/6.25	82	Pneumonia	No	Recovered
048-016	6304	51/M	Los/HCTZ	50/6.25	112	Encephalopathy, Hyperten.	Yes	Recovered (Death***)
048-017	6431	48/M	Los/HCTZ	50/12.5	43	Dizziness	Yes	Recovered
			Los/HCTZ	50/12.5	43	Nausea	Yes	Recovered
			Los/HCTZ	50/12.5	43	Vomiting	Yes	Recovered
			Los/HCTZ	50/12.5	43	Sweating	Yes	Recovered
048-023	6115	54/M	Off-drug	--	12	Colic, Renal	No	Recovered
048-024	6417	54/F	Los	50	7	Headache	No	Recovered
048-024	6439	51/M	Los/HCTZ	50/25	209*	Hematoma	Yes	Recovered
			Los/HCTZ	50/25	210*	Hypokalemia	Yes	Recovered
			Los/HCTZ	50/25	210*	Creatine Phosphokin. Inc.	Yes	Recovered
			Los/HCTZ	50/25	210*	Liver Function Abnorm.	Yes	Unknown
			Los/HCTZ	50/25	210*	Hyperbilirubinemia	Yes	Unknown
			Los/HCTZ	50/25	210*	Serum Creatinine Increase	Yes	Unknown
049-004	7102	55/M	Off-drug	--	10	Hypotension	Yes	Recovered
049-007	7137	50/F	Los/HCTZ	100/25	74	Gallbladder Disorder	No	Recovered
049-008	7156	48/M	Los/HCTZ	25/25	60	Urolithiasis	No	Recovered
049-010	7172	58/M	Off-drug	--	209	Hemiplegia	No	Present
049-013	7214	48/F	Los/HCTZ/Fel	50/6.25/5	261*	Myocardial Infarction	Yes	Present
049-014	7236	48/M	Los	50	59	Urolithiasis	No	Recovered

Serious Nonfatal Adverse Experiences in Hypertensive Patients From All Sources

Protocol # / Study #	Patient #	Age/Sex	Treatment	Dose (mg)	Relative Day of Onset	Adverse Experience	Discontinued	Outcome
049-015	7251	50/M	Los/HCTZ	50/25	58	Fracture, Ankle	Yes	Present
049-016	7447	49/M	Los/HCTZ	50/12.5	222*	Neoplasm, Metastatic	Yes	Present
			Los/HCTZ	50/12.5	222*	Neoplasm, Lung, Malignant	Yes	Present
049-017	7279	52/M	Los	50	267	Neoplasm, Tongue, Malig	Yes	Present
049-017	7280	62/M	Los/HCTZ	25/25	48	Lung Neoplasm, Malignant	Yes	Present
049-017	7288	34/F	Los/HCTZ	50/25	38	Neoplasm, Uterine, Benign	No	Recovered
			Los/HCTZ	50/25	40	Hemorrhage, Vaginal	No	Recovered
049-023	7411	61/M	Off-drug	--	293	Neoplasm, Kidney, Malig	Yes	Recovered
049-024	7418	64/M	Los/HCTZ	100/25	42	Neoplasm, Intestinal, Malig	Yes	Still Present
049-024	7425	51/M	Los	50	257*	Urolithiasis	No	Recovered
049-024	7427	41/M	Los/HCTZ	25/25	21	Anxiety	Yes	Present
			Los/HCTZ	25/25	21	Depression	Yes	Present
050-002	2020	75/M	Los	50	36	Angina Pectoris	Yes	Present
050-002	2022	66/M	Los	50	336	Neoplasm, Prostate, Malig	No	Present
050-003	2042	62/M	Los	50	217	Obstruction, Carotid Artery	Yes	Present
050-005	2084	54/M	Los	50	36	Tachycardia	No	Recovered
050-007	2109	39/M	Los/HCTZ	50/6.25	112*	Intervertebral Disc Disorder	No	Recovered
050-007	2121	60/M	Los/HCTZ/El	50/12.5/5	134*	Pain, Chest	Yes	Present
050-009	2161	44/F	Los	50	17	Pain, Abdominal	No	Recovered
			Los	50	17	Menstruation Disorder	No	Recovered
050-010	2170	45/F	Los	50	1	Dysphasia	Yes	Recovered
			Los	50	1	Hemiparesis	Yes	Recovered
050-013	2226	32/M	Off-drug**	--	323	Suicide Attempt	Yes	Recovered
050-014	2246	54/M	Los	50	127	Urolithiasis	No	Recovered
050-015	2266	50/F	Los	50	32	Angina Pectoris	Yes	Recovered
050-017	2289	60/M	Los	50	35	Hernia, Inguinal	No	Recovered
050-018	2316	47/F	Los	100	64	Dyspnea	Yes	Recovered
050-021	2373	59/M	Los/HCTZ/El	50/12.5/5	197	Myocardial Infarction	Yes	Recovered
050-023	2397	75/M	Los	50	5	Myocardial Infarction	Yes	Recovered
			Los	50	5	Heart Failure	Yes	Present
054-004	8095	48 M	Los/HCTZ	50/12.5	81*	Intervertebral Disc Disorder	No	Recovered
054-005	8120	66/M	Los/HCTZ	50/12.5	5*	Myocardial Infarction	No	Present
054-006	8153	42/F	Los/HCTZ	50/6.25	5*	Bronchitis	Yes	Recovered
054-011	8254	72/M	Los/HCTZ	50/6.25	204*	Neoplasm, Prostate, Malig	No	Present
054-015	8330	39/F	Los/HCTZ	50/6.25	271*	Neoplasm, Uterine, Malig	No	Recovered
054-018	8388	55/F	Los/HCTZ	50/6.25	101*	Contusion	No	Present
			Los/HCTZ	50/6.25	101*	Fracture, Rib	No	Present
054-019	8403	54/M	Los/HCTZ/El	50/12.5/5	255*	Myocardial Infarction	No	Present
054-019	8871	71/F	Los/HCTZ	50/6.25	273*	Neoplasm, Skin, Malignant	No	Recovered
054-019	8898	78 M	Los/HCTZ	50/6.25	83*	Cholecystitis	No	Recovered
054-020	8433	70/M	Los/HCTZ	50/50	19*	Neoplasm, Prostate, Malig	Yes	Present
054-022	8473	57/F	Los/HCTZ	50/12.5	139*	Fracture, Tibia, Lt.	No	Recovered
054-025	8521	67/M	Los/HCTZ	50/6.25	62*	Trauma, Muscle	No	Recovered
054-026	8560	44/F	Los/HCTZ/El	50/12.5/5	279*	Ulcer, Peptic	No	Recovered
			Los/HCTZ/El	50/12.5/5	279*	Adhesion, Peritoneal	No	Recovered
			Los/HCTZ/El	50/12.5/5	279*	Obstruction, Intestinal	No	Recovered
054-027	8562	70/M	Los/HCTZ	50/12.5	86*	Myocardial Infarction	Yes	Recovered
054-029	8602	70/M	Los/HCTZ	50/6.25	NA	Hernia, Inguinal	No	Recovered
054-035	8729	67/M	Los/HCTZ/El	50/12.5/5	50*	Benign Prostatic Hypertroph	No	Recovered
054-035	8733	59/M	Los/HCTZ	50/6.25	115*	Pain, Back	No	Present
054-035	8733	59/M	Los/HCTZ	50/6.25	179*	Obstruction, Intestinal	No	Recovered
054-038	8788	54 F	Los/HCTZ	50/12.5	56*	Bronchitis	No	Present
054-038	8788	54 F	Los/HCTZ	50/12.5	159*	Pain, Chest	No	Present
054-038	8792	54 F	Los/HCTZ	50/6.25	227*	Cholecystitis, Chronic	No	Recovered
054-038	8793	42/F	Off-drug	--	6	Pain, Chest	Yes	Recovered
054-039	8804	68/M	Los/HCTZ	50/6.25	85	Strain	No	Recovered

Serious Nonfatal Adverse Experiences in Hypertensive Patients From All Sources

Protocol # / Study #	Patient #	Age/Sex	Treatment	Dose (mg)	Relative Day of Onset	Adverse Experience	Discontinued	Outcome
055-010	5171	68/F	Los	50	39*	CVA	Yes	Recovered
055-010	5188	68/F	Los	100	82	Headache	No	Recovered
			Los	100	82	Influenza	No	Recovered
			Los	100	85	Hypokalemia	No	N/A
055-012	5307	67/M	Los	100	N/A	Malaise	Unknown	Unknown
055-012	5308	65/F	Los	50	66*	Pain, Chest	No	Recovered
055-015	5318	88/M	Los	100	125*	Falling	No	Recovered
056-001	3506	67/M	Los	100	254*	Neoplasm, Prostate, Malignant	Yes	Present
056-001	3559	74/M	Los	50	28*	Cholelithiasis	No	Recovered
			Los	50	28*	Jaundice	No	Recovered
056-015	3683	63/M	Los/Fel	100/10	206	Myocardial Infarction	No	Recovered
059-001	5501	38/M	Los	100	29	Seizure Disorder	Yes	Recovered
059-003	5525	44/M	Los/HCTZ	100/25	70	Pneumonia	Yes	Present
			Los/HCTZ	100/25	75	Hypotension	No	Present
			Los/HCTZ	100/25	76	Sinus Tachycardia	No	--
			Off-drug	--	76	Hemoptysis	No	Recovered
			Off-drug	--	76	Septicemia	No	Present
059-003	5527	50/M	Los/HCTZ/Fel	100/25/10	146	Hyperglycemia	No	Recovered
059-006	5551	41/M	Los/HCTZ/Fel	100/25/10	303	Occlusion, Vascular, Retinal	No	Recovered
059-021	5725	56/F	Los/HCTZ ¹	100/12.5	48	PVC	Yes	--
			Los Aten	100/25	48	Syncope	Yes	Recovered
			Los Aten	100/25	48	Premature Beat	No	Recovered
			Los Aten	100/25	48	Palpitation	No	Recovered
			Los Aten	100/25	48	Pulse Abnormality	No	Recovered
			Los Aten	100/25	49	Palpitation	No	Recovered
065-002	1109	41/F	Los	50	193*	Pain, Chest	No	Present
065-002	1110	45/M	Off-drug	--	34	Pain, Abdominal	No	Recovered
			Off-drug	--	34	Pain, Chest	No	Recovered
065-003	1607	40/M	Los	50	16	Pain, Chest	Yes	Recovered
			Los	50	16	Pain, Arm	Yes	Recovered
065-007	1673	61/M	Los Aten	100/100	115*	Obstruction, Carotid Artery	Yes	Recovered
065-009	1173	74/F	Off-drug	--	82*	Phlebitis/Thrombophlebitis	No	Recovered
065-011	1582	65/M	Unknown	--	40	Hematuria	No	Present
065-017	1336	60/M	Los	50	83*	Hypertension	Yes	Present
065-017	1338	66/M	Los	50	21*	Angina Pectoris	Yes	Recovered
065-021	1314	42/M	Los	25	68	Fracture, Patella, Right	No	Present
			Off-drug	--	69	Bone Fixation Device	No	Recovered
065-021	1317	56/M	Los/Fel	100/5	165*	Myocardial Infarction	Unknown	Present
065-029	1194	64/F	Los	50	15	Neoplasm, Malignant	No	Recovered
065-031	1144	53/M	Los Aten	100/Unknown	54*	Ileus	Yes	Recovered
A-201/RG954	1-9	49/F	Los	50	25	Liver Function Abnormality	Yes	Recovered
			Los	50	25	Somnolence	Yes	Recovered
			Los	50	25	Malaise	Yes	Recovered
076-005	0962	44/M	Los	50	1	Hypotension, Orthostatic	Yes	Recovered
			Los	50	1	Gastroenteritis	Yes	Recovered
049-013	7145	48/M	Los	50	286*	Neoplasm Skin, Malignant	No	Recovered
011-034	0710	50/F	Los	100	2*	Cervical Herniated Disk	No	Recovered
041-00	N/A	66/F	Los	50	42	Carcinoma	Yes	Recovered
082-00	N/A	68 F	Los	100	136	Neoplasm, Stomach, Malignant	Yes	Recovered

* Study day calculated from start of losartan therapy in open-label extension

** Unknown amount of Losartan and HCTZ

*** Patient died, but not considered related to hypertensive encephalopathy

¹ Dosage information for the serious adverse experience observed by CG (PVC) includes therapy from the prior day, i.e., 100 mg/HCTZ 12.5 mg, while dosage information for the clinical adverse experience includes atenolol 25 mg which was administered to treat the adverse experience.

Discontinuations Due to Clinical Adverse Experiences in Losartan-Treated Hypertensive Patients (Double-Blind)
 [Includes Patients from Studies Reviewed by Dr. Knudsen; Studies 48, 49 and 54]

Protocol No./ Study No.	Patient #	Age/Sex	Treatment	Daily Dose (mg)	Relative Day of Onset	Relative Day Discontinued	Adverse Experience	Outcome
011/019	0399	64/M	Losartan	10	15 32 32	36 36 36	Edema/Swelling* Angina Pectoris Dyspnea, Exertional	Present Present Present
011/024	0489	69/F	Off-drug	-	25 25 25	25 25 25	Tremor Rash IOP Increased	Recovered Recovered Recovered
011/031	0648	44/M	Losartan	25	1	88	Weight Losartans	Recovered
011/033	0684	52/F	Losartan	25	34	41	Headache	Recovered
011/005	0085	64/F	Losartan	50	30	34	Asthma	Recovered
048/004	6111	52/M	Losartan	50	59	70	Tachycardia	Present
050/014	2248	53/M	Losartan	50	1	217	Myalgia	Present
			Losartan	50	1	217	Swelling, Joint	Recovered
			Losartan	50	1	217	Edema/Swelling	Recovered
054/004	8081	55/M	Losartan	50	73	76	Asthma/Fatigue	Recovered
054/012	8265	56/F	Losartan	50	1	2	Dyspepsia	Recovered
054/013	8282	63/M	Losartan	50	2	9	Dizziness	Recovered
054/041	8848	64/M	Losartan	50	49	63	Hypotension	Recovered
065/034	1301	38/F	Losartan	50	3	4	Tachycardia	Recovered
011/014	0294	65/M	Losartan	100	34	36	Hematuria	Recovered
021/005	0088	58/M	Los/HCTZ	100/12.5	32	39	Vertigo	Recovered
021/008	0160	58/M	Losartan	100	13	20	Tinnitus	Recovered
			Losartan	100	13		Headache	Recovered
043/004	0056	62/M	Losartan	100	1	1	Hypotension	Recovered
005/003	0039	68/F	Losartan	150	2	2	Orthostatic Effects	Recovered
011/002	0033	56/M	Losartan	150	1	17	Pain, Chest*	Recovered
011/024	0488	73/F	Losartan	150	18	20	Edema, Eyelid	Recovered
			Losartan	150	18	20	Edema, Facial	Recovered
011/027	0548	52/M	Losartan	150	28	34	Hepatitis, Viral*	Recovered
			Losartan	150	30	34	Asthma/Fatigue	Recovered
			Losartan	150	30	34	Malaise	Recovered
			Losartan	150	30	34	Fever	Recovered
011/030	0617	43/M	Losartan	150	28	28	Tachycardia	Recovered
044/001	3025	63/M	Losartan	50	2	21	Cough	Recovered
			Losartan	50	2	21	Rhinitis, Allergic	Recovered
044/002	3036	56/M	Losartan	50	19	19	Orthostatic Effects	Recovered
044/002	3043	60/M	Losartan	50	24	24	Dizziness	Recovered
044/002	3044	55/M	Losartan	50	42	62	Headache	Recovered
044/003	3048	48/M	Losartan	50	4	55	Dizziness	Recovered
044/003	3049	59/F	Losartan	50	3	18	Psoriasis	Present
044/005	3078	67/F	Losartan	50	59	70	Dizziness	Recovered
			Losartan	50	59	70	Nausea	Recovered
			Losartan	50	62	70	Pain, Chest	Recovered
			Losartan	50	62	70	Hypertension, Increased	Present
044/007	3125	59/F	Losartan	100	66	69	Salpingo-Oophoritis*	Present
044/008	3142	37/M	Off-drug	-	85 91 97	84 84 84	Arthritis Gout Gout*	Recovered Present Present
044/013	3191	79/M	Losartan	100	51	53	Vomiting	Recovered
055/007	4061	33/F	Losartan	50	64	78	Dizziness	Recovered
045/009	4129	70/F	Losartan	50	2	40	Pain, Abdominal*	Present
055/003	5053	78/M	Losartan	50	9	10	Alaxia	Recovered
055/006	5271	66/F	Losartan	50	1	3	Vomiting	Recovered
			Losartan	50	1		Malaise	Recovered
055/006	5273	78/M	Losartan	50	40	42	Angina Pectoris	Recovered
			Off-drug	-	43		Hypotension	Recovered
065/003	1607	40/M	Losartan	50	16	16	Pain, Chest*	Recovered
			Losartan	50	16		Pain, Arm	Recovered
065/004	1415	61/F	Losartan	50	1	16	Dizziness	Recovered

* Serious

Discontinuations Due to Clinical Adverse Experiences in Losartan-Treated Hypertensive Patients (Double-Blind)
 [Includes Patients from Studies Reviewed by Dr. Knudson; Studies 48, 49 and 54] (con't)

Protocol No./ Study No.	Patient #	Age/Sex	Treatment	Daily Dose (mg)	Relative Day of Onset	Relative Day Discontinued	Adverse Experience	Outcome
065/011	1596	78/M	Losartan Losartan	50 50	41 41	41	CVA* Hypertension	Present
048/010	6320	36/F	Los/HCTZ	50/6.25	64	70	Discomfort, Pharyngeal	Recovered
048/011	6064	57/M	Los/HCTZ Los/HCTZ	50/6.25 50/6.25	67 67	74 74	Hemophthalmos* Edema, Macular	Present Present
048/016	6304	51/M	Los/HCTZ	50/6.25	112	112	Encephalopathy, *Hypertensive	Recovered
054/003	8065	44/F	Los/HCTZ Los/HCTZ	50/6.25 50/6.25	7 7	20 20	Headache Libido Decreased	Recovered Recovered
054/015	8883	32/F	Los/HCTZ	50/6.25	11	12	Dizziness	Recovered
054/037	8779	49/M	Los/HCTZ	50/6.25	1	19	Alopecia	Recovered
054/038	8793	42/F	Off-drug	-	6	4	Pain, Chest*	Recovered
048/004	6105	46/M	Los/HCTZ	50/12.5	29	35	Headache	Present
048/017	6431	48/M	Los/HCTZ Los/HCTZ Los/HCTZ Los/HCTZ	50/12.5 50/12.5 50/12.5 50/12.5	43 43 43 43	45 45 45 45	Dizziness* Nausea Vomiting Sweating	Recovered Recovered Recovered Recovered
054/020	8428	63/M	Los/HCTZ	50/12.5	46	46	Panic Disorder	Recovered
054/027	8567	57/F	Los/HCTZ Los/HCTZ	50/12.5 50/12.5	91 91	91 91	Pain, Abdominal Nausea	Recovered Recovered
054/028	8591	65/M	Los/HCTZ Los/HCTZ Los/HCTZ	50/12.5 50/12.5 50/12.5	1 1 1	2 2 2	Anxiety Palpitation Tachycardia	Recovered Recovered Recovered
054/037	8773	61/M	Los/HCTZ	50/12.5	27	33	Headache	Present
054/038	8786	46/F	Los/HCTZ	50/12.5	32	46	Rash	Present
050/002	2020	75/M	Losartan	50	36	36	Angina Pectoris*	Present
050/009	2160	42/F	Losartan Losartan	50 50	11 11	11 11	Headache Folliculitis	Present Present
050/010	2170	45/F	Losartan Losartan	50 50	1 1	1 1	Dysphasia* Hemiparesis	Recovered Recovered
050/015	2266	50/F	Losartan	50	32	32	Anginal Pectoris*	Recovered
050/016	2271	63/M	Losartan Losartan Losartan	50 50 50	22 22 22	47 47 47	Dizziness Headache Nausea	Present Present Present
050/022	2386	65/M	Losartan Losartan Losartan Losartan	50 50 50 50	9 9 9 9	21 21 21 21	Cough Fever Congestion, Nasal Pain, Musculoskeletal	Recovered Recovered Recovered Present
050/023	2397	75/M	Losartan Losartan	50 50	5 5	9 9	Myocardial Infarction* Heart Failure	Recovered Present
049/017	7280	62/M	Los/HCTZ	25/25	48	54	Neoplasm, Lung, *Malignant	Present
049/024	7427	41/M	Los/HCTZ Los/HCTZ	25/25 25/25	21 21	32 32	Anxiety* Depression	Present Present
048/011	6063	50/F	Los/HCTZ	50/25	40	42	Rash	Recovered
048/023	6128	74/M	Los/HCTZ	50/25	50	70	Asthenia/Fatigue	Present
049/004	7102	55/M	Los/HCTZ Los/HCTZ Los/HCTZ Off-drug	50/25 50/25 50/25 -	8 8 8 -	9 9 9 -	Dizziness Nausea Sweating Hypotension*	Recovered Recovered Recovered Recovered
049/007	7130	44/F	Los/HCTZ	50/25	21	63	Dermatitis, Atopic	Present
049/015	7251	50/M	Los/HCTZ	50/25	58	58	Fracture, Ankle*	Present
049/021	7378	62/F	Los/HCTZ	100/25	64	80	Dizziness	Recovered

* Serious

Discontinuations Due to Clinical Adverse Experiences in Losartan-Treated Hypertensive Patients (Double-Blind)
 [Includes Patients from Studies Reviewed by Dr. Knudson; Studies 48, 49 and 54] (con't.)

Protocol No./ Study No.	Patient #	Age/Sex	Treatment	Daily Dose (mg)	Relative Day of Onset	Relative Day Discontinued	Adverse Experience	Outcome
049/024	7418	64/M	Los/HCTZ	100/25	42	57	Neoplasm, Intestinal, Malignant*	Present
021/001	0011	52/F	Losartan	100	1	3	Diarrhea	Recovered
			Losartan	100	1		Nausea	Recovered
048/001	0193	53/M	Losartan	50	23	28	Hemorrhoids	Present

* Serious

Discontinuations Due to Clinical Adverse Experiences in Losartan-Treated Hypertensive Patients (Open-Label)

Protocol #/ Study #	Patient #	Age/Sex	Treatment	Daily Dose (mg)	Relative Day of Onset	Relative Day Discontinued	Adverse Experience	Outcome
011/004	0068	62/F	Losartan	100	114	117	Arthralgia	Recovered
011/009	0172	60/M	Losartan	50	581	589	Rash	Present
011/016	0322	51/M	Losartan	50	97	265	Libido Decreased	Present
011/020	0402	48/M	Los/HCTZ	100/12.5	176	178	Myalgia	Recovered
011/032	0666	58/F	Losartan	100	66	72	Neoplasm, Skin, Malig**	Present
011/039	0818	53/M	Losartan	50	419	419	Dyspnea**	Present
			Losartan	50	419	419	Atrial Fibrillation	Present
011/009	0170	53/F	Los/HCTZ	100/12.5	160	164	Rash	Recovered
011/024	0493	71/M	Los/HCTZ	100/12.5	175	181	Edema/Swelling	Recovered
			Los/HCTZ	100/12.5	175		Erythema	Recovered
			Los/HCTZ	100/12.5	175		Pain, Toe	Recovered
011/032	0882	53/F	Losartan	50	453	454	Aneurysm**	Present
011/037	0764	44/M	Losartan	150	206	206	Impotence	Present
011/005	0097	67/M	Losartan	100	269	269	Atrial Fibrillation	Recovered
011/009	0174	70/M	Losartan	100	89	89	Coma**	Recovered
			Losartan	100	89		CVA	Recovered (Death)
011/013	0260	71/F	Losartan	50	108	150	Arrhythmia	Present
			Losartan	50	108		Dyspnea	Present
011/031	0644	51/M	Los/HCTZ	100/12.5	323	383	Dyspnea, Exertional	Present
			Los/HCTZ	100/12.5	323		Pain, Chest	Present
011/038	0783	61/M	Los/HCTZ	100/12.5	218	286	Diarrhea**	Recovered
050/003	2042	62/M	Losartan	50	217	222	Obstruc., Carotid Artery**	Present
050/014	2241	46/M	Los/HCTZ	50/6.25	119	126	Agitation	Recovered
			Los/HCTZ	50/6.25	119		Malaise	Recovered
050/014	2246	54/M	Los/HCTZ/ Fel	50/12.5/5	166	228	Edema/Swelling	Present
050/023	2414	46/M	Los/HCTZ	50/6.25	244	244	Aneurysm, Cerebral**	Death
011/014	0276	53/F	Los/HCTZ	100/12.5	291	296	Dizziness	Present
			Los/HCTZ	100/12.5	291		Nausea	Present
011/020	0406	48/F	Losartan	150	113	114	Rash	Present
011/020	0407	50/M	Los/HCTZ	150/25	155	162	Impotence	Recovered
011/005	0095	51/M	Losartan	100	108	108	Angina Pectoris**	Recovered
			Losartan	100	108		Supravent. Tachycardia	Recovered
011/036	0740	39/F	Losartan	50	70	79	Pain, Chest	Recovered
			Losartan	50	70		Dyspnea	Recovered
011/037	0766	53/M	Losartan	100	206	218	Prostate Disorder	Present
059/001	5501	38/M	Losartan	100	29	29	Seizure Disorder**	Recovered
059/003	5525	44/M	Los/HCTZ	100/25	70	75	Pneumonia**	Present
059/019	5708	34/F	Los/HCTZ	100/25	32	42	Paresthesia	Recovered
			Los/HCTZ	100/25	32		Weakness, Muscle	Recovered
059/020	5675	39/F	Losartan	100	8	8	Anxiety	Recovered
			Losartan	100	8		Vertigo	Recovered
059/021	5725	56/F	Los/Aten	100/25	48	50	Syncope**	Recovered
			Los/Aten	100/25	48		Premature Beat**	Recovered
059/021	5729	55/F	Losartan	100	10	12	Depression	Recovered
054/039	8815	55/F	Los/HCTZ/ Fel	50/12.5/5	162	205	Depression	Present
050/011	2187	52/M	Los/HCTZ/ Fel	50/12.5/10	238	245	Edema/Swelling	Recovered
050/012	2212	70/M	Los/HCTZ	50/6.25	184	193	Asthma	Present
050/013	2217	52/F	Los/HCTZ	50/12.5	317	317	Dyspnea	Recovered
			Los/HCTZ	50/12.5	317		Pain, Chest	Recovered
			Los/HCTZ	50/12.5	317		Atrial Tachycardia	Recovered
050/013	2226	32/M	Off-drug*	--	323	322	Suicide Attempt**	Recovered
050/015	2255	48/M	Los/HCTZ/ Fel	50/12.5/10	216	273	Edema/Swelling	Recovered

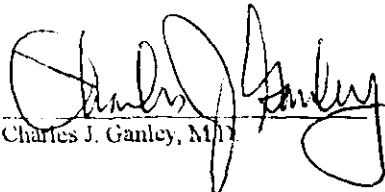
* Unknown amount of losartan, HCTZ, and other medications taken in attempted suicide. ** Serious Adverse Event

Discontinuations Due to Clinical Adverse Experiences in Losartan-Treated Hypertensive Patients (Open-Label) (con't.)

Protocol #/ Study #	Patient #	Age/Sex	Treatment	Daily Dose (mg)	Relative Day of Onset	Relative Day Discontinued	Adverse Experience	Outcome
050/016	2283	44/M	Losartan Losartan	50 50	206 206	264	Asthenia/Fatigue Hypotension, Orthostatic	Present Present
050/019	2336	61/M	Los/HCTZ/ Fel	50/12.5/10	172	202	Edema/Swelling	Present
049/016	7264	68/F	Losartan Losartan Los/Fel	50 50 50/5	85 203 259	267	Pain, Abdominal Rash Asthenia/Fatigue	Recovered Recovered Recovered
049/023	7414	56/M	Losartan	50	98	114	Myalgia	Present
049/012	7199	41/M	Los/HCTZ/ Fel	50/25/10	307	307	Gastroenteritis	Recovered
049/023	7453	52/M	Los/HCTZ/ Fel	50/25/5	168	181	Tachycardia	Recovered
049/017	7279	52/M	Losartan	50	267	338	Neoplasm, Tongue, Malig.**	Present
049/023	7411	61/M	Off-drug	-	293	286	Neoplasm, Kidney, Malig.**	Recovered
011/017	0339	53/F	Losartan	150	111	132	Asthenia/Fatigue	Recovered
011/018	0365	60/M	Losartan	100	86	90	Depression	Recovered
011/025	0519	63/M	Losartan	50	561	563	Rash	Present
011/031	0646	34/M	Los/HCTZ Los/HCTZ	150/12.5 150/12.5	128 128	133	Nocturia Urinary Frequency	Recovered Recovered
049/001	7016	52/M	Los/HCTZ/ Fel	50/25/10	292	326	Impotence	Present
049/014	7236	48/M	Los/HCTZ/ Fel	50/12.5/10	133	139	Edema/Swelling	Present
049/027	7361	45/M	Los/HCTZ/ Fel	50/12.5/5	147	159	Headache	Recovered
011/025	0510	40/M	Losartan	50	534	553	Hearing Loss**	Present
011/028	0579	70/M	Los/HCTZ	150/12.5	350	364	Pain, Chest	Present
050/019	2325	42/M	Losartan	50	99	153	Impotence	Recovered
050/021	2365	61/M	Losartan Losartan	50 50	59 59	59	Edema, Facial Rash	Present Present
050/021	2371	50/F	Los/HCTZ/ Fel Los/HCTZ/ Fel Los/HCTZ/ Fel	50/12.5/10 50/12.5/10 50/12.5/10	304 304 304	332	Tachycardia Weakness, Muscle Flushing	Present Present Present
050/021	2373	59/M	Los/HCTZ/ Fel	50/12.5/5	197	197	Myocardial Infarction**	Recovered

** Serious Adverse Event

NOTE: Counts total 57 discontinued but listing includes 58 discontinued, cannot identify error.



Charles J. Ganley, MD

cc: orig.
HFD-110 file
HFD-110/c.ganley/r.lipicky/cso/k.knudson/a.proakis
HFD-426/e.fadiran
HFD-110/w.nuri

CHEMISTRY

Review

Bayer

MAR 2 1995

DIVISION OF CARDIO-RENAL DRUG PRODUCT
Review of Chemistry, Manufacturing, and Control

NDA #: 20-386 **CHEM. REVIEW #:** 3 **REVIEW DATE:** 17-FEB-95

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
BC	21-OCT-94	25-OCT-94	27-OCT-94
BC	11-JAN-95	12-JAN-95	17-JAN-95
BL	27-JAN-95	30-JAN-95	30-JAN-95
BC	25-JAN-95	30-JAN-95	31-JAN-95
BC	08-FEB-95	09-FEB-95	13-FEB-95

NAME & ADDRESS OF SPONSOR

Merck Research Laboratories
Merck & Co. Inc.
West Point, PA 19486

Telephone: 610-397-2310

DRUG PRODUCT NAME

Proprietary: COZAAR
Nonproprietary/USAN: Losartan Potassium Tablets
Code Name/#: MK-954; DuP-753; 1-158,086; L-158,086-005H;E-3340
Chem.Type/Ther.Class: 1S

ANDA Suitability Petition/DESI/Patent Status:

U.S. Patent 5,138,069 expiration date - 8/11/2009;
USP 5,153,197 expiration date 10/06/2009 - both licensed from DuPont

PHARMACOL. CATEGORY/INDICATION:

An angiotensin II receptor agonist; said to reduce systolic and diastolic blood pressure in patients with mild to moderate essential hypertension.

DOSAGE FORM: Film coated tablets

STRENGTH: 20, 50, 100 mg

ROUTE OF ADMINISTRATION: ORAL

DISPENSED: Rx

CHEMICAL NAME:

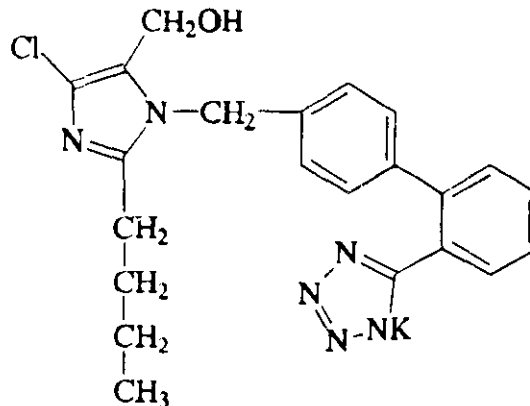
2-butyl-4-chloro-1[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]-methyl]-1H-imidazole-5-methanol, monopotassium salt.

CAS #: 124750-99-8

MOLECULAR FORMULA: C₂₂H₂₂ClKN₆O

MOLECULAR WEIGHT: 461.01

STRUCTURAL FORMULA:



SUPPORTING DOCUMENTS:

Covered in review # 1.

RELATED DOCUMENTS:

Covered in review # 1.

CONSULTS:

FUR was sent on February 2, 1995. Reply to Agency's EA was received on January 30, 95 and has been sent to HFD-102 for consultation.

Division of Biopharmaceutics has completed their review and recommended a change in dissolution specifications.

Confidential Revised Environmental Assessment and Non-Confidential Revised Environmental Assessment were received on February 9, 1995. These assessments have been sent to HFD-102 for consultation.

REMARKS/COMMENTS:

The applicant has withdrawn 100 mg losartan potassium tablets from the subject NDA, due to lack of marketing interest.

During scale up to a full- scale production during validation and initial imprinting of the final markings on the tablets, a slight picking was observed. As a result of this, minor manufacturing changes in blend time during lubrication were made and concavity of the tablets was slightly altered.

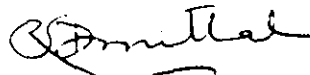
CONCLUSIONS & RECOMMENDATIONS:

Recommend that, so far, this Application is approvable, pending FUR, EA reviews.

CC:

Orig. NDA
HFD-110/Division File
HFD-110/Ram Mittal/date
HFD-110/CSO

R/D Init by: RWolters/
RWolters 2/22/95



Ramsharan D. Mittal Ph.D., Review Chemist
filename: C:\NDA\20386\20386.R03

PHARMACOLOGY

TOXICOLOGY

REVIEWS

**M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: 2/27/95

FROM: Anthony G. Proakis, Ph.D. *AGP*

SUBJECT: COZAAR (Losartan) Labeling

TO: Dr. Ray Lipicky

I have read the attached comments by ODE I on the Pharmacology/Toxicology portion of the labeling for Losartan.

Appropriate changes were made (Dr. Temple's mark-up) to address comments 1 and 2 (Note: the multiples of the human dose under Overdose/Lethality sections were corrected to 44 and 170 times rather than 75 and 300 times shown in the mark-up).

The 3rd comment regarding the inclusion of the statement on pancreatic acinar adenomas was discussed in the Exec-CAC (See last paragraph of attached Exec-CAC minutes). This statement should remain in labeling.

N. B.

DEC - 7 1994

NDA #20,386

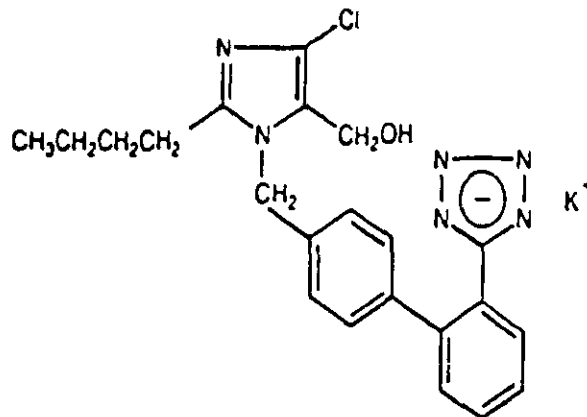
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

G. Jagadeesh, Ph.D.
A. Proakis, Ph.D.
12.6.1994

SPONSOR Merck Research Laboratories, Merck & Co., Inc.,
West Point, PA 19486

PRODUCT COZAAR® (Losartan potassium) Tablets

CHEMISTRY Losartan (also referred to as MK-954, L-158,086, DuP 753, E-3340) is the potassium salt of 2-n-butyl-4-chloro-5-hydroxymethyl-1-[[[(2'-1H-tetrazol-5-yl) biphenyl-4-yl] methyl]imidazole. The substance is a white to off-white crystalline solid with no chiral centers and a molecular weight of 461.01. Losartan potassium is hygroscopic and freely soluble in water. Solid losartan potassium drug substance, stored under ambient conditions of temperature and humidity, is claimed to be stable for at least three years.



PHARMACOLOGICAL CLASS Angiotensin II receptor antagonist

PROPOSED INDICATION Treatment of hypertension

FORMULATION AND ROUTE OF ADMINISTRATION Losartan is intended for oral use and is supplied as green teardrop-shaped or white scored oval tablets containing 25, 50 or 100 mg losartan potassium (excipients: microcrystalline cellulose, lactose hydrous, pregelatinized starch, magnesium stearate, hydroxypropyl cellulose or methylcellulose, titanium dioxide and approved coloring agents).

PROPOSED DOSAGE REGIMEN 50 mg once daily in most patients. The maximum recommended dose is 100 mg once daily.

IND UNDER WHICH CLINICAL TRIALS WERE CONDUCTED

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INTRODUCTION

Hypertension is a major public health problem affecting at least 10% of the adult population. A number of approaches to the development of the drug therapy of essential hypertension have been tried over five decades. Diuretics and β -adrenergic blockers have maintained a dominant position in this category of drugs. One of the approaches to the treatment of hypertension, which may be considered as a major scientific advancement, involves drugs affecting the renin angiotensin aldosterone system (RAAS).

Control of blood pressure by the RAAS is exerted through multiple actions of angiotensin II, a small peptide which, as the end product of the RAAS, is a potent vasoconstrictor hormone implicated in the genesis and maintenance of hypertension. The importance of the RAAS is reflected in the observation that angiotensin II levels are elevated in renovascular and malignant hypertension. Actions of angiotensin II involved in the control of arterial pressure and volume homeostasis include vasoconstriction, aldosterone formation, renal sodium absorption, and norepinephrine release. Furthermore, elevated plasma renin activity is associated with increased morbidity and mortality in patients with essential hypertension. Aldosterone, an important component of this system, is known to cause increased sodium retention and increased volume. Therefore, it is hypothesized that angiotensin II, because of its dual role in influencing both vasoconstriction and volume mechanisms, is a critical hormone in the development and maintenance of hypertension.

The drugs directed against the RAAS fall into three categories. First, the angiotensin converting enzyme (ACE) inhibitors, beginning with captopril. They act by blocking the conversion of angiotensin I to angiotensin II. A second approach is to inhibit selectively the enzyme renin which acts on angiotensinogen (renin substrate), to release the decapeptide angiotensin I. Renin inhibitors are as effective as ACE inhibitors experimentally, but progress has been limited by the lack of orally active compounds. Third, and newest approach to the treatment of hypertension, is the use of angiotensin II receptor antagonists. This approach dates back to saralasin, a peptidergic angiotensin II receptor antagonist. Because of its peptide structure, that compound had a short duration of action and its use was limited to parenteral administration only. In addition, saralasin had substantial partial agonist activity resulting in the elevation of blood pressure in some patients.

The introduction of nonpeptide angiotensin II receptor antagonists has opened new vistas in understanding the additional physiological effects of angiotensin II. The specific receptors with which angiotensin II binds are differentiated into subtypes AT_1 and AT_2 based on their sensitivity to non-peptide angiotensin II receptor antagonists. Losartan, the current drug candidate for approval, is about 10,000 times more selective for the AT_1 site than for the AT_2 site. Losartan potassium represents the first nonpeptide angiotensin II receptor antagonist which is orally bioavailable, lacks partial agonist activity and is highly specific for antagonizing receptors of angiotensin II linked to the cardiovascular system. The sponsor's NDA contains extensive preclinical data supporting this classification.

1. PHARMACODYNAMICS

1.1. Effects Related to Proposed Therapeutic Indication

1.1.1. Angiotensin II Receptor Antagonism

A. *In vivo* Inhibition of Exogenous Angiotensin II Pressor Response

a) *Pithed Rat*:

The ability of losartan to selectively antagonize angiotensin II-induced pressor response following i.v. or oral administration was evaluated in rats which were anesthetized, pithed, and maintained on artificial respiration. In this study a cumulative dose-pressor response curve for i.v. angiotensin II was constructed. Before injection of angiotensin II, each animal was pretreated with saline or losartan (3 or 10 mg/kg, i.v.). A similar protocol was followed with norepinephrine and vasopressin to determine specificity.

Losartan at 3 and 10 mg/kg i.v. shifted the log dose-pressor response curve for angiotensin II dose-dependently to the right without altering the maximal response to angiotensin II (Fig. 1) or angiotensin III, suggesting competitive angiotensin II antagonism. A dose of 10 mg/kg significantly lowered diastolic b.p. (26 mm Hg *versus* control of 41 mm Hg) but did not alter heart rate. Neither of these doses altered the dose-heart rate response curve for isoproterenol, suggesting that losartan does not have affinity for the β -1 adrenergic receptor. Losartan did not alter the dose response curves for norepinephrine or vasopressin, further evidence of its selectivity. Losartan given orally to pithed rats at a dose of 10 mg/kg shifted the dose-pressor response curve for angiotensin II about 20- and 5-fold to the right at 2 hr and 24 hr postdose, respectively (Fig. 2). Diastolic b.p. was significantly decreased to 31 mm Hg at 2 hr

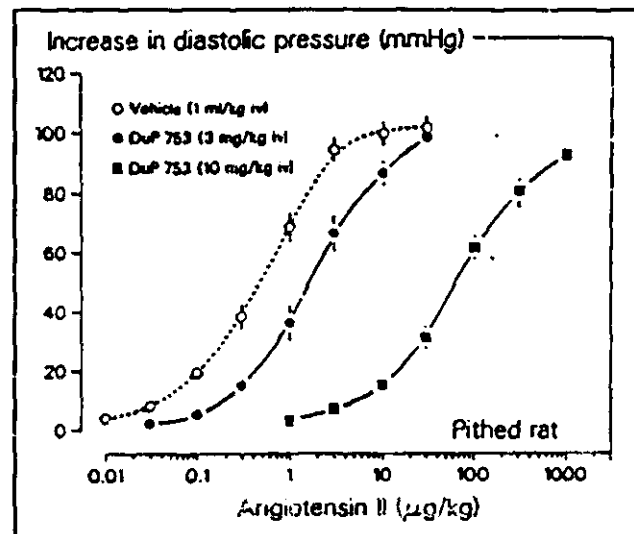


Figure 1: Effects of losartan (3 and 10 mg/kg i.v.) on the pressor response for angiotensin II in the pithed rat

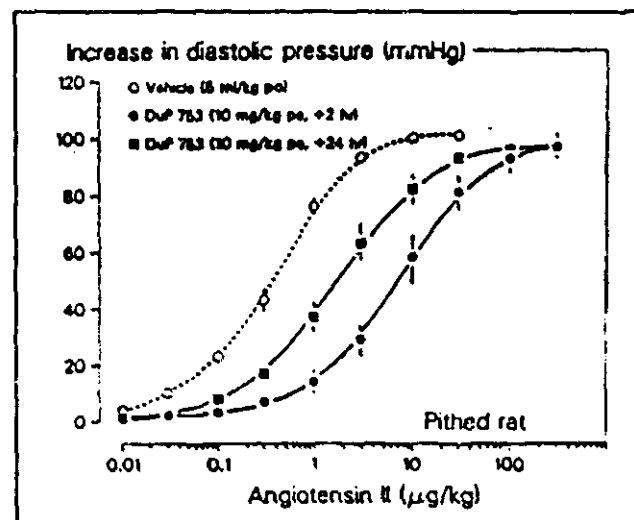


Fig. 2: Effect of losartan at 10 mg/kg p.o. at 2 and 24 hr postdose on the log dose-pressor response curve for angiotensin II in the pithed rat

and to 32 mm Hg at 24 hr postdose versus vehicle control response of 40 mm Hg, suggesting a long duration of angiotensin II antagonism.

In a separate study, the potency and selectivity of E-3174 (L-158641, EXP3174), a major metabolite found in rat plasma after the oral administration of losartan, was evaluated utilizing the protocol discussed above. E-3174 at 0.03, 0.1 and 0.3 mg/kg i.v. shifted the log dose-pressor response curve dose-dependently to the right and reduced the maximal pressor response to angiotensin II (Fig. 3), suggesting noncompetitive antagonism. The mean diastolic b.p. for the vehicle control and the 0.03, 0.1 and 0.3 mg E-3174-treated groups were 41, 40, 30 ($P \leq 0.05$) and 25 mm Hg ($P \leq 0.05$), respectively. E-3174 did not alter heart rate, suggesting that it is devoid of a myocardial depressant activity. However, at 0.1 and 0.3 mg/kg i.v. E-3174 *per se* lowered b.p. The inhibitory effect of E-3174 on the response to angiotensin II is selective, since E-3174 did not alter the pressor dose response curve for norepinephrine or vasopressin at an effective angiotensin II inhibitory dose (0.3 mg/kg i.v.).

b) Normotensive Conscious Rat:

The tolerance to the inhibitory effects of losartan on the blood pressure response to angiotensin II was evaluated in normotensive conscious rats. These rats were treated daily with losartan at 10, 30 and 100 mg/kg p.o. for 11 days. The blood pressure response to angiotensin II at 0.1 $\mu\text{g/kg}$ i.v. was measured 2 hr after the first dose of losartan in one group and on the 11th day of dosing before and two hours after losartan or vehicle in the second group. In both groups of rats losartan caused a dose-dependent inhibitory effect on the pressor response to angiotensin II (Fig. 4), both acutely and after 11 days of treatment. Thus, no tolerance developed to the angiotensin II antagonistic effects of losartan.

In a second study, chronically catheterized conscious rats were challenged with intravenous

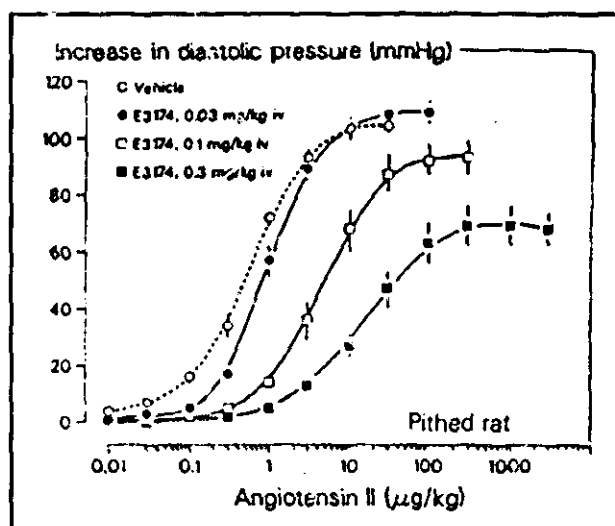


Fig. 3: Effects of E-3174 at 0.03, 0.1, and 0.3 mg/kg i.v. and the vehicle on the log dose-pressor response curve for angiotensin II in the pithed rat

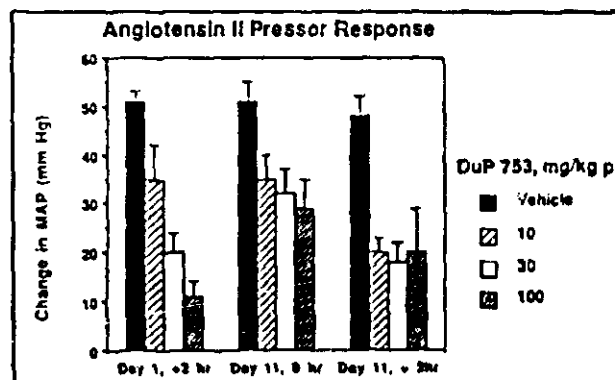


Fig. 4: Effects of losartan at 10, 30, and 100 mg/kg/day p.o. for 11 days on the pressor response to angiotensin II at 0.1 $\mu\text{g/kg}$ i.v. in normotensive rats

bolus doses of angiotensin II (0.1 $\mu\text{g}/\text{kg}$) and methoxamine (50 $\mu\text{g}/\text{kg}$). Following calibration, rats were dosed orally or intravenously with losartan (0.3, 1 and 3 mg/kg) and percent pressor responses to angiotensin II challenges during the subsequent 6 hours and at 24 hours were used as a measure of efficacy. Following an oral dose of 1 mg/kg, losartan had a duration of action greater than 6 hours with a peak inhibition of 56% (Fig. 5), while after an i.v. dose of 1 mg/kg, losartan had a duration of action greater than 6 hours with a peak inhibition of 78% (Fig. 6) of the pressor response to an exogenous angiotensin II challenge. Further, losartan at 3 mg/kg i.v. produced a peak inhibition of 93% and had a duration greater than 24 hours, suggesting the duration of action was dose-related. The ED₅₀ (dose that produces a 50% reduction in the angiotensin II response) for losartan p.o. and i.v. was 0.66 and 0.28 mg/kg, respectively. Losartan did not change either the basal b.p. or pressor responses to methoxamine. At 1 and 3 mg/kg, the inhibition of pressor response to angiotensin II was biphasic with a transient peak inhibition at 5 min followed by a subsequent gradual increase in blockade of the angiotensin II pressor response over 3 hours, suggesting the formation of one or more active metabolites.

Utilizing the same methods as described above, E-3174 at 0.1, 0.3 and 1 mg/kg i.v. and 0.3, 1, 3 and 10 mg/kg p.o. was evaluated for its effects on angiotensin II-induced (0.1 $\mu\text{g}/\text{kg}$, i.v.) pressor responses. Both oral and i.v. doses of E-3174 produced a dose-related inhibition of the pressor response to angiotensin II. Maximal inhibitory effect was evident at 5 min post-injection, and significant inhibitory effects were evident at 6 hours post-treatment with the 0.3 and 1 mg/kg i.v. doses and the 1-10 mg/kg p.o. doses, suggesting E-3174 is likely to contribute to the long duration of the angiotensin II inhibitory effect of losartan. E-3174 at these doses did not alter basal blood pressure and heart rate.

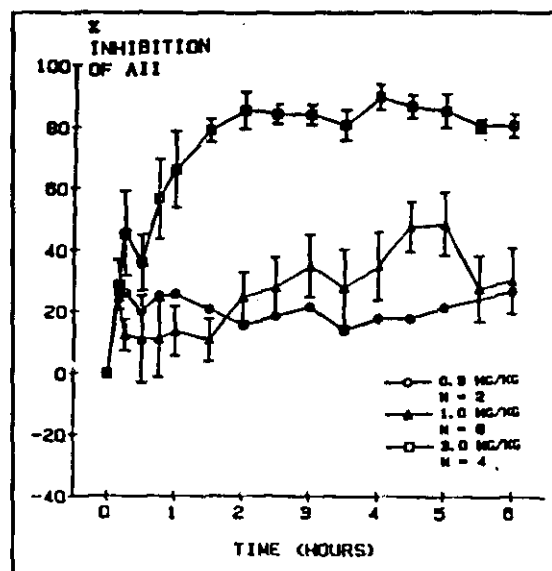
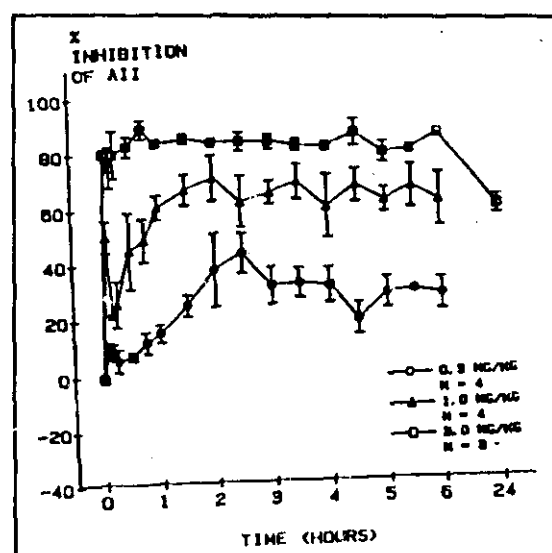


Fig. 5: Inhibition of the pressor response to angiotensin II after oral administration of losartan (0.3, 1, and 3 mg/kg) in conscious rats.



Since brain RAS appears to have an important physiological role in the regulation of b.p., losartan was evaluated for its ability to gain access to the brain angiotensin II receptors. In chronically catheterized conscious rats, angiotensin II was given at 0.35 μg in 10 μl of CSF intracerebroventricularly and i.v. (0.1 $\mu\text{g}/\text{kg}$) before and after the administration of losartan at 3.5 $\mu\text{g}/\text{rat}$ i.c.v. in 10 μl of CSF or 10 mg/kg p.o. Oral losartan at 10 mg/kg blocked pressor responses to i.v. angiotensin II but not to i.c.v. angiotensin II (up to 3 hr after administration). On the other hand, losartan given i.c.v. blocked the pressor responses to i.c.v. angiotensin II, suggesting that losartan at 10 mg/kg does not penetrate the brain. However, higher doses or longer periods of administration (over 3 hr) have not been explored by the sponsor.

In another study, conscious catheterized normotensive rats were made hypertensive by a constant infusion of angiotensin II (80 ng/kg/min). Thirtyfive minutes after the beginning of angiotensin II infusion, vehicle or losartan at 0.1, 1 or 10 mg/kg was given i.v. and its effect on blood pressure was monitored for another hour. The study demonstrated that without pretreatment losartan is still effective in antagonizing the angiotensin II-sustained blood pressure in a dose-dependent manner (Fig. 7). Rats treated with losartan at 10 mg/kg showed a small decrease in mean arterial pressure even after the angiotensin II infusion was stopped. Though the mechanism is not clear, the intrinsic influence of angiotensin II in the maintenance of vasoconstriction is implied.

The effect of losartan on angiotensin II-induced aldosterone release was studied in conscious normotensive rats that were surgically prepared with arterial and venous catheters one day before the experiment. The following day, the rats were given i.v. losartan (10 mg/kg) or saline vehicle 15 minutes before an i.v. infusion of angiotensin II (0.1 $\mu\text{g}/\text{kg}/\text{min}$) for 30 min. At the end of the infusion, rats were decapitated and serum aldosterone levels determined from aortic blood samples. Increases in blood pressure and aldosterone release by angiotensin II were effectively blocked by losartan at 10 mg/kg (Fig. 8).

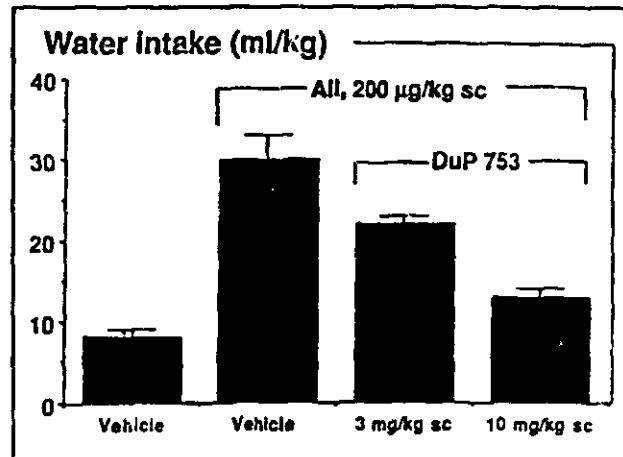


Fig. 9: Effects of losartan (3 and 10 mg/kg s.c.) on the drinking response to angiotensin II in conscious normotensive rats

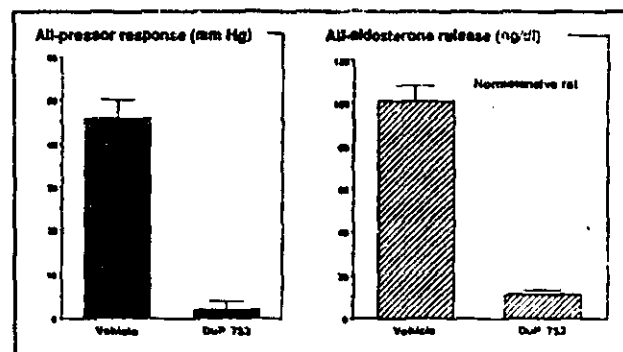


Fig. 8: Effects of losartan (10 mg/kg, i.v.) or the vehicle on the pressor (left) and aldosterone (right) responses to A-II (0.1 $\mu\text{g}/\text{min}$) in conscious rats

Systemic as well as central administration of angiotensin II has been demonstrated to stimulate water drinking in a variety of animals. After two days of habituation in metabolic cages, rats were given losartan 3 or 10 mg/kg or saline s.c. 1 hour before angiotensin II at 200 μ g/kg s.c. Water intake was measured for 2 hours after the administration of angiotensin II or the vehicle. Angiotensin II-induced drinking response was blocked dose-dependently by losartan at 3 and 10 mg/kg s.c. (Fig. 9), suggesting that angiotensin II-induced drinking is mediated by its receptor activation. In a related study, losartan was given to a group of rats via the drinking water and liquid consumption and urinary output monitored. Losartan at 35 mg/kg/day had no effect on basal drinking behavior, urinary output or sodium and potassium excretions. Studies done by independent investigators (outside of Merck and DuPont Laboratories), while confirming the above observations, have also shown the specificity of this effect in the rat by demonstrating that losartan does not block the drinking response to isoproterenol, serotonin, 5-hydroxytryptophan, carbachol, hypertonic saline or polyethylene glycol. Further, these investigators have shown that losartan at 3 mg/kg p.o. for three days did not block the drinking response to i.c.v. angiotensin II (50 ng). In contrast, losartan administered centrally (10-100 ng) blocked the drinking response to angiotensin II at 0.1 ng i.c.v.

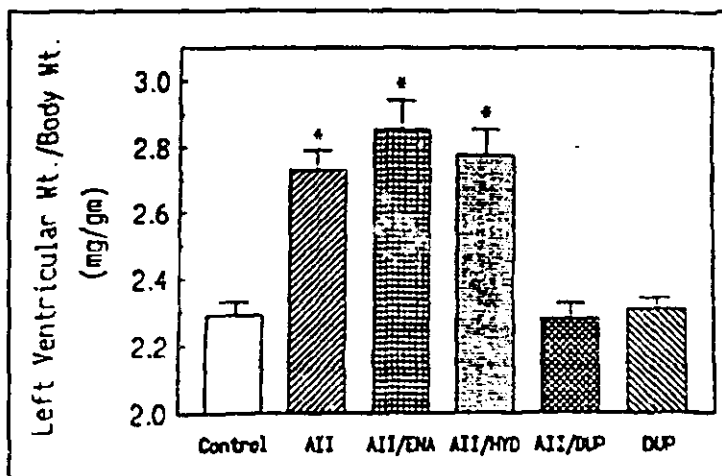


Fig 10: At 14 days, lv/bw ratios of AII+enalapril/hydralazine groups were significantly higher than control groups compared with groups receiving losartan $\pm$ AII

Angiotensin II has been reported to have positive chronotropic, inotropic and hypertrophic actions in cardiac tissue. The hypertrophic effects of the peptide have been described as direct wherein it stimulates the local release of growth factors from non-muscle cell types such as sympathetic neurons and fibroblasts in the heart. These factors could have a paracrine effect on cardiomyocytes to regulate or modulate growth-dependent mechanisms. Angiotensin II may also indirectly produce hypertrophy by increasing blood pressure (increased afterload) as a result of increase in vascular resistance. Cardiac hypertrophy was induced in conscious rats by infusing angiotensin II continuously (with the implantation of osmotic pumps on day 0 and day 7 of the experiment to deliver angiotensin II at a rate of 30 ng/min) throughout the 14-day time course of the experiment. Each rat was given 4 mg losartan (in 1 ml water) by gavage once a day. Enalapril maleate and hydralazine were administered in the drinking water at concentrations of 0.2 and 0.13 mg/ml, respectively. Blood pressure was monitored using a tail cuff method. The rats were killed on days 7 or 14 of the study and the atria and right and left ventricles removed. The tissue weights were indexed by dividing the weight of the tissue (in mg) by the body weight (in gm) of the animal.

The chronic infusion of angiotensin II significantly increased blood pressure (from 106 mm

Hg to 116 mm Hg, and from 108 mm Hg to 119 mm Hg, respectively, after 7 and 14 days) and left ventricular weight/body weight ratio (18.6% and 17.3% at 7 and 14 days, respectively). Animals with elevated blood pressure showed no significant correlation between increases in left ventricular mass and mean arterial pressure at 7 days, whereas at 14 days there was a correlation. This suggests that left ventricular hypertrophy induced by angiotensin II infusion is a result of hormonal rather than mechanical (afterload effect) mechanisms. Losartan completely prevented the rise in blood pressure and the cardiac hypertrophy (Fig. 10) at 14 days. The ACE inhibitor had no significant effect on either parameter. On the other hand, hydralazine (a vasodilator) normalized the blood pressure with no effect on the cardiac hypertrophy. These data provide evidence that the AT₁ cardiac receptor is mechanistically coupled to left ventricular muscle growth.

c) *Rhesus Monkeys:*

The effects of losartan on the pressor responses to angiotensin II following oral and i.v. administration were evaluated in conscious sodium/volume depleted rhesus monkeys. Chronic aortic catheters for recording mean blood pressure were placed in each monkey 2 weeks before the experiment. One week before the study monkeys were placed on a low sodium diet and 18 hours prior to the experiment given furosemide at 5 mg/kg i.m. On the days of study, monkeys were chair restrained and prepared with a saphenous or brachial vein catheter for i.v. drug injection. Monkeys were initially challenged with methoxamine (50 µg/kg, i.v.), which was followed by bolus i.v. injections of angiotensin II (0.1 µg/kg) at times before and after losartan (3 and 10 mg/kg, p.o. or 0.3 and 1 mg/kg, i.v.) or its vehicle. Losartan at 3 and 10 mg/kg, p.o., produced peak effects of 22 ± 9 and 50 ± 7% inhibition, respectively. At 0.3 and 1 mg/kg, i.v., the peak effects were 49 ± 5 and 76 ± 9% inhibition, respectively. ED₅₀'s (95% confidence interval), based on the peak effect (i.e., percent inhibition of angiotensin II pressor response) for oral and i.v. administration were 10.22 (6.96-15.03) and 0.32 (0.18-0.58) mg/kg, respectively. The duration of action (the time from onset of activity to the last time point where inhibition of the angiotensin II was >30%) was 0.08 hr for the 0.3 mg/kg i.v. dose and 2.1 ± 0.9 hr for the 10 mg/kg p.o. dose.

d) *Chimpanzees:*

The potency and duration of action of losartan on angiotensin II-induced pressor effects was evaluated in anesthetized chimpanzees. Fasted adult male chimpanzees were anesthetized and cannulated for direct measurement of blood pressure and i.v. administration of drugs. Administration of angiotensin II (100 ng/kg bolus) or arginine vasopressin (AVP, 50 ng/kg bolus) elevated arterial pressure by 32 ± 4.7 and 52 ± 9.7 mm Hg, respectively. The duration of the pressor response was approximately 5 min with angiotensin II administration and approximately 10 min with AVP administration. Each chimpanzee was given repeated bolus i.v. injections of angiotensin II or AVP after 180 min of initial challenge. The chimpanzees were returned to their cages for recovery and were reanesthetized for study at 10 and 24 hr post drug effect. The pressor responses to AVP did not differ significantly from baseline throughout the studies, confirming the selectivity of the angiotensin II receptor antagonists for

angiotensin II-mediated increases in blood pressure, and verifying that the sensitivity of the chimpanzees to pressor stimuli was not altered. Losartan at 1 mg/kg i.v. significantly inhibited angiotensin II pressor responses for 10 hours after administration. Maximal inhibition ($93 \pm 4\%$) was obtained by 5 min post losartan. At 10 hours, inhibition of the angiotensin II response was $44 \pm 6\%$ and at 24 hours, the inhibition was not significant.

B. *In vivo* Inhibition of Endogenous Angiotensin II

a) *Hormonal Activity:*

The role of RAS in the control of blood pressure was studied in two models of hypertension. In the first study, SHR (11 week old) and age-matched WKY (normotensive rats) were dosed with losartan at 10 mg/kg/day by gavage for 14 days. Blood pressure and heart rate were monitored before, and after 7 and 14 days of treatment. At the end of 2 weeks of treatment, the rats were anesthetized and blood was withdrawn by aortic puncture for measuring plasma immunoreactive angiotensin I and angiotensin II, PRA, aldosterone and ACE.

TABLE 1.1.

Plasma components of the renin-angiotensin system and aldosterone in control and losartan-treated WKY and SHR.

	WKY		SHR	
	Control (n=6)	Losartan (n=6)	Control (n=7)	Losartan (n=8)
PRA (ng/ml per h)	3.85 ± 0.55	9.96 ± 1.40^a	3.18 ± 0.20	21.24 ± 3.16^{ac}
P-Ang I (pg/ml)	1.49 ± 0.18	3.37 ± 0.36^a	1.44 ± 0.10	5.36 ± 0.72^{ac}
P-Ang II (pg/ml)	6.85 ± 1.23	16.67 ± 2.49^a	3.65 ± 0.25^c	25.36 ± 3.59^a
ACE (U/ml)	76.8 ± 4.4	67.7 ± 3.2	56.7 ± 0.9	57.8 ± 1.7
Aldosterone (ng/dl)	40.5 ± 3.2	13.2 ± 1.7^b	72.7 ± 11.7^c	19.1 ± 6.0^a

Values are means $\pm$ S.E.M. PRA=plasma renin activity; ACE=angiotensin converting enzyme; P=plasma; ^aP<0.01; ^bP<0.001, compared with respective control groups; ^cP<0.05, compared with control WKY.

Losartan at 10 mg/kg p.o. produced a significant reduction in systolic blood pressure in SHR one week after the treatment, and a further decline in blood pressure was observed 2 weeks after the administration. This suggests a relatively slow onset of antihypertensive action of losartan and no tolerance to its antihypertensive effect. However, other reports suggest a marked fall in blood pressure within 15 to 30 min after a single oral administration of losartan in 18-21 week old SHR. The antihypertensive effect was not associated with a significant increase in heart rate. In contrast, losartan had no effect on the blood pressure of the normotensive rats. Compared with the control, the PRA and plasma levels of angiotensin I

and angiotensin II were markedly elevated in losartan-treated animals. The increase in these parameters tended to be greater in SHR than in the WKY. In contrast, losartan treatment significantly lowered aldosterone in both the SHR and WKY. No significant difference between the control and the drug-treated groups was found in plasma ACE activity (either SHR or WKY, Table 1.1). Additional *in vitro* studies have also shown the lack of effect of losartan (up to 0.1 mM) on plasma renin or ACE activities.

In the second study, the effects of losartan were studied in salt-depleted conscious dogs as the RAS is activated and the hypotensive response to blockers of the system is enhanced in this model. Beagle dogs prepared with chronic carotid arterial loops were each given a bolus i.v. dose of furosemide (5 mg/kg) on day 1 and placed on a low sodium diet (3 mmol/day) for 3 days. Blood pressure and heart rate were monitored continuously and arterial blood sampling was done at various intervals to measure plasma angiotensin II, renin and norepinephrine.

Infusion of losartan (30 $\mu\text{g}/\text{kg}/\text{min}$) over a period of 180 min produced a significant fall in systolic and diastolic blood pressure; both of which stabilized by 30 min. Mean arterial pressure also fell significantly from base line (110.9 ± 11.2 mm Hg to 95 ± 12.8 mm Hg). These changes were associated with a rise in heart rate from base line (84.6 ± 15.1 to 103 ± 15.2 beats per min). The heart rate response developed over a similar time course to the blood pressure changes. Using the same protocol, the effect of losartan on the MAP to pressor infusion of angiotensin II (54 ng/kg/min) was studied. During the control period (30 min before losartan administration), angiotensin II produced a 35.3 ± 11.6 mm Hg increase in MAP. This was significantly reduced at 15 min and at all points thereafter during constant infusion of the inhibitor (4.3 ± 3.3 mm Hg at 3 hr). There was no rebound response of blood pressure on stopping infusion of losartan, probably because its inhibitory effect persisted for several hours (approximately 30% recovery 2 hr after stopping drug infusion). It should be noted that in the dog there is only a limited conversion of losartan to its primary metabolite E-3174. This explains the shorter duration of action on MAP and may also play a part in the rise in heart rate in the dog. Circulating plasma angiotensin II (42.5 ± 11.8 pg/ml) and renin (64.5 ± 92.7 μ -units/ml) concentrations were elevated during the baseline D-glucose infusion (control period) in keeping with the sodium-deplete status of the animals. Infusion of losartan caused highly significant increases in plasma levels of angiotensin II (from 52.6 ± 22.2 pg/ml 30 min before the start of the losartan infusion to a maximum of 226 ± 70.5 pg/ml) and renin (average increase of 500 μ -units/ml). A large part of this response is thought to result from blockade of the inhibitory effect of angiotensin II on renin release, a calcium-mediated process at the renal juxtaglomerular cell. No effect on plasma norepinephrine was noted throughout the 180 min losartan infusion.

b) Decreased Response to Sympathetic Nerve Stimulation.

It has been demonstrated that both exogenous and endogenous angiotensin II enhances noradrenergic transmission by acting at presynaptic sites in both isolated smooth muscle preparations and intact animals. The blockade of RAS results in the inhibition of the adrenergic facilitating effect of angiotensin II. Anesthetized, adrenalectomized, pithed and

artificially respired rats were cannulated for arterial pressure measurement and i.v. drug injection. In addition, cardiac output, heart rate and total peripheral resistance (TPR) were measured.

Stimulation of sympathetic neurons or exogenous administration of norepinephrine (0.3-3 $\mu\text{g}/\text{kg}$, i.v.) in the pithed rat caused increases in blood pressure by increasing cardiac output and TPR. Losartan at 10 mg/kg i.v. (but not PD123177, an AT_2 receptor antagonist, at a dose of 100 mg/kg i.v.) significantly reduced the maximum change in arterial pressure and TPR while having little effect on the maximum change in cardiac output or heart rate in both maneuvers. This suggests that circulating angiotensin II gains ready access to the vascular but not to the cardiac sympathetic synapses in the pithed rat. Another explanation advanced in the literature is that the cardiac prejunctional angiotensin II receptor in rats may be absent or does not function *in vivo* since angiotensin II does not have a direct cardiac contractile effect. Similar experimental design has been used to study the effects of losartan on the renal vasoconstrictor responses to renal nerve stimulation and intraarterial injection of norepinephrine in anesthetized dogs. Both these studies suggest that the prejunctional angiotensin II receptors in the vasculature and renal adrenergic nerve are AT_1 receptors.

C. In vitro Inhibition of Exogenous Angiotensin II

a) Contraction:

Angiotensin II-induced contractions of isolated rabbit aortic strips were inhibited by losartan in a concentration-dependent manner. The rightward shift of the dose-response curve occurred in a parallel fashion with no changes in the maximum angiotensin II response (Figure 11). The pA_2 (defined as the negative logarithm of the concentration of antagonist required to shift the concentration/response curve two-fold to the right) of losartan was 8.48 (slope of the Schild plot was 0.9 ± 0.1). Further, losartan (10 μM) did not change the concentration-response curve for norepinephrine or KCl, nor did it (at 10 μM) cause contraction of rabbit aorta. These data are consistent with losartan being a selective, competitive angiotensin II receptor antagonist lacking partial agonist effects on the angiotensin II receptors.

In the same preparation, E-3174, at 10^{-10} to 10^{-6}M , caused nonparallel shifts to the right of the angiotensin II concentration-response curves and reduced the maximal response to angiotensin II (Figure 12), suggesting E-3174 is a noncompetitive antagonist of angiotensin II. The estimated K_B ($-\log \text{pA}_2$) value was 9.96. The reduction (25%) of the maximum contractile response to angiotensin II by E-3174 was reduced in the presence of increasing concentrations of losartan, indicating interaction with the same binding site. These results indicate (a) slow dissociation kinetics of E-3174, and (b) the existence of a saturable AT_1 receptor subpopulation sensitive to E-3174. E-3174 did not change the concentration-response curves for norepinephrine or KCl.

The extent of losartan specificity for the angiotensin II receptor was studied in a number of monoreceptor systems in a variety of preparations such as: aorta, jugular vein, and pulmonary

artery of the rabbit; stomach, urinary bladder, and portal vein of the rat; urinary bladder, colon, and ileum of the human; and the guinea pig ileum. In all these studies, the pA_2 values for losartan (against contractile responses to angiotensin I or angiotensin II) were 8.19 to 8.66. Losartan did not alter contractile responses to bradykinin, norepinephrine, substance P, neurokinin, bombesin, histamine, serotonin and acetylcholine. Further, in all of the above preparations, losartan (10 μ M) did not cause contraction by itself, suggesting that it lacks partial agonistic effects on the angiotensin II receptors.

b) Functional Studies:

The biochemical mechanism for the vasoconstrictor response to angiotensin II has been investigated extensively. It is now known that angiotensin II stimulates the phosphoinositide (PI) turnover signalling system by binding to specific cell surface receptors leading to the formation of second messengers, (a) inositol 1,4,5-triphosphate (IP_3) that mobilizes Ca^{++} from intracellular stores and stimulates the sodium-proton (Na^+/H^+) antiport, and (b) diacylglycerol that activates protein kinase C. Intracellular free calcium and stimulation of the Na^+/H^+ antiport function as intracellular signalling mechanisms for various cellular processes like vasoconstriction of vascular smooth muscle cells and cell growth (or hypertrophy of cells). The other major effect of angiotensin II on signal transduction pathways is the inhibition of adenylyl cyclase. Though both pathways (PI turnover and adenylyl cyclase inhibition) are mediated through activation of the AT_1 receptor, it is not yet clear whether different cellular responses are mediated through closely related subtypes of the AT_1 receptor.

The effect of losartan on angiotensin II-induced formation of IP_3 was evaluated in primary cultures of rat aorta vascular smooth muscle cells. In this study, losartan at 1 μ M completely inhibited the angiotensin II-induced elevation of IP_3 . Losartan at 0.1 μ M reduced the angiotensin II response from an increase of 390% to an increase of 150%. In isolated rat hepatocytes, angiotensin II stimulates both the labeling of phosphatidylinositol (resynthesis) and the release of inositol phosphates (breakdown). Both effects were blocked by losartan but not by PD123177 (an AT_2 receptor antagonist). Angiotensin II has no effect on the low levels of cAMP found in unstimulated membranes, but in membranes stimulated with GTP and lithium chloride angiotensin II can reduce the rate of production of cAMP. Losartan (10 μ M) shifted the angiotensin II-concentration-adenylyl cyclase inhibitory response curve in rat liver membranes, whereas PD123177 was without effect. No significant agonist activity was seen with losartan in both studies. The results indicate that the same receptor subtype, AT_1 , may couple uniquely to these two separate second messenger pathways, or the two subpopulations of the same receptor subtype, AT_1 , may couple independently to different transducing mechanisms, leading to different responses.

In vascular smooth muscle cells, angiotensin II induces vasoconstriction by facilitating the influx of extracellular Ca^{++} (by activating receptor-operated channels) and/or release of intracellular Ca^{++} . The latter event can be measured by monitoring the efflux of preloaded radiolabeled Ca^{++} (calcium mobilization) from rat aortic smooth muscle cells. Angiotensin II-induced $^{45}Ca^{++}$ efflux in these cells was inhibited in a concentration-dependent manner by

losartan with complete inhibition observed at concentration of 0.3 μM . Angiotensin II-induced release of calcium from intracellular stores (chiefly from endoplasmic reticulum) through the action of phosphoinositides (formation of second messenger IP_3) was studied as indicated by changes in Ca^{++} -Fura-2 fluorescence in rat aortic smooth muscle cells, liver cells and cardiomyocytes. In all these studies, angiotensin II (1 nM-1 μM) caused increases in $[\text{Ca}^{++}]_i$ in a concentration-dependent manner. Losartan inhibited this angiotensin II response in a concentration-dependent manner. Complete blockade was seen at a concentration of 1 μM . Losartan up to a concentration of 1 μM did not alter baseline levels of $[\text{Ca}^{++}]_i$ except in rat vascular smooth muscle cells, where 1 μM was shown to produce a small increase in $[\text{Ca}^{++}]_i$. By contrast, PD123177 (1 nM to 10 μM) did not effect the $[\text{Ca}^{++}]_i$ response of angiotensin II or the other agonists.

The effects of losartan on the cellular hypertrophy responses to angiotensin II were measured by studying the angiotensin II-induced changes in DNA and protein synthesis in cultures of rat aortic smooth muscle cells. In this study, angiotensin II (0.1 μM) provoked a 45% increase in protein synthesis and a 56% increase in DNA synthesis over the unstimulated control in a 24 hour period. Addition of losartan (10 μM) before the addition of angiotensin II to cells inhibited greater than 90% of angiotensin II-induced protein and DNA synthesis, while PD123177 (10 μM) was without any inhibitory effect. Increased protein synthesis is a hypertrophic response that contributes to cell growth in atherosclerosis. Both hypertension and atherosclerosis are the result of alteration in intracellular Ca^{2+} handling and abnormal growth of vascular smooth muscle cells. However, it should be noted that losartan is inactive against platelet-derived growth factor-induced cell protein synthesis, suggesting the specificity of action of losartan.

c) Receptor-mediated Release Studies:

Angiotensin II can release arachidonic acid metabolites both directly and indirectly via vasoconstriction (to release PGE_2) in coronary vessels, renal vessels, vas deferens and astrocytes. However, angiotensin II can exert vasodilatory effects presumably due to release of depressor prostaglandins (PGI_2) in cultured rat mesenteric and aortic smooth muscle cells. It has no stimulatory effect to release PGI_2 in cultured human vascular endothelial cells, porcine endothelial cells, bovine aortic and pulmonary arterial endothelial cells, and rat C_6 glioma cells and spleen macrophages. Thus, it could be concluded that angiotensin II release of prostacyclin (PGI_2) is cell type specific. Losartan (10 μM) but not PD123177 blocked these responses, characterizing the angiotensin II-stimulated prostaglandin formation as an AT_1 receptor-mediated event. According to the sponsor, losartan *per se* does not stimulate PGI_2 or PGE_2 release. However, two published reports describe a very significant release of PGI_2 or PGE_2 from porcine smooth muscle cells or human astrocytes by losartan. Additional studies are needed to clarify under what conditions, if any, losartan can release prostaglandin(s) directly.

The hypertensive action of angiotensin II is believed to be contributed to by its enhancing effect on sympathetic function. Enhancement of nerve-stimulated norepinephrine release and

the release of epinephrine from the adrenal medulla are believed to be major mechanisms by which angiotensin II acts to increase sympathetic activity. The effect of losartan to inhibit the actions of angiotensin II on norepinephrine release was evaluated in rat portal vein and guinea pig and rat adrenal medullary slices. In these studies, angiotensin II (10-100 nM) produced a dose-related increase in norepinephrine release, and losartan (1-3 μ M) significantly reduced (in some studies completely prevented) the effect of angiotensin II, suggesting an AT₁ receptor-mediated event.

The pharmacology of angiotensin II-stimulated aldosterone production was investigated in both rat and bovine adrenal glomerulosa cells. In these studies, angiotensin II-stimulated aldosterone production was inhibited completely by losartan and to a lesser extent or insignificantly by AT₂ antagonists.

D. *In vitro* Inhibition of Angiotensin II binding

The selectivity of losartan for angiotensin II receptors was evaluated by receptor binding techniques using the AT₁ receptor predominant rat aortic smooth muscle and adrenal cortical microsomes. In these preparations, losartan displaced ($IC_{50} = 19-20$ nM, $K_i \sim 19$ nM) specifically bound [¹²⁵I]angiotensin II in a monophasic manner. Similar binding results have been reported with losartan in adrenal cortex in rabbits and monkeys, glomerular, cortical tubular and outer medullary membranes from rat kidney, and human platelets. There are species differences in the relative abundance of losartan-sensitive angiotensin II receptors in kidney. In rat and rabbit, AT₁ predominates. In monkey kidney cortex, over half of the receptors are losartan-insensitive. Angiotensin II binding studies have also been carried out in fetal and adult human kidneys. In fetal kidney, AT₂ sites predominate. In adult kidney, losartan inhibits angiotensin II binding with high affinity.

In a rabbit left ventricular membrane preparation, losartan (as well as PD121981) displayed a shallow, biphasic curve with generally incomplete displacement of bound [¹²⁵I]angiotensin II (even at higher concentrations) with two K_i 's, 19 nM and 60 μ M. The K_i (the dissociation constant of an inhibitory nonradioactive ligand) for adrenal cortex in the same study was 14 nM. The biphasic displacement curve for losartan in the heart appears to have a smaller, higher affinity component as well as a larger, lower affinity one. These results suggest that cardiac angiotensin II receptors are functionally (and possibly structurally) different from angiotensin II receptors in the adrenal and vascular smooth muscle. If this is true, then losartan demonstrates some organ selectivity in binding well to adrenal and vascular smooth muscle cell receptors, but poorly to cardiac receptors. This means, losartan lowers blood pressure without affecting cardiac performance directly. From *in vitro* studies, the cardiac inotropic potency of angiotensin II (though mediated *via* AT₁ sites) is much less than the vasoconstrictor potency in vascular preparations. This suggests that angiotensin II in the plasma will affect b.p. before stimulating the heart. However, this needs substantiative proof. Similar results were reported in cardiac tissue from rat and monkey.

Angiotensin II acts on the brain to stimulate drinking, to increase sodium appetite, to increase

blood pressure, and to release pituitary hormones. The brain contains all the enzymes and precursors for angiotensin II synthesis and degradation. The angiotensin II receptor heterogeneity in the rat brain has been extensively studied using autoradiographic techniques and receptor ligand binding. Based on the differential sensitivities to losartan and PD123177, the midbrain, and thalamus-septum regions contain mostly AT₂ receptors and the hypothalamus contains a mixture of AT₁ and AT₂ receptors. The vascular organ of the lamina terminalis, subfornical organ, median preoptic nucleus, area postrema, and nucleus of the solitary tract contain exclusively AT₁ receptors. The pituitary gland contains mostly AT₁ sites. In the human brain there are many similarities with, but also important differences from, the rat brain. The similarities include the nucleus of the solitary tract and ventrolateral medulla, which contain AT₁ receptors, and the inferior olivary nucleus which contains AT₂ receptors in both species. Differences include locus ceruleus and subthalamic nucleus, which contain AT₂ receptors in rat brain, but contain exclusively AT₁ receptors in human brain. The subtype-specific receptor mapping is relevant to understanding the roles of angiotensin in the CNS and to central actions of angiotensin II receptor antagonists.

The specificity of the affinity of losartan for angiotensin II binding sites has been shown in binding assays with other ligands in various tissue preparations. Losartan had no affinity (at concentrations 10-100 μ M) for binding to receptor sites for: α -adrenergic ligand, muscarinic ligand, nicotinic, serotonin, dopamine, glycine, phencyclidine, nitrendipine, neurotensin or opiates. Losartan is a weak inhibitor of the specific thromboxane A₂/prostaglandin H₂ receptor in human platelets. Inhibition of platelet aggregation was only observed at concentrations greater than 40 μ M (i.e., greater than 1000-fold higher than required for angiotensin II inhibition).

1.1.2. Antihypertensive Effects

A. Renal Hypertension

The antihypertensive effects of losartan were evaluated in conscious rats with the right kidney intact and with the left kidney with a complete renal artery ligation. Six days after the ligation, the mean blood pressure and PRA were respectively elevated to 174 ± 7 mm Hg and 26.8 ng angiotensin I/ml/hr compared to 107 ± 3 mm Hg and 5.4 ng angiotensin I/ml/hr for sham operated rats. Hypertension in these animals is primarily due to the activation of the RAS. Given orally, losartan decreased blood pressure dose-dependently at 0.3 to 10 mg/kg (Fig. 13). The maximal hypotensive effect was achieved at 10 mg/kg. A dose of 100 mg/kg caused an earlier lowering of blood pressure but did not increase the magnitude of effect at 10

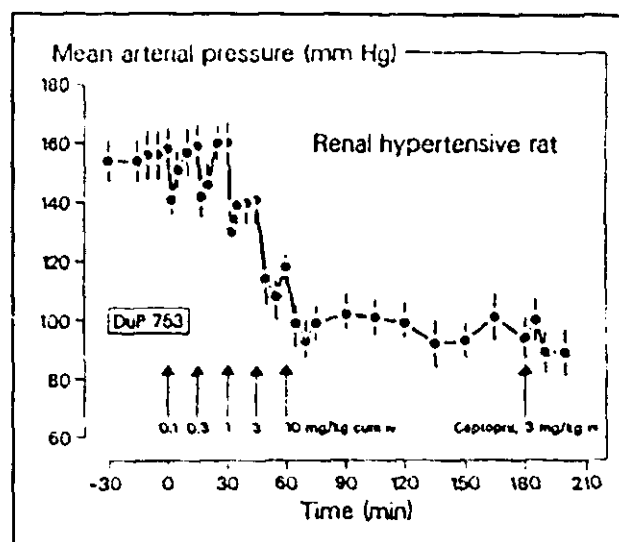


Fig. 14: Effects of losartan at 0.1, 0.3, 1, 3 and 10 mg/kg i.v. on mean arterial pressure in renal artery-ligated rats

mg/kg. The calculated oral ED30 for losartan was 0.59 mg/kg. A single oral dose of 3 mg/kg in renal artery-ligated rats produced a long duration of antihypertensive effect (at least 24 hr) with an onset of effect at 15-30 min and the maximal effect reached at 5-6 hr. None of the above doses increased heart rate compared to the vehicle control.

Cumulative i.v. injections of losartan (0.1 to 10 mg/kg) caused a dose-dependent decrease in mean arterial pressure in 6 day old renal artery ligated rats. At 10 mg/kg, losartan lowered mean blood pressure to a normotensive level and captopril, 3 mg/kg i.v., given after 180 min, did not further decrease mean arterial pressure (Fig. 14). When angiotensin II (0.1 µg/kg/min) was administered to renal artery-ligated rats before and after increasing doses of losartan, losartan at 0.03-3 mg/kg i.v. produced a dose-related decrease in the pressor response to angiotensin II (Fig. 15). Two hours following the injection of losartan (3 mg/kg i.v.), the *per se* effect on mean arterial pressure (Fig. 14) and the pressor response to angiotensin II (Fig. 15) were still markedly reduced. Losartan did not reduce the pressor response to vasopressin.

The selectivity and potency of E-3174 was evaluated in a series of renal hypertensive rats as described above for losartan. Cumulative i.v. injections of E-3174 at 0.003 to 0.3 mg/kg caused a dose-dependent decrease in mean arterial pressure. The calculated ED30 for E-3174 was 0.038 mg/kg (about 20 times more potent than losartan). Given orally, E-3174 was also effective in decreasing blood pressure dose-dependently at 0.3 to 10 mg/kg (Fig. 16). The calculated oral ED30 for E-3174 was 0.66 mg/kg. E-3174 did not alter heart rate when given either orally or intravenously.

Antihypertensive effects of losartan have also been evaluated in other renal hypertensive models such as 2-kidney 1-clip, 1-kidney 1-clip, reduced renal mass, aortic-coarctation renal hypertensive rats as well as renal hypertensive cynomolgus monkeys and dogs. Full reports of these studies are not available. To summarize, losartan prevented the development of hypertension in all of the above rat models. The antihypertensive efficacy of losartan studied in conscious instrumented 2-kidney 1-clip (Goldblatt hypertension) hypertensive cynomolgus monkeys indicated a markedly shorter duration of action (peak activity 1-2 hours, recovery 6 hours) compared to hypertensive rats (response > 24 hours). E-3174 dose-dependent reductions in mean arterial blood pressure, glomerular filtration rate and renal blood flow were observed in dogs which had been uninephrectomized and the remaining renal artery clamped to reduce renal blood flow by approximately 50%.

B. Genetic Hypertension

The antihypertensive effects of losartan were evaluated in conscious, catheterized (for measuring blood pressure and for drug administration) spontaneously hypertensive rats. Losartan given orally decreased mean arterial pressure in a dose-dependent manner at 3 and 10 mg/kg during a 3 hour observation period, while the vehicle had no effect (Fig. 17). Heart rate was not significantly changed. In a second experiment, losartan given intravenously at 3, 10 and 30 mg/kg caused a dose-dependent decrease in mean arterial pressure. The blood pressure lowering effects of losartan at these doses were sustained for at least 2 hours.

Losartan at 10 mg/kg i.v. significantly elevated basal PRA from 10.4 ± 1.2 to 63.1 ± 5.3 ng angiotensin I/ml/hr. In another study, losartan at 10 mg/kg i.v. reduced both mean arterial pressure and the pressor response to i.v. bolus injection of angiotensin II (0.1 μ g/kg). The maximum inhibition of the angiotensin II response was observed within 2 hours, whereas the maximum pressure reduction was observed at approximately 6 hours. Both parameters were still reduced after 24 hours. In another series of experiments using SHR, it was shown that losartan at 10 mg/kg i.v. significantly reduced the pressor response to angiotensin II (0.1 μ g/kg i.v.) but not to norepinephrine (0.3 μ g/kg i.v.). However, losartan increased the pressor response to vasopressin (0.03 I.U./kg i.v.) in SHR but did not affect the response to vasopressin in normotensive chimpanzees and dogs.

To study the chronic antihypertensive effect of losartan, SHRs were treated orally with losartan or vehicle for 4 days, and on the 5th day the rats were surgically prepared for blood pressure measurements. After the resting blood pressure (which was significantly lower for the losartan group than for the vehicle-treated group, 130 vs. 167 mm Hg) and heart rate were obtained, the animals were given the fifth dose (10 mg/kg p.o.) and the experiments were monitored for 3 hours. This dose caused a modest but significant decrease in mean blood pressure from 130 to 128, 122 and 120 mm Hg at 1, 2 and 3 hours postdose, respectively. Thus, no tolerance to the antihypertensive effect of losartan was noted as the 5th dose decreased blood pressure to a similar level as that of the single oral dose of 10 mg/kg of losartan. In two different studies losartan was administered chronically, in one case orally for 14 days, and in the other losartan was given at 15 mg/kg/day in the drinking water for 10 weeks. In both cases, no tolerance to the antihypertensive effect of losartan was seen. [Since losartan did not reduce blood pressure in WKY rats, these data suggest that RAS plays an important role in the control of blood pressure in SHRs.] As PRA is normal in the SHR, it is unlikely that circulating angiotensin II is responsible for the high blood pressure. On the other hand, vascular renin derived from the kidney contributes to the local generation of (tissue) angiotensin II for the maintenance of the vascular tone in SHRs.

The antihypertensive effects of losartan were evaluated in furosemide pretreated SHR. Furosemide-treated (10 mg/kg s.c. at 22 and 4 hours prior to dosing with losartan) SHR displayed significantly elevated levels of PRA (from 10.4 ± 1.2 to 24.9 ± 1.1 ng angiotensin I/ml/hours), resulting in the formation of circulating angiotensin II in addition to tissue angiotensin II. Thus, furosemide pretreatment enhanced the blood pressure lowering effect of losartan at 3 and 10 mg/kg i.v.

The removal of both kidneys reduced the PRA to almost undetectable levels. Losartan at 10 mg/kg i.v. had no significant effect on blood pressure in these low renin (bilateral nephrectomized) SHR.

Losartan was also evaluated in conscious, trained, genetically (Penn) hypertensive dogs with systolic blood pressure of 140 to 220 mm Hg and diastolic blood pressure >100 mm Hg. The animals were treated with losartan (1, 3, 10 or 30 mg/kg i.v.) over a period of 4 weeks. Parameters assessed were the pressor responses to angiotensin I (1.0 μ g/kg i.v.) and

angiotensin II (0.3 µg/kg), PRA and renal function (creatinine, PAH clearance).

Losartan caused a dose-related slight but significant reduction (40-70 mm Hg) in blood pressure response to angiotensin I (10 and 30 mg/kg) and angiotensin II (1-30 mg/kg). The reduction in blood pressure in hypertensive dogs is relatively small when compared to the antihypertensive effects described in other models of hypertension. Losartan dose-dependently increased glomerular filtration rate and effective renal plasma flow, while significantly reducing renal vascular resistance. All doses of losartan increased the fractional excretion of sodium while only higher doses (10 and 30 mg/kg) increased the fractional excretion of potassium. Although a trend towards an increase in PRA was observed at 45 to 75 min after administration of losartan, these increases were not statistically significant at any of the doses studied.

C. DOCA-Salt Hypertension

The antihypertensive effects of losartan were evaluated in conscious rats made hypertensive by implanting DOCA pellets subcutaneously and providing 0.1% saline for drinking for 7-8 weeks. Hypertension in this model is fully developed by 7-8 weeks (mean arterial pressure 156 ± 9 mm Hg,) with low PRA (0.47 ± 0.44 ng angiotensin I/ml/hr), which in turn results in low levels of angiotensin II and a suppressed RAS. In this model, losartan at 10 mg/kg i.v. did not lower blood pressure. On the other hand, hydralazine (0.3 mg/kg i.v.), a direct acting vasodilator, lowered blood pressure in these rats.

1.1.3. Effects in Normotensive Animals

A. Studies in Conscious Rats

Since angiotensin II does not normally contribute to the maintenance of arterial pressure, an AT₁ angiotensin II receptor antagonist would not be expected to affect blood pressure in normotensive animals. Losartan (10 mg/kg p.o. or 1 to 100 mg/kg i.v.) had no acute effect on blood pressure of normotensive rats for 3 hours post-treatment. Though heart rate was more variable, no significant effect was observed. Chronic oral administration of losartan (10 mg/kg/day p.o.) for 14 days in normotensive Wistar-Kyoto (WKY) rats was shown to have no effect on systolic blood pressure, suggestive of lack of partial agonistic action at the AT₁ receptor. Additionally, losartan pretreatment blocked the pressor effect of saralasin (0.1 to 10 µg/kg i.v.) indicating that saralasin exerts its agonist action at the AT₁ receptor.

In contrast, a single subcutaneous injection of losartan (10 mg/kg) significantly decreased systolic blood pressure of normotensive rats 6 hours post-treatment and after 21 days of daily treatment. Although the blood pressure had returned to control values by 24 hours post-injection on each day, the pressor response to an i.v. bolus injection of angiotensin II (0.1 µg/kg) was significantly attenuated in chronic losartan treated rats 24 hr after the last injection. The significant reduction in blood pressure in normotensive animals (with an intact sympathetic nervous system) would suggest that the RAS may play a more significant role in

blood pressure maintenance/regulation in the presence of a fully functional sympathetic nervous system than previously thought. The fact that blood pressure returned to normal levels 24 hours post-injection of losartan would suggest that compensatory actions of the sympathetic nervous system and/or other regulatory mechanisms have occurred.

B. Studies in Conscious Dogs

In conscious dogs with normal renin, losartan at 1 to 10 mg/kg i.v. produced a dose-dependent and transient decrease in blood pressure. E-3174 had no effect on the blood pressure. It is not clear from the studies whether the transient hypotensive effects of losartan are unrelated to angiotensin II receptor antagonism. This transient effect does not contribute to the blood pressure lowering or hemodynamic effects of losartan beyond the first few minutes postdose. In furosemide-treated dogs with high renin, both losartan (10, 30 mg/kg p.o. and 3, 10, 30 mg/kg i.v.) and E-3174 (3, 10, 30 mg/kg i.v. and 10 mg/kg p.o.) produced marked and long lasting reductions (more than 3 hours) in mean arterial pressure. The maximum reductions in blood pressure were dose-related.

1.2. *General Pharmacological Studies*

1.2.1. **Cardiovascular Effects**

A. Hemodynamic

Acute hemodynamic effects of losartan were evaluated in furosemide-treated (10 mg/kg i.m. at 18 and 2 hours before the experiment) anesthetized dogs. Losartan at 3 (and not at 1) mg/kg i.v. reduced mean arterial pressure and total peripheral resistance while having little effect on heart rate or cardiac output or dp/dt or blood flow in the coronary, renal, or iliac vascular beds. However, in sodium-deplete anesthetized dogs (animals maintained on low sodium diet for 7 days and treated with furosemide at 10 mg/kg i.m. for 4 days) with high PRA, losartan at 5 mg/kg i.v. decreased blood pressure, increased renal blood flow and decreased renal vascular resistance in a similar fashion. These effects were less pronounced in sodium replete anesthetized dogs with low PRA, suggesting the dependence of renal effects of losartan on the basal PRA. Thus, the potent action of losartan on renal function could be seen only in sodium-deplete anesthetized dogs.

The acute cardiovascular and autonomic effects of losartan were evaluated in anesthetized dogs. Losartan at 10 mg/kg i.v. antagonized the mean arterial pressure and heart rate response to angiotensin II but had no significant effects on mean arterial pressure, heart rate, lead II ECG recordings or meaningful effects on autonomic responses.

B. Cardiac

The direct effect of losartan on myocardial rate and force of contraction was evaluated in isolated guinea pig atrial preparations. Losartan at concentrations of 0.1 to 10 μ M did not

significantly alter atrial rate in spontaneously beating atrium and developed tension (inotropism) in left paced atrium.

The cardiac cell electrophysiologic effects of losartan and E-3174 were evaluated in left ventricular Purkinje fibers isolated from dogs. Both losartan and E-3174 (at concentrations 0.3 to 10 μ M) showed a lack of direct electrophysiological activity.

1.2.2. Renal Effects

The acute effects of losartan on renal function were assessed in anesthetized normotensive (WKY) and SHR and in a group of anesthetized euvoletic Munich-Wistar rats. The SHR and WKY were volume expanded with a 0.9% sodium chloride infusion of 100 μ l/min. The euvoletic rats were infused with 0.9% sodium chloride at a rate of 20 μ l/min. Losartan at 2 or 10 mg/kg i.v. had no effect on urine volume, sodium excretion, renal blood flow or glomerular filtration rate in WKY. In SHR, losartan at 2 mg/kg decreased urine flow (24%), increased renal blood flow (30%), but sodium excretion, GFR, and arterial pressure were not significantly altered. Losartan at 10 mg/kg i.v. significantly reduced arterial pressure, urine volume, and sodium excretion while significantly increasing renal blood flow (34%). In euvoletic rats, losartan at 2 mg/kg i.v. increased PRA, renal blood flow, urine flow, and sodium excretion, while mean arterial pressure and GFR were unaltered. It was concluded that the limited renal effects of losartan do not contribute to the initial antihypertensive action.

The renal effects of losartan were studied in anesthetized dogs maintained on either normal sodium diet (104 mEq/day) or on a low sodium diet (5 mEq/day, also received furosemide at 10 mg/kg i.v. on days 2 to 5). In sodium replete dogs (PRA 1.2 ± 0.3 ng angiotensin I/ml/hr), losartan at 5 mg/kg i.v. decreased mean arterial pressure, renal vascular resistance, and filtration fraction, and increased renal blood flow, urinary sodium, and potassium and urine volume. In sodium depleted dogs (PRA 21 ± 2.7 ng angiotensin I/ml/hr), losartan at 5 mg/kg i.v. produced significant reductions in arterial pressure, renal vascular resistance, and filtration fraction while increasing renal blood flow. The urinary excretion of sodium, potassium or water and GFR were not significantly altered. The data thus shows that losartan produces potent action on renal function only in sodium-deplete anesthetized dogs (which are RAS dependent since PRA levels are elevated).

Further, losartan has also been evaluated for its renal protective effect in SHR. Losartan at 1 and 10 mg/kg/day i.p. decreased urinary protein excretion to the same extent as enalapril. This suggests that losartan, like ACE inhibitors, is effective in models of renal failure.

1.2.3. Neuropharmacological Effects

Losartan administered orally to rats at doses ranging from 13 to 100 mg/kg, equivalent to 22 to 167 times its antihypertensive ED₃₀ in the rat (0.6 mg/kg p.o.) produced no overt signs. In mice, losartan at 100 mg/kg p.o. produced ptosis in 2 of 15 animals. No other symptoms were observed. In other studies in mice, it was found that losartan does not have analgesic,

neuroleptic, opiate antagonistic, anticonvulsant, or dopamine antagonistic activity. In the models of cognition, losartan at 1 and 30 mg/kg s.c. in the mouse, and 10 and 30 mg/kg s.c. in the rats reversed the scopolamine-induced deficit in the passive avoidance test. Also, at 3 mg/kg s.c. losartan reversed the deficit in the delayed-matching-to-position test (working memory task) induced by scopolamine. These effects are similar to that reported for ACE inhibitors.

Losartan at 3, 10, 25, 50 and 100 mg s.c. produced significant changes in the cortical EEG profile in conscious rats. The observed EEG changes were similar to those of a general vigilance-enhancing profile.

It is known that acute and chronic RAS inhibition do not always result in the same antihypertensive effect. When the ACE inhibitors are administered repeatedly over a long time, the reduction in blood pressure below the pretreatment level persists long after discontinuation of treatment. This "persistent" antihypertensive effect of ACE inhibition is of particular importance when the regimen is started before hypertension is completely established. In this regard, the effects of angiotensin II blockade by losartan on the development and maintenance of hypertension in stroke-prone SHR (SHR-SP) was evaluated. In this study animals were dosed with losartan (1 or 10 mg/kg in drinking water) at 5 to 13 weeks of age. Rats were sacrificed either at 13 or 29 weeks of age. Systolic blood pressure was measured by the tail-cuff method.

Losartan at 10 mg/kg/day like enalapril (3 mg/kg/day) inhibited the age-related development of hypertension in SHR-SP. Heart weight was significantly lower than the controls. In SHR-SP, PRA markedly increases in adults (from 16 to 29 weeks of age) with concomitant development of extremely high blood pressure, thereby suggesting that RAS plays an important role in the pathophysiology of this animal model. Losartan at 10 mg/kg significantly lowered PRA and immunoreactive renin content in the juxtaglomerular cells compared to controls. Thus, continuous inhibition of RAS from the pre-hypertensive stage of SHR-SP may be important for exerting the persistent antihypertensive effect. In SHR-SP, more than 80% of rats develop cerebral hemorrhage and/or infarction when the animals are somewhat over 20 weeks of age. Cerebrovascular lesions determined at the age of 29 weeks were significantly prevented by losartan. None of effects were observed at 1 mg/kg/day.

1.2.4. Gastrointestinal Effects

Losartan at 10 mg/kg s.c. had no effect on intestinal motility in conscious mice. In another study in mice, losartan at 10, 30 and 100 mg/kg p.o. showed no effect on intestinal propulsion. The effects of losartan on gastric secretion were evaluated in rats with pylorus ligation. In this study, 30 but not 3 mg losartan/kg, administered by oral gavage, significantly inhibited gastric secretion by 22%, and gastric output by 45%. In contrast, losartan at 10 mg/kg, administered directly into the stomach via the fistula cannula in dogs, did not significantly alter basal gastric acid secretion or that stimulated by exogenous gastrin.

1.2.5. Anti-inflammatory Effects

Losartan at 2 mg/kg i.p. showed no effects on inflammation induced by carrageenan in rat paw.

1.2.6. Effects on Platelet Aggregation

Aggregation of platelets induced by the addition of arachidonate *in vitro* was inhibited by losartan at a concentration of 1 mM. Losartan at 100 but not at 10 mg/kg p.o. significantly reduced arachidonate-induced, but not ADP-induced platelet aggregation *ex vivo* in rats.

2. PHARMACOKINETICS

2.1. Absorption and Pharmacokinetic Studies

2.1.1. Absorption and Pharmacokinetics of Losartan in Rats

Study Facility: E.I. duPont Pharmaceutical Labs, Wilmington DE

Study No: MP 89-033

Study Dates: Not stated; Report dated 5/10/89

GLP Compliance: Not indicated.

Animals: Male Sprague-Dawley rats (250-350 gm)

Procedure: Losartan was dissolved in sterile normal saline and administered intravenously (1.0 or 3.0 mg/kg) as a single bolus (4 rats/dose group) or administered orally (10 mg/kg) by gavage (3 rats). Samples of venous blood were obtained from rats via indwelling cannulas at 0, 5, 15, 30, 45 min, 1, 2, 3, 6 and 8 hours after IV administration and at similar intervals including 24 hours after oral administration. Plasma concentrations of losartan were measured by reverse phase HPLC; these measurements were used for calculating plasma half-life, clearance, volume of distribution and plasma AUC. Oral bioavailability was calculated according to:

$$\frac{AUC_{\text{oral}} \times \text{IV dose}}{AUC_{\text{iv}} \times \text{PO dose}} \times 100 = \% \text{ Oral Bioavailability}$$

Results: Plasma levels of losartan declined in an apparent biexponential fashion following IV administration with a terminal half-life of 100 to 113 min. The mean oral bioavailability was approximately 33% for a 10 mg/kg oral dose. The terminal half-life after an oral dose, 166 min, was longer than that observed after the IV doses. This could be due to the slow and continuous absorption of the oral dose or enterohepatic recirculation. Pharmacokinetic results are summarized as follows:

TABLE 2.1.1.1
PHARMACOKINETIC PARAMETERS FROM IV LOSARTAN

Parameter	1 mg/kg IV	3 mg/kg IV
Half-life (min)	100 +/- 17	113 +/- 7
Clearance (ml/min/kg)	6.2 +/- 0.7	7.8 +/- 0.3
Vdss (L/kg)	0.57 +/- 0.04	0.92 +/- 0.12
AUC _{0-inf} (ug.min/ml)	168.5 +/- 18.2	388.5 +/- 17.8

Values are the mean +/- SEM from 4 rats/dose group
 Vdss = apparent volume of distribution at steady-state
 AUC_{0-inf} = Area under the plasma concentration vs time curve

TABLE 2.1.1.2
PHARMACOKINETIC PARAMETERS FROM PO (10 MG/KG) LOSARTAN

Parameter	Mean +/- SEM
Half-life (min)	166 +/- 29
Tmax (min)	130 +/- 61
Cmax (ug/ml)	1.57 +/- 0.28
AUC _{0-inf} (ug.min/ml)	428.5 +/- 192.3
Clearance (ml/min/kg)	56.2 +/- 39.0
F (%)	33.4 +/- 14.9

Values are the mean +/- SEM from 3 rats
 F = Oral bioavailability

2.1.2. Absorption and Pharmacokinetics of Losartan in Dogs

Study Facility: E.I. duPont Pharmaceutical Labs., Wilmington, DE

Study No: MP 89-032

Study Dates: Not stated; Report dated 5/10/89

GLP Compliance: Not stated.

Animals: Male Beagle dogs (7-10 kg)

Procedure: Losartan was dissolved in sterile normal saline and administered intravenously (3 mg/kg) as a single bolus (5 dogs) or administered

orally (5, 10 or 20 mg/kg) by gavage (4 dogs/dose group). Samples of venous blood were obtained from dogs by repeated venipuncture at 0, 5, 10, 15, 30 min, 1, 1.5, 2, 4, 6, 8 and 24 hours after dosing. Plasma concentrations of losartan were measured by reverse phase HPLC; these measurements were used for calculating plasma half-life, clearance, volume of distribution, C_{max}, T_{max} and plasma AUC.

Results: Plasma concentrations of losartan in dogs given a single 3 mg/kg IV bolus declined in a multiexponential fashion with a mean terminal plasma half-life of 41 min. After oral dosing there was a linear relationship between the dose and AUC or C_{max}. Pharmacokinetic results are summarized as follows:

TABLE 2.1.2.1
PHARMACOKINETIC PARAMETERS FROM IV (3 MG/KG) LOSARTAN

Parameter	Mean +/- SEM
Half-life (min)	41 +/- 10
Clearance (ml/min/kg)	22.2 +/- 2.9
V _{dss} (L/kg)	0.30 +/- 0.03
AUC _{0-inf} (ug.min/ml)	144.5 +/- 18.3

V_{dss} = Apparent volume of distribution at steady state

AUC_{0-inf} = Area under the plasma concentration vs time curve

TABLE 2.1.2.2
PHARMACOKINETIC PARAMETERS FROM PO LOSARTAN

Parameter	5 mg/kg PO	10 mg/kg PO	20 mg/kg PO
Half-life (min)	144 +/- 31	108 +/- 10	153 +/- 22
T _{max} (min)	25 +/- 12	45 +/- 9	53 +/- 8
C _{max} (ug/ml)	0.79 +/- 0.22	1.97 +/- 0.04	2.94 +/- 0.84
AUC _{0-inf} (ug.min/ml)	54.7 +/- 9.3	156.7 +/- 18.2	257.1 +/- 57.2
F (%)	22.5 +/- 0.6	33.2 +/- 1.7	25.7 +/- 2.2

Values are the mean +/- SEM from 4 dogs/dose group

F = Oral bioavailability

2.1.3. Oral Bioavailability of Losartan and Metabolite (L-158,641) in Adult Chimpanzees

Study Facility: MSD Research Laboratories, West Point, PA and New Iberia Research Center, New Iberia, LA

Study No: # 9201-805-062-0229

Study Dates: Not stated; Report dated 6/11/93

GLP Compliance: Not stated.

Subjects: Four adult chimpanzees (49-63 kg)

Procedure: Losartan and its metabolite were dissolved in sterile normal saline and administered intravenously (40 mg of losartan or 20 mg of L-158,641) as a single dose over 20 min or administered orally (100 mg of losartan or 100 mg of L-158,641) by nasogastric tube in a 4-way randomized, crossover design (each animal received each of the four doses in the crossover design). About six to seven days separated treatments. With IV administration, 6 ml venous blood samples were collected at 0, 10, 20, 25, 30 and 60 min and at 2, 3, 4, 6, 9, 16 and 24 hours after dosing.. Six-ml venous blood samples were collected at 0, 20, 40 and 60 min and 2, 3, 4, 6, 9, 12, 16 and 24 hours after oral administration. Urine samples were collected from the animals in metabolism cages prior to dosing and at 0-12, 12-24, 24-36, 36-48 and 48-72 hr intervals. Blood and urine were assayed for parent drug and metabolite by HPLC and these measurements used in calculating the pharmacokinetic parameters summarized below.

Results: Based on a comparison of IV to PO AUCs, the absolute oral bioavailabilities of losartan and its metabolite, L-158,641, were 35% and 34%, respectively.

TABLE 2.1.3.1
PHARMACOKINETIC PARAMETERS FROM IV ADMINISTRATION

Parameter	Losartan 40 mg IV		L-158,641 20 mg IV
	Losartan	L-158,641	
C max, ng/ml	2582*	165	4370*
Tmax, hr	NA	1.25	NA
AUC _{0-inf} , ng.hr/ml	1278	677	5267
t1/2, hr	1.02	NA	6.70
Vd _s , L	16.3	NA	15.1
CL, ml/min	619	NA	71
% Dose in urine	16%	2.3%	60%

NA = Not Applicable

* Concentrations immediately after drug administration.

TABLE 2.13.2.
PHARMACOKINETIC PARAMETERS FROM PO ADMINISTRATION

Parameter	Losartan 100 mg PO		L-158,641 100 mg PO
	Losartan	L-158,641	
C _{max} , ng/ml	189	66	966
T _{max} , hr	7.0	10.5	7.8
AUC _{0-∞} , ng.hr/ml	1392	998	13207
CL, ml/min	67	22	23
% Dose in Urine	4.3%	1.3%	17%
Oral Bioavailability	35.4%	NA	34.4%

NA= Not Applicable

2.1.4. Oral Bioavailability and Pharmacokinetics of Losartan and Metabolite (L-158,641) in Humans.

Study Facility: MSD Research Laboratories, West Point, PA and Jefferson Medical College, Clinical Research Unit, Philadelphia, PA

Study No: MA # 060

Study Dates: Not stated; Report dated 3/19/93

GLP Compliance: Not stated.

Animals: Six healthy, adult, male subjects

Procedure: ¹⁴C-losartan and its metabolite (non-radiolabelled) were dissolved in sterile normal saline and administered intravenously (30 mg of losartan or 20 mg of L-158,641) as a single dose over 20 min or administered orally (losartan only, 100 mg) as a single dose in a randomized, crossover design. Seven days separated adjacent treatments. With IV administration, 6 ml venous blood samples were collected at 0, 10, 20, and 30 min and at 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36 and 48 hours after dosing. Six-ml venous blood samples were collected at 0, 15, 30 and 45 min and 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36 and 48 hours after oral administration. Urine samples were collected prior to dosing and at 0-2, 2-4, 4-6, 6-8, 8-12, 12-18, 18-24, 24-36, 36-48, 48-72 and 72-96 hr intervals. Blood and urine were assayed for parent drug and metabolite by HPLC and resulting values used in calculating pharmacokinetic parameters summarized below.

Results: The observed and calculated pharmacokinetic values are summarized in the

tables below. A comparison of AUCs from oral and IV losartan showed that oral bioavailability of losartan in normal male subjects was 36.5%.

TABLE 2.1.4.1
PHARMACOKINETIC PARAMETERS FROM IV ADMINISTRATION

Parameter	Losartan 30 mg IV		L-158,641 20 mg IV
	Losartan	L-158,641	
C max, ng/ml	1453*	149	3721*
Tmax, hr	NA	4.0	NA
AUC _{0-inf} , ng.hr/ml	851	1332	5969
t1/2, hr	3.2	5.3	6.3
Vd _s , L	46.6	NA	10.3
CL, ml/min	559	NA	47
% Dose in urine	11.5%	7.6%	55%

NA = Not Applicable

* Concentrations immediately after drug administration

TABLE 2.1.4.2
PHARMACOKINETIC PARAMETERS FROM PO ADMINISTRATION

Parameter	Losartan 100 mg PO	
	Losartan	L-158,641
Cmax, ng/ml	659	653
Tmax, hr	0.46	2.3
AUC _{0-inf} , ng.hr/ml	1091	4072
CL, ml/min	64	27
% Dose in Urine	4.8%	7.6%
Oral Bioavailability	36.5%	NA

NA= Not Applicable

2.2. Distribution Studies

2.2.1. Tissue Distribution of Radiolabelled Losartan in Rats

Study Facility: E.I. duPont Research Labs, Wilmington, DE

Study No.: MP89-005

Study Dates: Not stated; Report date-2/02/89

GLP Compliance: Not indicated.

Animals: Male Sprague-Dawley rats (250-290 gm)

Procedure: ^3H -Losartan was prepared as an aqueous solution and administered orally at a dose of 10 mg/kg to 28 rats by gavage. Groups of 4 rats were sacrificed at 0.5, 1, 4, 8, 24, 48 and 96 hours after dosing. Whole blood was collected and major tissues and organs were removed and combusted in a tissue oxidizer. The trapped radioactivity was measured by liquid scintillation spectrometry.

Results: Absorption from the GI tract was rapid with peak blood and tissue levels appearing 30 to 60 min after dosing. Overall, 33% and 38% of the dose was contained in all tissues sampled at 30 and 60 min, respectively. Radioactivity in liver, lungs and kidney declined over the first 8 hours with half-lives of 3 to 4 hours. At 24 hours postdose all tissues, including blood, contained less than 1% of the dose. Tissues and organs containing > 0.5% of the administered dose at any sampling time are summarized below.

TABLE 2.2.1.1
MEAN % OF RADIOACTIVITY CONTAINED IN TISSUES AFTER 10 MG/KG ORAL LOSARTAN

Tissue	0.5 Hr	1 Hr	4 Hr	8 Hr	24 Hr
Kidney	0.86	0.52	0.25	0.11	0.02
Sm. Intest. Distal	0.18	1.56	12.2	0.77	BQL
Sm. Intest. Proximal	3.83	13.6	3.58	0.34	BQL
Stomach	1.33	0.71	0.11	0.03	BQL
Liver	19.7	15.5	9.56	4.67	0.47
Muscle	3.22	2.53	1.59	1.34	BQL
Skin	1.02	0.95	0.83	0.49	BQL
Plasma	2.34	2.51	1.44	0.48	0.16
Whole Blood	2.21	2.16	1.17	0.53	0.24

BQL= Below Quantifiable Limit (240 dpm)

2.2.2. Distribution of Radiolabelled Losartan in Rats

Study Facility: Tokai Research Laboratories, Daiichi Pure Chemical Co, Japan

Study No: AE-1565

Study Dates: 5/29/91 - 9/10/91

GLP Compliance: Not indicated.

Animals: Male Sprague-Dawley rats (185-249 gm)

Procedure: ^{14}C -Losartan was dissolved in phosphate buffer and administered intravenously (3 mg/kg; 15 rats) or orally (10 mg/kg; 21 rats) by gavage. The animals were kept in metabolism cages and urine and feces were collected up to 168 hours after dosing. Groups of 3 rats were sacrificed at 0.5, 1, 4, 8, 24 and 96 hours after oral administration and 0.25, 1, 8 and 48 hours after IV administration. Whole blood was collected and major tissues and organs were removed and combusted in a tissue oxidizer. The radioactivity was trapped and measured by liquid scintillation spectrometry. Radioactivity in urine and in acidified methanol extracts from feces was measured by liquid scintillation spectrometry.

Results: Tissues containing concentrations of radioactivity above 3 ug equivalent of losartan/gm are presented in the following tables. Negligible levels of radioactivity were detected in brain or fat tissue. The results of this study conducted by a Japanese pharmaceutical company are qualitatively similar (in terms of relative tissue concentrations) to those of the previous oral administration study conducted at duPont Research Labs.

TABLE 2.2.2.1.
CONCENTRATION OF RADIOACTIVITY (UG EQUIV. LOSARTAN/GM) CONTAINED IN TISSUES
AFTER 10 MG/KG ORAL LOSARTAN

Tissue	0.5 Hr	1 Hr	4 Hr	8 Hr	24 Hr
Kidney	10.1	11.6	3.42	3.48	0.08
Small Intestine	11.3	13.2	4.12	1.34	BQL
Stomach	16.6	20.7	1.66	1.54	BQL
Heart	4.40	1.32	0.30	0.31	BQL
Liver	72.4	61.0	36.2	40.7	0.65
U. Bladder	3.51	3.02	2.64	2.45	BQL
Trachea	3.48	1.16	0.69	0.75	BQL
Plasma	6.38	8.04	2.55	2.56	0.12
Whole Blood	3.71	4.54	1.40	1.41	BQL

BQL= Below Quantifiable Limit (240 dpm)

TABLE 2.2.2.2.
CONCENTRATION OF RADIOACTIVITY (UG EQUIV. LOSARTAN/GM) CONTAINED IN TISSUES
AFTER 3 MG/KG IV LOSARTAN

Tissue	0.25 Hr	1 Hr	8 Hr	48 Hr
Kidney	3.70	6.31	0.83	0.02
Small Intestine	2.10	1.55	0.59	BQL
Bone Marrow	1.24	2.15	0.15	BQL
Lung	0.49	1.30	0.18	0.02
Liver	41.7	60.3	13.0	0.09
U. Bladder	0.75	0.61	0.19	BQL
Cecum	0.24	0.46	2.80	0.01
Plasma	2.09	3.71	0.16	0.03
Whole Blood	1.23	2.26	0.44	BQL

BQL= Below Quantifiable Limit (240 dpm)

2.2.3. Transfer of Radiolabelled Losartan into Fetus and Milk in Rats

Study Facility: Tokai Research Laboratories, Ibaragi-ken, Japan

Study No: AE-1721

Study Dates: 5/28/92 - 9/22/92

GLP Compliance: Not stated; QA audit report included.

Animals: Pregnant and lactating Sprague Dawley rats (pregnant rats weighed 279-233gm and nursing rats weighed 320-347gm).

Procedure: ¹⁴C-Losartan was dissolved in distilled water and administered as a single oral dose (10 mg/kg) by gavage to 9 pregnant rats on days 18 of gestation or to 18 lactating rats on day 11 after delivery. Pregnant rats were sacrificed at 1, 8 and 24 hours (3 rats/time period). Maternal and fetal blood samples were collected in heparinized tubes. Maternal and fetal tissues and amniotic fluids in the same litter were pooled, solubilized using a tissue solubilizer and radioactivity measured by liquid scintillation spectrometry. In lactating rats, maternal blood was collected from the tail veins and milk was collected from the nipples at 0.5, 1, 2, 4, 8, 24 and 48 hours after dosing (3 rats/time period). Radioactivity in the milk and blood of lactating rats was measured by liquid scintillation spectrometry.

Results: Radioactivity was detected in fetal tissue following administration of radioactive losartan to pregnant rats. Fetal concentration of radioactivity was barely detectable 1 hour after treatment of dams, but fetal radioactivity levels increased at 8 and 24 hours. The concentrations of radioactivity measured in maternal and fetal tissues are as follows:

TABLE 2.2.3.1.
RADIOACTIVITY CONCENTRATION (UG EQUIVALENT/GM) AFTER 10 MG/KG PO DOSE OF
14C-LOSARTAN

Tissue	1 hour	8 hours	24 hours
Maternal Plasma	3.8	0.79	0.08
Blood	2.5	0.51	0.05
Lung	1.1	0.25	0.05
Liver	84.7	22.0	2.36
Kidney	10.3	2.2	0.53
Uterus	1.0	0.28	0.09
Fetal Blood	0.02	0.14	0.18
Brain	BQL	0.01	0.01
Heart	BQL	0.04	0.05
Lung	BQL	0.05	0.05
Liver	0.04	0.17	0.15
Kidney	BQL	0.08	0.09
% of Dose/Fetus	0.00	0.01	0.01

BQL=Below quantifiable limit (<0.01 ug equiv/gm)

Radioactivity was detected in the milk of lactating rats as early as 30 min after dosing and the radioactivity levels increased up to 8 hours following the single 10 mg/kg dose. Radioactivity was still detected in the milk up to 48 hours after dosing.

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TABLE 2.2.3.2.
RADIOACTIVITY CONCENTRATION (UG EQUIVALENT/ML) IN MATERNAL PLASMA AND MILK IN LACTATING RATS AFTER 10 MG/KG PO OF ¹⁴C-LOSARTAN.

Time (hr)	Maternal Radioactivity Concentration Milk	Plasma
0.5	0.03	1.26
1	0.04	1.02
2	0.09	1.01
4	0.16	1.18
8	0.30	0.76
24	0.11	0.33
48	0.05	0.11

2.2.4. Binding of Losartan to Rat, Dog and Human Plasma Protein:

Study Facility: Du Pont Haskell Research Center, Newark, NJ

Study No.: DMP 93-008

Study Dates: Not stated

GLP Compliance: Not indicated

Blood/Plasma: Fresh blood and plasma were obtained from male Sprague-Dawley rats and Beagle dogs. Human plasma was obtained from normal male volunteers.

Procedure: Plasma from Beagle dogs (n=4), human volunteers (n=4) or rats (n=4) were added to glass tubes containing ¹⁴C-losartan or ³H-carboxylic acid metabolite (E-3174) to give final concentrations of 0.5, 1.0, 2.0 and 5.0 ug/ml of losartan or 0.1, 1.0, and 10.0 ug/ml of E-3174. The samples (in triplicate) were mixed and incubated for 30 min at 37°C, centrifuged and aliquots of plasma analyzed by liquid scintillation spectrometry to determine the fraction of drug unbound to plasma protein. In a separate series of experiments, solutions of other drugs (aspirin, naproxen, warfarin, ibuprofen, diazepam) were added to plasma containing losartan or E-3174 to determine drug-drug interaction of plasma protein binding.

Results: Losartan binding to plasma protein was extensive in rat, human and dog plasma. Unbound fraction of losartan was lowest in the rat (0.7% to 1.0%), followed by human (1.3% to 1.4%) and then dog (2.7% to 3.1%). The fraction unbound appeared to be concentration-independent. Plasma binding of the pharmacologically active

metabolite, E-3174 (L-158,641), was greater than that of the parent compound.

TABLE 2.2.4.1.
PERCENT UNBOUND (FREE) FRACTION OF DRUG IN PLASMA

Conc. ug/ml	Losartan			E-3174	
	Man	Dog	Rat	Man	Rat
0.1	ND	ND	ND	0.2	0.1
0.5	1.4	3.1	0.7	ND	ND
1.0	1.3	2.7	0.8	0.2	0.2
2.0	ND	2.9	1.0	ND	ND
5.0	1.2	ND	ND	ND	ND
10.0	ND	ND	ND	0.2	0.1

Neither losartan nor E-3174 was displaced *in vitro* from human plasma proteins by coinubation with pharmacologically relevant concentrations of naproxen (50 ug/ml), ibuprofen (20 ug/ml), diazepam (0.25 and 3.5 ug/ml) or warfarin (2 and 20 ug/ml). Suprapharmacologic concentrations of aspirin (300 and 3000 ug/ml), naproxen (500 ug/ml) and ibuprofen (200 ug/ml) increased the fraction of unbound losartan and metabolite 2- to 7-fold.

2.3. Metabolism

2.3.1. Metabolism of Losartan by Rat, Monkey and Human Liver Slices.

Study Facility: Merck Research Labs, Rahway, NJ

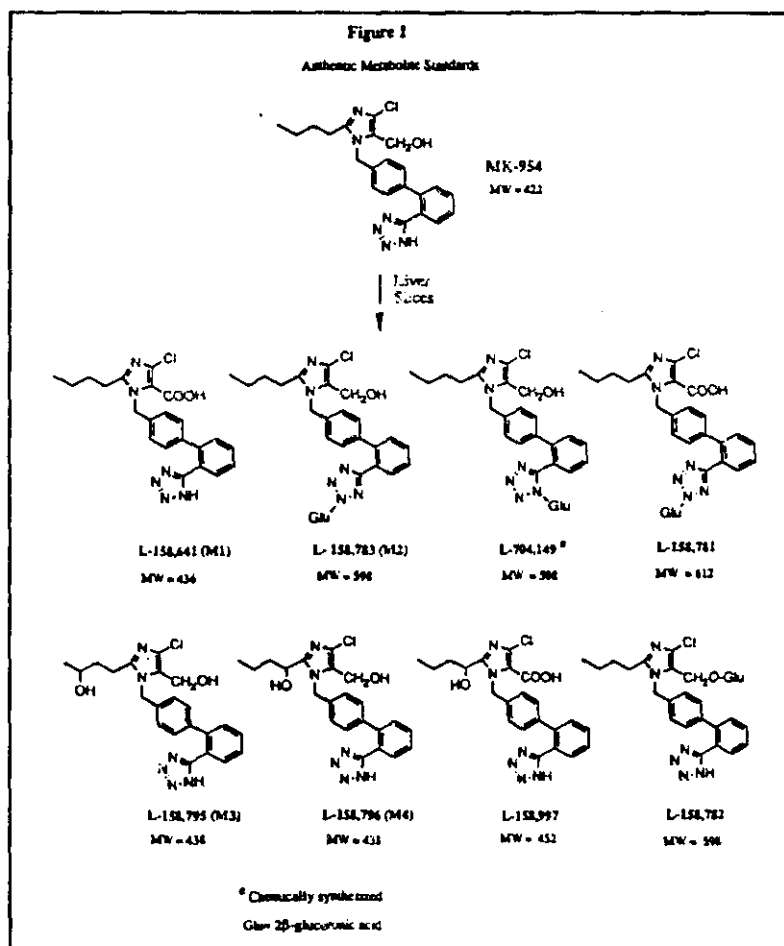
Study No: This is a report by RA Stearns et al published in DRUG METABOLISM AND DISTRIBUTION: Vol. 20: 281-287 (1992).

GLP Compliance: Not stated

Tissues: Rat livers were obtained from male Sprague-Dawley rats, monkey livers were obtained from from control group Rhesus monkeys sacrificed in toxicology studies and normal human liver tissue was obtained as excess tissue surgically removed from patients with metastatic cancer.

Procedure: ³H-Losartan was dissolved in medium containing 3.7 gm wet weight of rat or monkey liver slices or 2.1 gm wet weight of human liver slices and incubated for 5 hr at 37°C. Aliquots of the incubation medium were removed and metabolites measured by HPLC. Radioactivity was also determined from aliquots of the incubation medium by liquid scintillation spectrometry.

Results: Incubation of radiolabelled losartan with rat liver slices resulted in the formation of 7 metabolites (designated M-1 to M-7). In rat liver, the primary route of hepatic metabolism was oxidative, leading to either monohydroxylated (M-1, M-2, M-5) or oxidized (carboxylic acid, M-6) metabolites and, to a lesser extent, the tetrazole-N-glucuronide (M-7). The M-6 metabolite accounted for about 25% of all metabolites in the rat liver incubation. The major metabolites formed with monkey liver slices, each accounting for 40% of the total radioactivity, were the tetrazole-N-glucuronide (M-7) and the hydroxymethyl-O-glucuronide (M-3). Incubation of losartan with human liver slices yielded six metabolites (M-3 excluded) an equal mixture of both oxidized and glucuronic acid conjugated metabolites. With the exception of M-3, the same metabolites isolated from incubations with rat and monkey slices were observed in human liver slices. The metabolism of losartan by human liver slices was characterized by an approximately equal distribution of both oxidized and glucuronidated metabolites.



2.3.2. Urinary Metabolites After Oral and IV Losartan in Rats

Note: A portion of this study was reviewed and described under Elimination.

Study Facility:

Study No: JDM#92-A6

Study Dates: 4/21/92 - 1/07/93

GLP Compliance: Not stated; QA audit report included.

Animals: Male and female Sprague-Dawley rats (165-240 gm)

Procedure: ^{12}C -Losartan was dissolved in phosphate buffer (pH 7.4) and administered to rats orally (10 mg/kg) by gavage or intravenously (3 mg/kg) as single doses (3/sex/dose group). Samples of arterial blood (from cannulated carotid) were collected at intervals up to 48 hours after oral and IV administration. Urine and feces were collected at 8, 24 and 48 hours after dosing. Radioactivity in the biological samples was measured by liquid scintillation spectrometry; metabolites were measured by HPLC.

Results: Urinary excretion of drug related products with both routes of administration appeared to be higher in females than males. Urinary excretion of parent drug and metabolites in males was negligible; urinary excretion of losartan metabolites in females represented a small fraction of the drug-related excretory products.

TABLE 2.3.2.1
LOSARTAN METABOLITES EXCRETED IN URINE AFTER IV AND ORAL DOSE IN RATS

Metabolite	% of Dose Excreted in Urine in 24 Hrs			
	Male		Female	
	IV	PO	IV	PO
Parent Drug	ND	0.28	13.1	8.1
1-hydroxylated	ND	ND	0.73	0.66
3-hydroxylated	0.18	ND	1.52	1.06
Carboxylic acid	ND	ND	ND	0.06
Others (Unknown)	3.9	2.9	3.0	1.7

ND= Not detected

2.3.3. Metabolism of Losartan in Dog Primary Cultured Hepatocytes

Study Facility:

Study No: 91-M018

Study Dates: 7/09/91 - 7/31/91

GLP Compliance: Not stated; QA audit report included.

Cell Culture: Isolated dog liver was digested with collagenase and dispersed cells were filtered, centrifuged and resuspended. Aliquots of the hepatocyte suspension were plated on growth media and incubated overnight for cell stabilization.

Procedure: Losartan was dissolved in DMSO in concentrations of 2.5 and 25 mM and 4 uL of the drug solution was added to the cell culture and incubated for 24 hours. Aliquots of the incubation medium were removed for measurement of losartan and metabolites by HPLC.

Results: Incubation of the higher concentration of losartan for 24 hours produced six detectable metabolites. The major metabolite was identified as the glucuronide of losartan; two other prominent metabolites were hydroxylated derivatives. Only a small amount of the carboxylic derivative (biologically active metabolite, L-158,641) was produced. The remaining metabolites were unidentified.

2.3.4. Metabolism of Losartan in Humans

Note: A portion of this study was reviewed and described under Absorption.

Study Facility: MSD Research Laboratories, West Point , PA and Jefferson Medical College, Clinical Research Unit, Philadelphia, PA

Study No: MA # 060

Study Dates: Not stated; Report dated 3/19/93

GLP Compliance: Not stated.

Animals: Six healthy, adult, male subjects

Procedure: ¹⁴C-Losartan and its metabolite (non-radiolabelled L-158,641) were dissolved in sterile normal saline and administered intravenously (30 mg of losartan or 20 mg of L-158,641) as single doses over 20 min or administered orally (100 mg of losartan) as single doses in a randomized, crossover design. Seven days separated

adjacent treatments. With IV administration, 6 ml venous blood samples were collected at 0, 10, 20, and 30 min and at 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36 and 48 hours after dosing. Six-ml venous blood samples were collected at 0, 15, 30 and 45 min and 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36 and 48 hours after oral administration. Urine samples were collected prior to dosing and at 0-2, 2-4, 4-6, 6-8, 8-12, 12-18, 18-24, 24-36, 36-48, 48-72 and 72-96 hr intervals. Feces were collected up to 168 hours after dosing. Blood, feces and urine were assayed for parent drug and metabolites by HPLC.

Results: Recovery of radioactivity following IV administration of losartan was 43.3% of the dose in urine and 49.5% of the dose in feces; following oral administration of losartan, recovery in urine and feces was 35.2% and 57.7%, respectively. Three major metabolites were identified in urine, L-158,795 (1-hydroxylated derivative), L-158,796 (3-hydroxylated derivative) and L-158,641 (biologically active carboxylic acid metabolite). The N2-glucuronide derivative was a minor metabolite in urine. In feces, the parent drug accounted for 7.8%-12.8% of the dose after IV administration of losartan; the hydroxylated derivatives were approximately equal and combined accounted for 16%-18% of the administered dose. The carboxylic acid metabolite was detected in feces as approximately 7%-13% of the IV dose. No metabolic profiling was conducted on feces following oral losartan.

2.4. *Elimination*

2.4.1. Urinary and Fecal Excretion of Radioactivity After Oral and IV ¹⁴C-Losartan in Rats

Study Facility:

Study No: JDM#92-A6

Study Dates: 4/21/92 - 1/07/93

GLP Compliance: Not stated; QA audit report included.

Animals: Male and female Sprague-Dawley rats (165-240 gm)

Procedure: ¹²C-Losartan was dissolved in phosphate buffer (pH 7.4) and administered to rats orally (10 mg/kg) by gavage or intravenously (3 mg/kg) as single doses (3/sex/dose group). Samples of arterial blood (from cannulated carotid) were collected at intervals up to 48 hours after oral and IV administration. Urine and feces were collected at 8, 24 and 48 hours after dosing. Radioactivity in the biological samples was measured by liquid scintillation spectrometry; metabolites were measured by HPLC.

Results: Radioactivity was predominantly eliminated via fecal excretion following

either oral or IV dosing. Approximately 80% and 82% of the radioactivity was eliminated by 24 hours following IV dosing in males and females, respectively; approximately 92% and 82% of the radioactive dose was eliminated in 24 hours after oral dosing in males and females, respectively. By 48 hours, elimination was essentially complete.

TABLE 2.4.1.1
RADIOACTIVITY EXCRETED IN URINE AND FECES AFTER IV AND ORAL DOSE IN RATS

Parameter	% of Radioactive Dose Eliminated in 48 Hrs.			
	Male		Female	
	IV	PO	IV	PO
Urinary Excretion	4.2	3.6	19.5	13.4
Fecal Excretion	89.9	93.3	68.7	80.2
Total Excretion	94.1	96.9	88.2	93.6

2.4.2. Urinary, Biliary and Fecal Excretion of Radioactivity After Oral and IV ³H-Losartan in Rats

Study Facility: E.I. duPont Research Labs, Wilmington, DE

Study No: MP-89-015

Study Dates: Not indicated; report date 3/29/89

GLP Compliance: Not indicated.

Animals: Male Sprague -Dawley rats (250-300 gm)

Procedure: ³H-Losartan was prepared as an aqueous solution and administered intravenously (10 mg/kg) or orally (10 mg/kg) by gavage to intact rats (4/route); a separate group (4) of bile-duct cannulated rats was administered a single oral dose (10 mg/kg) by gavage. Animals were placed in individual metabolic cages and urine and feces were collected from 0-24 hr and 24-48 hr following dosing. Bile was collected from bile-duct cannulated rats at 24 hr intervals up to 144 hours postdose. Blood was drawn from all rats by cardiac puncture at termination of the study and radioactivity in urine, plasma and feces measured by liquid scintillation spectrometry.

Results: The excretion of radioactivity, reflecting the sum of all metabolites, as well as unchanged losartan, after a single oral or IV dose is summarized below. Recovery of radioactivity from feces and urine was somewhat lower than that noted in previously described studies and appears to be related to the use of the tritium as

the radiolabel. The investigators determined that some loss of radioactivity from the fecal and urine samples had occurred after the samples were lyophilized, indicating that exchange of the radiolabel had occurred, presumably forming tritiated water which was removed during lyophilization.

TABLE 2.4.2.1
EXCRETION OF RADIOACTIVITY IN INTACT RATS AFTER IV OR ORAL (10 MG/KG)
³H-LOSARTAN

Sample	% of Administered Oral Dose		% of Administered IV Dose	
	0-24 Hr	24-48 Hr	0-24 Hr	24-48 Hr
Feces	67.3	3.9	54.8	8.9
Urine	2.3	0.1	4.9	0.1
TOTAL	73.7%		68.8%	

TABLE 2.4.2.2
EXCRETION OF RADIOACTIVITY (% OF DOSE) IN BILE-DUCT CANNULATED RATS AFTER 10
MG/KG ORAL DOSE OF ³H-LOSARTAN

Time (Hr)	Bile	Urine	Feces	TOTAL
0-24	37.5	2.8	37.8	78.0
24-48	1.9	0.5	1.7	4.2
48-72	0.4	0.3	0.1	0.8
72-96	0.1	0.3	<0.1	0.4
0-96	39.9	3.9	39.6	83.8

2.4.3. Biliary Excretion of Radioactivity after Oral and IV ¹⁴C-Losartan in Rats

Study Facility:

Study No: JDM #91-A6

Study Dates: 8/12/91- 9/21/92

GLP Compliance: Not stated; QA audit report included.

Animals: Male and female Sprague-Dawley rats (156-228 gm)

Procedure: ¹⁴C-Losartan was dissolved in phosphate buffer (pH 7.4) and administered orally (10 mg/kg) by gavage to 3 male and 3 female bile-duct cannulated rats or intravenously (3 mg/kg) to male bile-duct cannulated rats. Bile was collected for up to 48 hours after dosing and metabolite identified by HPLC. Radioactivity was measured by liquid scintillation spectrometry.

Results: Radioactivity in the 48 hour bile samples was low and metabolites in these samples could not be identified. Thus, metabolite measurements are only for the 24-hour post-drug period. Metabolites found in the bile were 3-hydroxylated derivative (M-1), 1-hydroxylated derivative (M-2), carboxylic acid derivative (M-4) and N₂-tetrazole glucuronide derivative (M-5). M-5 was the predominant biliary excretory product with either route of administration of the parent drug. M-4 was also a main biliary excretion product following oral dosing but not following IV dosing.

TABLE 2.4.3.1.
METABOLITE COMPOSITION IN BILE 24 HR AFTER IV OR ORAL ADMINISTRATION

Metabolite	Mean Percent of Biliary Excretion		
	IV Males	PO Males	PO Females
Parent Drug	14.6	11.9	12.3
M-1	12.1	9.6	5.2
M-2	7.1	4.0	6.4
M-4	26.6	29.2	36.7
M-5	7.8	23.4	26.9
Others	8.2	2.4	0.7
Adsorbed*	24.1	19.5	11.8

*Fraction not effectively eluted with methanol

2.4.4. Excretion of Radioactivity After Oral and IV ¹⁴C-Losartan in Dogs

Study Facility: Merck Research Labs, West Point, PA

Study No: None indicated; Report # G-34

Study Dates: Not indicated; report date 5/19/93

GLP Compliance: Not indicated

Animals: Male Beagle dogs (8-10 kg)

Procedure: ¹⁴C-Losartan was dissolved in phosphate buffer (pH 7.4) and administered as a single oral dose (10 mg/kg) to 3 dogs by gavage. Two weeks later the same animals were administered ¹⁴C-losartan intravenously (2 mg/kg) as a solution in DMSO. Urine and feces were collected at 24-hr intervals for 168 hours after dosing. Radioactivity in the urine and feces was measured by liquid scintillation spectrometry.

Results: Approximately 96% of the radioactivity was recovered within 120 hours after oral dosing and approximately 91% was recovered within 120 hours after intravenous dosing. Fecal elimination was the major route for the excreted products.

TABLE 2.4.4.1
EXCRETION OF RADIOACTIVITY (% OF DOSE) AFTER ORAL AND IV ¹⁴C-LOSARTAN IN DOGS

Time (hr)	% of Total Oral Dose			% of Total IV Dose		
	Urine	Feces	Total	Urine	Feces	Total
0-24	10.5	79.7	90.2	18.6	64.0	82.6
24-48	0.4	4.5	4.9	0.4	7.4	7.8
48-72	0.05	0.6	0.65	0.05	0.5	0.6
72-96	ND	ND	-	0.05	0.13	0.18
96-120	ND	0.09	0.09	0.04	ND	0.04
120-168	ND	ND	-	ND	ND	-
TOTAL	11.0	84.9	95.9	19.1	72.0	91.2

ND=Not detected

3. TOXICOLOGY

3.1. Acute Toxicity Studies

3.1.1. Acute Oral Toxicity Study in Mice

Study Facility: E.I. du Pont de Nemours and Company, Wilmington, DE

Study Number: 88-4-5

Study Dates: 4/15/88-7/13/88

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: CF-1 mice (19M, 20F; 17-27gm)

Drug Administration: Losartan (Lot E-3340-9) was prepared as a solution in sterile water for injection and administered to mice as a single dose by gavage.

Dose Levels: 0 (vehicle), 500, 1000 and 2000 mg/kg (5/sex/group; only 4M in lowdose group.

Observations/Measurements: Mice were observed daily for 14 days for clinical signs of toxicity and mortality. Body weights were measured prior to dosing and on days 2, 7 and 14 after dosing. Gross examination was performed on all mice that died and those that survived to scheduled sacrifice.

Results:

TABLE 3.1.1.1
MORTALITY

Dose (mg/kg)	No. Dead/No. Treated	
	Males	Females
0	0/5	0/5
500	0/4	0/5
1000	0/5	1/5
2000	4/5	1/5

Deaths occurred within 3 hours after dosing with 2000 mg/kg and approx. 48 hours after dosing with 1000 mg/kg. Clinical signs of toxicity seen prior to death included decreased motor activity, ataxia, prostration, loss of righting reflex, enophthalmia and colored material around the mouth. Mice that survived treatment with 1000 mg/kg and

2000 mg/kg exhibited enophthalmia, decreased motor activity and perianal staining. Gross postmortem examination revealed discoloration of the stomach mucosa and/or red-colored contents in the intestinal tract of mice that died after a dose of 2000 mg/kg. Mice treated with 500 mg/kg showed no signs of toxicity. The acute oral no-observed-adverse-effect-level of losartan in mice was 500 mg/kg.

3.1.2. Acute Intraperitoneal Toxicity Study in Mice

Study Facility: E.I. du Pont de Nemours and Company, Wilmington, DE

Study Number: 88-10-5

Study Dates: 10/06/88 - 10/21/88

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: CF-1 mice (25M, 25F; 19-32 gm)

Drug Administration: Losartan (Lot No. E-3340-15) was dissolved in sterile water for injection and administered to the mice by intraperitoneal injection.

Dose Levels: 0 (vehicle), 25.6, 64, 160 and 400 mg/kg (5/sex/dose group)

Observations/Measurements: Mice were observed daily for 14 days for clinical signs of toxicity and mortality. Body weights were measured prior to dosing and on days 2, 7 and 14 after dosing. Gross examination was performed on all mice that died and those that survived to scheduled sacrifice.

Results:

TABLE 3.1.2.1
MORTALITY

Dose (mg/kg)	No. Dead/No. Treated	
	Males	Females
0	0/5	0/5
25.6	0/5	0/5
64	0/5	0/5
160	0/5	0/5
400	4/5	5/5

Deaths occurred 1 to 3 days post-dose. Clinical signs of toxicity seen prior to death included ataxia, decreased motor activity, tremors, ptosis, perianal and urogenital staining and

decreased respiration. Doses of 160 mg/kg and lower produced no clinical signs of toxicity or treatment-related pathology on gross examination.

Note: A subsequent acute intraperitoneal study (TT#90-2649) in female mice only was conducted by MSD Research Labs using doses of 156, 312, 625, 1250, 2500 and 5000 mg/kg and a limited number (3) of mice per dose group. 3/3 mice died with doses = or > 625 mg/kg. No mortality occurred with doses of 156 or 312 mg/kg.

3.1.3. Acute Oral Toxicity Study in Rats

Study Facility: E. I. du Pont de Nemours and Co., Wilmington, DE

Study Number: 88-4-4

Study Dates: 4/14/88 - 7/13/88

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Sprague-Dawley rats (15M, 15F, 8 weeks old)

Drug Administration: Losartan (Lot E-3340-9) was prepared as a solution in sterile water for injection and administered to rats as a single dose by gavage.

Dose Levels: 0 (vehicle), 1000 and 2000 mg/kg (5/sex/group)

Observations/Measurements: Rats were observed daily for 14 days for clinical signs of toxicity and mortality. Body weight was measured predose, and on days 2, 7 and 14 after treatment. Gross examination was performed on all rats that died and those that survived to scheduled sacrifice.

4 Results:

TABLE 3.1.3.1.
MORTALITY

Dose (mg/kg)	No. Dead/No. Treated	
	Males	Females
0	0/5	0/5
1000	0/5	0/5
2000	3/5	0/5

Deaths occurred between two and five hours after dosing. Clinical signs of toxicity seen prior to death included decreased motor activity, loss of righting reflex, prostration, enophthalmus, loose stools, perianal staining and colored material around the mouth. Among surviving animals, 3/5 rats treated with 1000 mg/kg had loose stools on day 1; animals surviving the 2000 mg/kg dose exhibited decreased motor activity, enophthalmus, loose stools, facial and perianal staining. Fluid distention of the GI tract was noted in the 3 rats that died. No significant lesions or pathology were noted in surviving rats upon gross examination at scheduled sacrifice.

3.1.4. Acute Intraperitoneal Toxicity Study in Rats

Study Facility: E. I. du Pont de Nemours and Co., Wilmington, DE

Study Number: 88-10-4

Study Dates: 10/4/88 - 10/19/88

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Sprague-Dawley rats (25M, 25F, 8 weeks old)

Drug Administration: Losartan (Lot INE-3340-15) was prepared as a solution in sterile water for injection and administered to rats as a single intraperitoneal dose.

Dose Levels: 0 (vehicle), 25, 50, 100 and 200 mg/kg (5/sex/group)

Observations/Measurements: Rats were observed daily for 14 days for clinical signs of toxicity and mortality. Body weight was measured predose and on days 2, 7 and 14 after dosing. Gross examination was performed on all rats that died and those that survived to scheduled sacrifice.

Results: Deaths occurred between 3 and 5 days post-dose. Clinical signs of toxicity seen prior to death included ataxia, decreased motor activity, perianal and urogenital staining, colored material around eyes, nose, paws and mouth, soft stools, dehydration and labored respiration. Surviving rats treated with 200 mg/kg exhibited ataxia, decreased motor activity, perianal and urogenital staining and soft stools. One male treated with 100 mg/kg exhibited perianal staining and one male treated with 50 mg/kg exhibited soft stools. No other clinical signs of toxicity were noted with rats treated with 25-100 mg/kg of losartan. Gross examination revealed losartan-related distension and thickened walls of the jejunum and cecum in animals dosed with 200 mg/kg. The intraperitoneal no-observable-adverse-effect level in mice was considered to be 100 mg/kg.

TABLE 3.1.4.1
MORTALITY

Dose (mg/kg)	Males	No. Dead/No. Treated Females
0	0/5	0/5
25	0/5	0/5
50	0/5	0/5
100	0/5	0/5
200	3/5	1/5

3.2. SUBCHRONIC, CHRONIC AND CARCINOGENICITY STUDIES

Studies in Rats

3.2.1. Fourteen-Week Oral Range Finding Toxicity Study in Rats

Study Facility: MSD Research Laboratories, West Point, PA

Study No: TT #90-013-0

Study Dates: 1/25/90- 1/27/90

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Male and female CrI:CD(SD) BR rats (39 days old at initiation of study).

Drug Administration: Losartan (Lot # 005H004 and 005H010) was dissolved in deionized water and administered orally by gavage.

Dose Levels: 0 (vehicle), 50, 150, 250 and 450 mg/kg/day (15/sex/dose group)

Observations/Measurements: Rats were observed daily for mortality and clinical signs of toxicity. Food consumption was measured weekly and body weights were measured prior to treatment, during week 1 and twice weekly, thereafter. Ophthalmoscopic examinations were conducted on all surviving control and high dose rats during weeks 3 and 11 of treatment. Blood samples were obtained from the orbital sinus or tail vein during weeks 5, 8 and 13 for hematologic and serum chemistry measurements. Urine was collected from 10 rats/sex/group during treatment weeks 8 and 13 for urinalysis. Rats that survived to scheduled necropsy were weighed, sacrificed and examined for gross pathology. Major organs were removed and weighed. Sections of major organs and tissues from the control and high dose animals were fixed on slides, stained and examined for microscopic pathology.

Results: A total of 5 high dose rats died during the study (3F, 1M during week 5 and 1M during week 8 of treatment).

Some rats in the 150-450 mg/kg/day dose groups had occasional dyspnea which was associated with excessive salivation following dosing. Most high dose rats had excessive salivation following dosing that was gone within 1 hour.

Body weight gain was decreased in a dose-related and statistically significant manner; food consumption was not affected by treatment.

TABLE 3.2.1.1.
MORTALITY

Dose (mg/kg/day)	#Died/#Treated	
	Males	Females
0	0/15	0/15
50	0/15	0/15
150	0/15	0/15
250	0/15	0/15
450	2/15	3/15

TABLE 3.2.1.2.
BODY WEIGHT AND BODY WEIGHT GAIN

Dose (mg/kg/day)	% Difference from Control Weight (Wt. Gain)	
	Males	Females
150	-10 (-15)	-5 (-8)
250	-13 (-18)	-8 (-13)
450	-14 (-21)	-8 (-16)

Mean erythrocyte, hemoglobin and hematocrit values were decreased approximately 10% in drug weeks 5, 8 and 13 in males and females dosed with 450 mg/kg/day; mean erythroid values in rats treated with 250 mg/kg/day were slightly depressed during drug weeks 5, 8 and 13 and no effects on these parameters were noted in 50 and 150 mg/kg/day groups. Mean leukocyte counts were increased 20%-50% in drug weeks 5, 8 and 13 in high dose animals relative to controls.

Dose-related increases in mean serum urea nitrogen were observed in all dose groups (19% to 161% higher than concurrent control females and 15% to 229% higher than concurrent control males) in drug weeks 5, 8 and 13. Mean ALT value was increased 40% above concurrent control in the male high dose group in week 13 of treatment. Mean potassium values were significantly increased about 10% in high dose males and females in drug weeks 5 and 13. Mean glucose values tended to be lower (10%-20%) in both male and female high dose groups relative to controls in drug weeks 5, 8 and 13. There were no treatment-related effects on urinalysis parameters.

No treatment related ocular abnormalities were observed. Macroscopic examination revealed the presence of dark, red-brown foci in the glandular mucosa of the stomach. Most of these foci were confirmed microscopically as focal erosions of the glandular epithelium with adjacent hyperemia, hemorrhage and mild inflammation.

TABLE 3.2.1.3
INCIDENCE OF FOCAL EROSIONS IN STOMACH MUCOSA

Dose (mg/kg/day)	Incidence of Focal Erosions in Stomach	
	Males	Females
50	1/15	0/15
150	0/15	0/15
250	7/15	3/15
450	6/15	4/15

Absolute and relative heart weights were significantly decreased in females treated with 150, 250 and 450 mg/kg/day and males at all dose levels.

TABLE 3.2.1.4
EFFECTS ON ABSOLUTE AND RELATIVE HEART WEIGHTS

Dose (mg/kg/day)	% Difference from Control Absolute (Relative) Heart Weight	
	Males	Females
50	-16.4 (-12.5)	-3.7 (-2.8)
150	-24.0 (-15.6)	-12.0 (-8.3)
250	-26.9 (-15.6)	-13.9 (-5.6)
450	-23.4 (-6.2)	-15.7 (-8.3)

Microscopic examination revealed treatment-related hyperplasia of the JG apparatus of the kidneys in both males (3/15, 5/15, 8/15) and females (1/15, 1/15, 3/15) given 150, 250 and 450 mg/kg/day, respectively.

3.2.2. Fifty-three Week Oral Toxicity Study in Rats

Study Facility: MSD Research Labs, West Point, PA

Study No: 90-001-0

Study Dates: 1/02/90 - 1/04/91

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Crl:CD(SD) BR rats (M=118-182gm; F=114-165gm)

Drug Administration: Losartan (Lot # 005H002 and 005H010) was dissolved in deionized water and administered daily to rats orally by gavage.

Dose Levels: 0 (vehicle), 15, 45 and 135 mg/kg/day (30/sex/dose group)

Observations/Measurements: Animals were observed daily for mortality and clinical signs of toxicity. Body weights were obtained predose, once during week 1, twice weekly through week 13, then once weekly thereafter. Food consumption was measured weekly until week 34 then once every 4 weeks. Ophthalmoscopic exams were conducted on all rats in the control and high dose groups during weeks 12, 25, 39 and 51 of treatment. Blood samples were obtained during weeks 4, 12 and 25 by orbital puncture on 10 rats/sex/group (rats designated for interim necropsy) and on all surviving rats during weeks 39 and 51 for hematologic and serum biochemical exams. Urine was collected for urinalysis during weeks 12 and 25 on 10 rats/sex/group (rats designated for interim necropsy) and on all animals surviving during weeks 39 and 51. Ten rats/sex/dose group were preselected for a 27-week interim necropsy and the remaining rats were necropsied at the termination of the 53-week treatment. Following gross examination major organs were removed and weighed. Sections of major organs and tissues from control and high dose groups and from rats that died prior to scheduled necropsy were fixed on slides and examined for histopathology.

Results: Mortality among losartan-treated animals was not significantly different from control. Post-dose salivation was observed occasionally throughout the study in mid and high dose animals.

Treatment-related, statistically significant ($P \leq 0.05$) decrements in body weight and body weight gain were observed at the high-dose level in both male and female rats and at the middle dose level in female rats. Data summarizing body weight gains over the course of this 53-week study are shown in the following table 3.2.2.2.

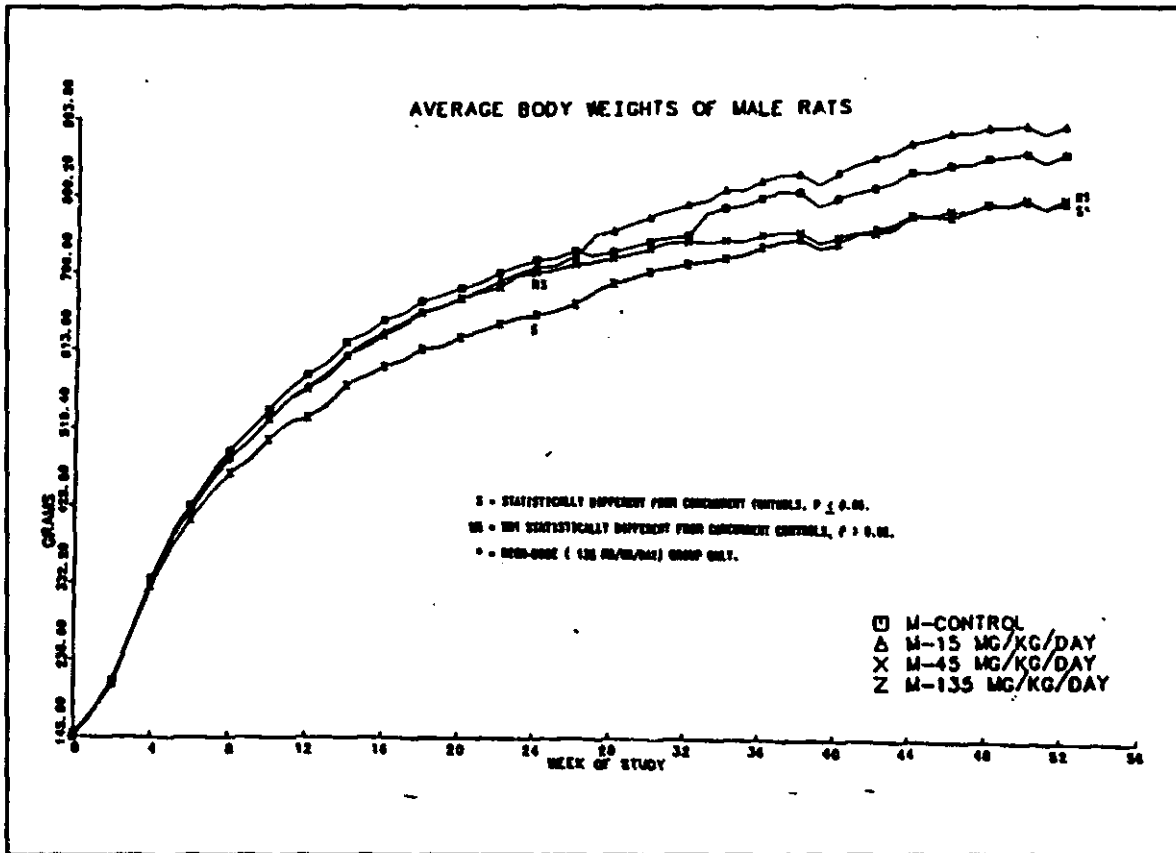
TABLE 3.2.2.1.
MORTALITY

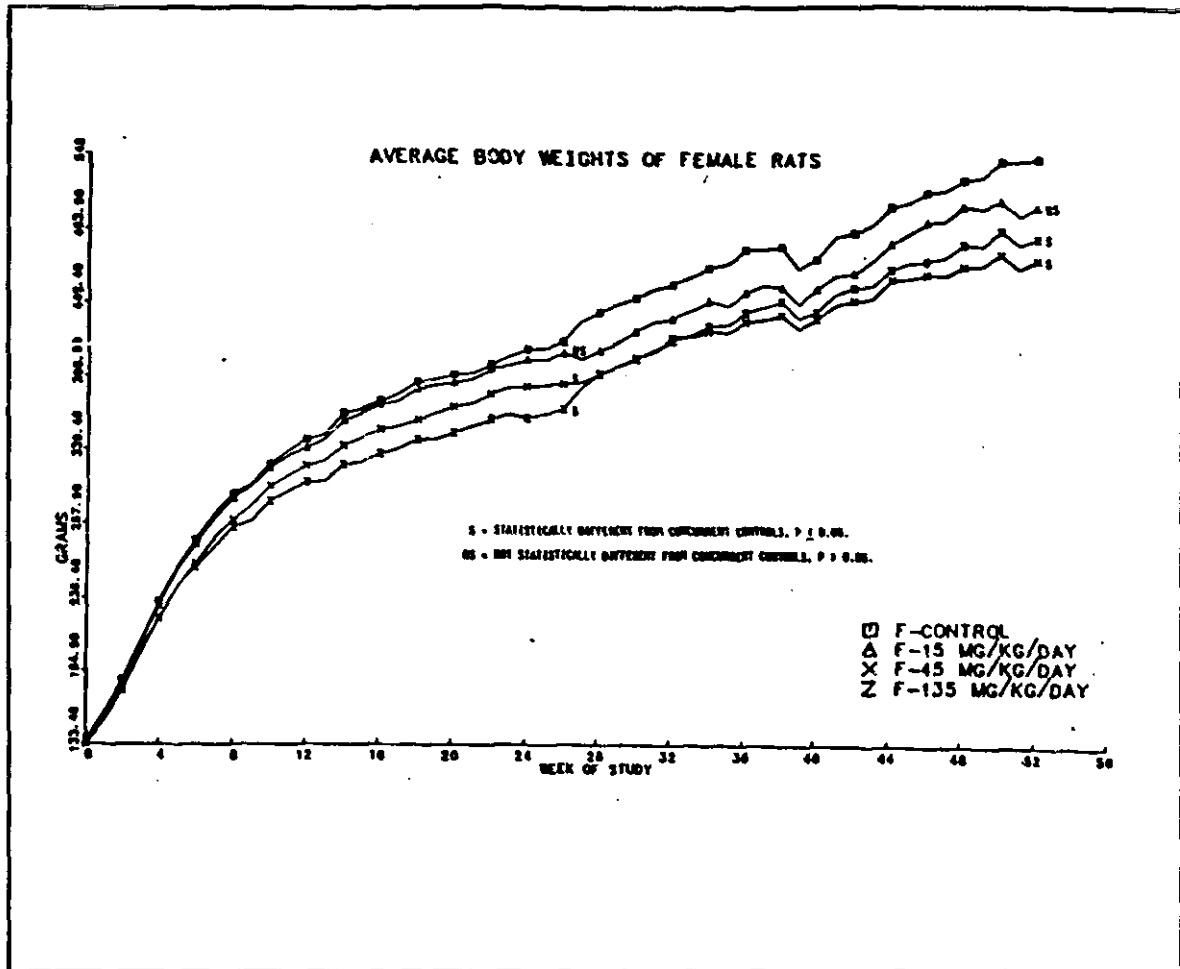
Dose (mg/kg/day)	Dead Rats	
	Males	Females
0	2 (Wks 33-37)	3 (Wks 13-50)
15	3 (Wks 34-50)	0
45	4 (Wks 5-24)	2 (Wks 26-46)
135	3 (Wks 41-47)	2 (Wks 28-42)

TABLE 3.2.2.2.
% CHANGE IN BODY WEIGHT (GAIN) VS. CONCURRENT CONTROLS
- DRUG WEEK 52

Dose	Males	Females
15 mg/kg/day	+4% (+4%)	-6% (-7%)
45 mg/kg/day	-6% (-9%)	-13%* (-16%)*
135 mg/kg/day	-7%* (-10%)*	-10%* (-14%)*

* P ≤ 0.05.





Significant, non-dose dependent decreases of -8% and -6% in food consumption were observed in female rats receiving the mid (45 mg/kg/day) and high (135 mg/kg/day) doses of losartan, respectively, through Study Week 26. By Study Week 50, a slight, but not significant decrease (5%), in food consumption was noted in high dose females; food consumption all other treated groups were comparable to control.

No treatment-related ocular effects were observed.

Losartan treatment caused statistically significant decreases in hemoglobin concentrations, hematocrit and erythrocyte counts in high dose males (treatment weeks 21, 39 and 51) and in high dose females (treatment weeks 39 and 51).

TABLE 3.2.2.3.
GROUP MEAN ERYTHROID VALUES IN RATS RECEIVING LOSARTAN

<i>MALES</i>									
DRUG WEEK									
Treatment Groups	25			39			51		
	Hb ^a	Hct ^b	RBC ^c	Hb	Hct	RBC	Hb	Hct	RBC
Control	15.8	43	8.7	15.4	42	8.6	15.4	41	8.4
15 mg/kg/day	15.8	43	8.4	15.6	43	8.5	15.7	43	8.5
45 mg/kg/day	15.6	42	8.5	15.1	42	8.4	14.8	40	8.1
135 mg/kg/day	15.2*	41*	8.1*	14.8*	41*	8.1*	14.3*	39*	7.9*

<i>FEMALES</i>									
DRUG WEEK									
Treatment Groups	25			39			51		
	Hb ^a	Hct ^b	RBC ^c	Hb	Hct	RBC	Hb	Hct	RBC
Control	15.1	41	7.6	15.2	41	7.7	14.6	40	7.4
15 mg/kg/day	15.4	41	7.6	15.2	41	7.6	14.9	40	7.5
45 mg/kg/day	15.5	42	7.8	15.0	41	7.4*	14.6	40	7.3*
135 mg/kg/day	15.2	41	7.6	14.8*	40*	7.3*	14.4*	39*	7.1*

a = g/dl, b = %, c = million/mm³

* Statistically different from concurrent controls at $P \leq 0.05$.

Higher than control levels of blood urea nitrogen (BUN) were observed in high-dose male rats throughout the study period, and in mid-dose male rats beginning during Drug Week 39. The greatest relative increase (100%) was observed in high-dose male rats during Drug Week 25. Similar, but less marked elevations were observed in high-dose female rats in Drug Weeks 4, 12, 25, and 39; these gradually declined to concurrent control levels by the last evaluation in treatment week 51.

TABLE 3.2.2.4
GROUP MEAN BUN CONCENTRATIONS (MG/DL)

Treatment Groups	Males				
	Drug Week				
	4	12	25	39	51
Control	13	17	15	14	14
15 mg/kg/day	13	16	16	14	14
45 mg/kg/day	14	17	16	18(+28%)	17(+21%)
135 mg/kg/day	18(+38%)*	25(+47%)	30(+100%)	22(+57%)	25(+78%)

Treatment Groups	Females				
	Drug Week				
	4	12	25	39	51
Control	14	15	15	14	13
15 mg/kg/day	14	15	15	15	13
45 mg/kg/day	14	16	17(+13%)	15	13
135 mg/kg/day	19(+36%)*	18(+20%)	18(+20%)	16(+14%)	13

*Percent change from concurrent control value.

Treatment-related, dose-dependent decreases in average serum triglycerides were observed in female rats relative to concurrent control females. The following table summarizes the magnitude of this effect in female rats:

TABLE 3.2.2.5
GROUP MEAN SERUM TRIGLYCERIDE CONCENTRATIONS IN FEMALE RATS (MG/DL)

Treatment Groups	Drug Week				
	4	12	25	39	51
Control	49	80‡	160‡	175	295
15 mg/kg/day	38(-22%)*	72(-10%)	106(-34%)	170(-3%)	257(-13%)
45 mg/kg/day	35(-29%)	54(-32%)	73(-54%)	117(-33%)	153(-48%)
135 mg/kg/day	31(-37%)	53(-34%)	57(-64%)	103(-41%)	132(-55%)

* Percent change from concurrent control value.

‡ Outlying values of 404 and 783 mg/dl in one control female (90-0055F) during Drug Weeks 12 and 25 were not included in average.

Slight, non-dose-dependent decreases (2%-7%) in urinary protein values were found in males and females at all dosage levels during treatment weeks 39 and 51.

Mean absolute heart weight and heart weight relative to brain weight were decreased at the interim necropsy in the high-dose males (16.9% and 17.2%) and females (14.6% and 10.3%) and in mid-dose males (9.2% and 10.3%). Statistically significant decreases in these parameters were observed only in mid-dose (9.6% and 8.7%) and high-dose males (15.5% and

15.2%) at the interim necropsy. There was no histologic correlate. This effect on heart weight is a pharmacodynamic property of losartan since similar decreases in heart weight were observed following treatment with many other antihypertensive agents, including diuretics and beta-blockers.

Juxtaglomerular cell hyperplasia, characterized by thickening of the afferent glomerular arterioles, was identified in 2/10 mid-dose and 5/10 high-dose males at the interim necropsy. At terminal sacrifice, very slight JG cell hyperplasia was identified in 14/20 low-dose, 17/18 mid-dose and 19/20 high-dose males and in 5/20 low-dose, 10/20 mid-dose and 12/20 high-dose females. Coincident with this effect on the JG apparatus were decreases in the incidence (29/40, 14/40, 9/38, 14/40 for control, low, mid and high dose groups respectively) and severity of chronic nephritis at all dosage levels of losartan.

Focal erosions of the glandular mucosa of the stomach were noted in one high-dose male at the interim necropsy and in 1 low-dose and 3 high-dose males among rats dying or necropsied at terminal sacrifice. No gastric lesions were found in concurrent control animals.

Gross and microscopic examinations revealed no other treatment-related pathologies.

3.2.3. One Hundred-Five Week Oral Carcinogenicity Study in Rats

Study Facility: MSD Research Laboratories, West Point, PA

Study No: TT #90-099-0

Study Dates: 7/11/90 - 7/13/92

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Male and female Sprague-Dawley CrI:CD (SD) BR rats (115-175 gm females, 119-194 gm males, 38 days old, housed individually).

Drug Administration: Losartan (Batch # 9, 10, 19 and 29) was dissolved in deionized water and administered orally by gavage once daily.

Dose Levels: 0 (Vehicle; 130/sex), 15, 45 and 135/270 mg/kg/day * (75/sex/group)

** Note: High dose raised from 135 to 270 mg/kg/day in week 6 of treatment because previous dose did not appear (from 1-year chronic rat study) to be the maximally tolerated dose (MTD).*

Observations/Measurements: Animals were observed daily for mortality and observed weekly for clinical sign of toxicity. Rats were palpated for the presence of masses every 4th week beginning Drug Week 26. Body weights were recorded prior to study initiation, twice per week through Drug Week 13 and once weekly thereafter. Ophthalmologic examinations were conducted in Drug Weeks 52 and 102. A complete necropsy was performed on all animals. Sections of major tissues and organs were fixed on slides and examined microscopically. Treatment-related increases in tumor incidence was assessed by use of a trend test (Mantel-Haenszel procedure).

Results: *Mortality and Survival:* Two high dose rats (1M,1F) died and one high dose female was sacrificed between Drug Weeks 18 and 34 due to marked weight loss associated with cecal erosive inflammation. Two additional high dose rats were sacrificed (1F & 1M in Drug Weeks 49 and 70, respectively) due to marked weight loss with associated intestinal lesions. In addition, moderate to marked edema of the lungs, presumably due to hypotension, was the cause of death or sacrifice of a high dose female and 7 high dose males between Drug Weeks 25 and 92. Although these deaths were related to drug treatment, they did not significantly affect the overall incidence of mortality at termination of the study. In fact, there was a statistically significant decrease in mortality (increase in survival) in males with increasing dose.

TABLE 3.2.3.1.
ANIMAL SURVIVAL

Rat Sex	Percent Survival at Study Termination			
	Control	15 mg/kg	50 mg/kg	135/270 mg/kg
Females	28.5	26.7	26.7	25.3
Males	16.2	25.3	34.7	34.7

The incidence of chronic nephritis (moderate, marked or severe grades) as a specific cause of death in male rats not surviving to termination was considerably higher in control males (27%) than in low dose (16%), mid dose (8%) and high dose (8%) treated males.

Physical Signs: Excessive salivation immediately after dosing and lasting up to approximately 45 min was seen occasionally throughout the study in high dose rats. Tarry stools occurred in 3 high dose rats (1M, 2F) between Drug Weeks 18 and 34.

Body Weight: Male and female rats given 135 mg/kg/day for the first 5 weeks had body weights slightly below control values at the end of those 5 weeks (mean decrement less than 10%). After increasing the high dose to 270 mg/kg/day, body weight in this group was further reduced compared to controls. Body weight gains of high dose females were 10-23% less than controls from Drug Week 8 until termination. Body weight gain of high dose females at study termination was 18.5% less than control. High dose males had body weight gains 10-17% less than control from Drug Week 8 to Drug Week 83; after this time the decrease became less and at termination the body weight gains in high dose males were similar to control.

TABLE 3.2.3.2.
EFFECT ON MEAN BODY WEIGHT

Dose Group	Percent Difference From Control Weight									
	5 Wks		26 Wks		52 Wks		78 Wks		104 Wks	
	F	M	F	M	F	M	F	M	F	M
Low Dose	-1	-2	-3	-1	-1	+1	+3	+3	-4	+7
Mid Dose	-4	-5	-6	-5	-6	-2	0	+5	-7	+10
High Dose	-2	-5	-10	-11	-14	-11	-13	-8	-13	+4

Mean Pretest Weight: Control=147gm, Low Dose=145gm,
Mid Dose=143gm, High Dose=147gm

Ophthalmologic Effects: No treatment-related ocular effects were observed.

Gross Pathology: No evidence of treatment-related pathology on gross examination.

Microscopic Pathology:

Neoplastic Lesions: The sponsor's analysis revealed no evidence of a statistically significant increased trend in the incidence of any neoplasm in either sex of rat (Appendix I for tumor type and site). Summary of tumor incidence is as follows:

TABLE 3.2.3.3.
SUMMARY OF NEOPLASMS IN MALE RATS

	Number (% Incidence)			
	Control	Low Dose	Mid Dose	High Dose
# Rats with Neoplasms				
Malignant	28 (22)	24 (32)	23 (31)	20 (27)
Benign	91 (70)	59 (79)	63 (84)	49 (65)
Malignant or Benign	98 (75)	68 (91)	67 (89)	54 (72)
Total # of Neoplasms:				
Malignant	30 (23)	25 (33)	24 (32)	21 (28)
Benign	170 (131)	105 (140)	116 (155)	95 (127)
Malignant or Benign	200 (154)	130 (173)	140 (187)	116 (155)

Control= 130 rats, Other Groups=75 rats

TABLE 3.2.3.4.
SUMMARY OF NEOPLASMS IN FEMALE RATS

	Number (% Incidence)			
	Control	Low Dose	Mid Dose	High Dose
# Rats with Neoplasms				
Malignant	42 (32)	26 (35)	29 (39)	13 (17)
Benign	126 (97)	68 (91)	70 (93)	65 (87)
Malignant or Benign	128 (98)	70 (93)	74 (99)	68 (91)
Total # of Neoplasms				
Malignant	45 (35)	30 (40)	31 (41)	14 (19)
Benign	261 (201)	144 (192)	135 (180)	129 (172)
Malignant or Benign	306 (235)	174 (232)	166 (221)	143 (191)

Control=130 rats, Other Groups=75 rats

Analysis of the tumor data By FDA Statistical Section (See Statistical Review and Evaluation) revealed a statistically significant trend (P value= 0.0084) in pancreatic acinar adenomas (0, 0, 0, 3 for control, low, mid and high dose groups, respectively) in female rats. The pairwise comparison (high dose vs. control) also showed a statistically significant (P value = 0.043) difference.

Non-Neoplastic Lesions: There was a treatment-related, dose-dependent increase

in the incidence of juxtaglomerular (JG) cell hyperplasia in the kidneys of both sexes. This effect was characterized by an increase in the size and number of the JG cells comprising the wall of the afferent arteriole of the glomerulus. Increased incidences of renal focal tubular hypertrophy were seen in male rats in the mid and high dose groups compared to controls.

TABLE 3.2.3.5.
RENAL EFFECTS

Renal Effect		% Incidence			
		Control	Low Dose	Mid Dose	High Dose
JG Cell Hyperplasia	F	0	4.0	12	43
	M	0	11	43	71
Renal Tubular Hypertrophy	F	1.5	4.0	2.7	5
	M	2.3	1.3	7.1	15

A slight increase in the incidence of losartan-related cecal erosive inflammation was noted in high dose males (5%) and females (7%) compared to controls (1% and 0% for males and females, respectively). Also, an increased incidence of gastric lesions was noted in losartan-treated males.

TABLE 3.2.3.6.
GASTROINTESTINAL EFFECTS

Gastric Lesion	% Incidence in Male Rats			
	Control	Low Dose	Mid Dose	High Dose
Fundus, Erosion/Ulcer	11	23	17	20
Pylorus, Erosion/Ulcer	8	15	5.3	15
Nonglandular Mucosa, Focal Hyperplasia	1.3	1.3	12	2.3

A non-dose-dependent increase in the incidence of focal vacuolation of the adrenal cortex was seen in rats in all losartan-treated groups. The incidence of this change was 22%, 45%, 44% and 51% for the control, low, mid and high dose groups, respectively. The change was characterized by the presence of one or more focal regions of cytoplasmic lipid-like vacuolation in the cortex, primarily in the zona fasciculata.

Appendix I

Primary Neoplasms in Rats

LOSARTAN: 105-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT #90-099-0
SUMMARY OF PRIMARY NEOPLASMS

NUMBER NECROPSIED	GROUP 1		GROUP 2		GROUP 3		GROUP 4	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
	130	130	75	75	75	75	75	75
STOMACH:								
LEIOMYOMA	-	-	-	-	-	-	1	-
LEIOMYOSARCOMA	-	1	-	-	-	-	-	-
NONGLANDULAR MUCOSA, PAPILLOMA	-	1	-	-	-	-	1	-
NONGLANDULAR MUCOSA, SQUAMOUS CELL CARCINOMA	-	-	-	-	-	1	-	-
SMALL INTESTINE								
ADENOCARCINOMA	-	-	-	1	-	-	-	-
LEIOMYOMA	1	-	-	-	-	-	-	1
POLYP	1	-	-	-	-	-	-	-
LARGE INTESTINE								
FIBROMA	1	-	-	-	-	-	-	-
POLYP	-	1	-	-	-	-	-	1
LIVER								
BILE DUCT, CARCINOMA	-	-	-	-	-	1	-	-
HEPATOCELLULAR ADENOMA	4	4	1	2	3	2	3	4
HEPATOCELLULAR CARCINOMA	-	4	-	4	1	3	1	5
PANCREAS								
ACINUS, ADENOMA	-	4	-	2	-	-	3	5
ISLET, ADENOMA	10	20	10	10	9	14	3	6
ISLET, CARCINOMA	1	4	3	3	-	1	1	3
PERITONEUM								
LEIOMYOSARCOMA	1	-	-	-	-	-	-	-
BENIGN MESOTHELIOMA	-	-	-	-	1	-	-	-
MALIGNANT MESOTHELIOMA	1	-	-	-	-	-	-	-
OSTEOSARCOMA	-	1	-	-	-	-	-	-
ADRENAL								
CORTEX, ADENOMA	4	1	2	1	2	-	2	2
CORTEX, CARCINOMA	1	-	2	1	1	2	1	-
BENIGN PHEOCHROMOCYTOMA	4	16	3	7	1	7	1	4
MALIGNANT PHEOCHROMOCYTOMA	-	2	1	-	-	3	-	-
PARATHYROID								
ADENOMA	1	2	-	-	-	2	-	1

KEY: GROUP 1 = CONTROL
GROUP 2 = 15 MG/KG/DAY
GROUP 3 = 45 MG/KG/DAY
GROUP 4 = 135/270 MG/KG/DAY

CONTINUED
 LOGARICAN: 105-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT #90-099-0
 SUMMARY OF PRIMARY NEOPLASMS

	GROUP 1		GROUP 2		GROUP 3		GROUP 4	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
PITUITARY								
ADENOMA	107	63	63	45	66	55	57	39
CARCINOMA	1	-	-	-	-	-	-	-
THYROID								
FOLLICULAR CELL, ADENOCARCINOMA	-	2	1	-	1	3	-	1
PARAFOLLICULAR CELL, ADENOMA	16	15	7	11	7	3	3	7
FOLLICULAR CELL, ADENOMA	4	4	-	1	-	4	-	3
PARAFOLLICULAR CELL, CARCINOMA	1	-	-	-	1	1	-	1
BENIGN GANGLIONEUROMA	1	-	-	-	-	-	-	-
KIDNEY								
TUBULAR ADENOMA	1	-	-	-	-	1	-	2
HEMANGIOMA	-	-	-	-	-	-	-	1
BENIGN MESENCHYMAL TUMOR	-	-	-	-	1	-	-	-
URINARY BLADDER								
TRANSITIONAL CELL CARCINOMA	-	-	-	-	-	1	-	-
OVARY								
BENIGN SERTOLI CELL TUMOR	1	-	-	-	-	-	-	-
UTERUS								
FIBROMA	-	-	1	-	1	-	-	-
LEIOMYOSARCOMA	-	-	1	-	1	-	-	-
POLYP	2	-	6	-	-	-	1	-
ENDOMETRIAL STROMA, SARCOMA	-	-	-	-	1	-	-	-
VAGINA								
LEIOMYOSARCOMA	-	-	-	-	1	-	-	-
TESTIS								
LEYDIG CELL, ADENOMA	-	11	-	4	-	3	-	3
BENIGN MESOTHELIOMA	-	-	-	2	-	-	-	-
PROSTATE								
CARCINOMA	-	-	-	-	-	1	-	-
SKIN								
FIBROMA	5	6	2	1	1	4	2	3
FIBROSARCOMA	1	1	-	2	-	-	2	1
HEMANGIOMA	-	-	1	-	-	-	-	-
MALIGNANT FIBROUS HISTIOCYTOMA	-	-	-	-	1	-	-	-
BENIGN KERATOACANTHOMA	-	4	1	2	-	1	-	2

KEY: GROUP 1 = CONTROL
 GROUP 2 = 15 MG/KG/DAY
 GROUP 3 = 45 MG/KG/DAY
 GROUP 4 = 135/270 MG/KG/DAY

CONTINUED

LOSARTAN: 105-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT #90-099-0
SUMMARY OF PRIMARY NEOPLASMS

	GROUP 1		GROUP 2		GROUP 3		GROUP 4	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
SKIN								
LEIOMYOMA	1	-	-	-	-	-	-	-
LIPOMA	5	4	3	1	1	3	-	2
LIPOSARCOMA	-	-	-	1	-	-	-	-
NEUROFIBROMA	-	-	-	-	-	1	-	-
PAPILLOMA	-	3	-	2	2	2	-	3
RHABDOMYOSARCOMA	-	1	-	-	-	-	-	-
UNDIFFERENTIATED SARCOMA	-	-	-	-	-	-	-	1
MALIGNANT FIBROMA	-	1	-	-	-	-	-	-
SEBACEOUS ADENOMA	-	-	-	-	-	2	-	-
BENIGN TRICHOEPITHELIOMA	-	2	-	1	-	-	-	-
MAMMARY GLAND								
ADENOCARCINOMA	27	-	15	1	18	1	5	2
ADENOLIPOMA	1	-	-	-	-	-	-	-
ADENOMA	9	-	5	1	3	-	3	-
FIBROADENOMA	78	3	37	7	37	6	45	4
LUNG								
ADENOCARCINOMA	-	-	-	-	-	-	-	1
ADENOMA	-	-	-	1	-	1	2	-
PLEURA								
MALIGNANT MIBEROMA	-	-	1	-	-	-	-	-
HEART								
ATRIUM, EPITHELIAL BENIGN MESOTHELIOMA	-	-	-	-	-	1	-	-
SPLEEN								
HEMANGIOMA	-	-	-	1	-	-	-	-
HEMANGIOSARCOMA	-	1	-	-	-	-	-	-
LEIOMYOMA	-	-	1	-	-	-	-	-
LYMPH NODE								
HEMANGIOMA	-	5	1	-	-	-	1	1
THYMUS								
BENIGN THYMOMA	1	-	-	-	-	-	1	-
BONE								
OSTEOSARCOMA	3	1	-	1	-	-	-	-
SKELETAL MUSCLE								
FIBROSARCOMA	-	-	1	-	-	-	-	-

KEY: GROUP 1 = CONTROL

GROUP 2 = 15 MG/KG/DAY

GROUP 3 = 45 MG/KG/DAY

GROUP 4 = 135/270 MG/KG/DAY

CONTINUED

LOGARTAN: 105-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT #90-099-0
SUMMARY OF PRIMARY NEOPLASMS

	GROUP 1		GROUP 2		GROUP 3		GROUP 4	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
BRAIN								
MALIGNANT GLIOMA	4	1	1	-	1	-	1	-
BENIGN GRANULAR CELL TUMOR	3	1	-	1	-	4	-	1
MALIGNANT MENINGIOMA	-	-	-	-	-	1	-	-
EAR								
ZYMBAL'S GLAND, CARCINOMA	1	1	1	-	-	1	1	1
MALIGNANT SCHWANNOMA	-	-	1	-	-	-	-	1
PRIMARY SITE UNDETERMINED								
ADENOCARCINOMA	-	1	-	-	-	-	-	-
HISTIOCYTIC SARCOMA	1	4	1	3	-	3	-	2
GRANULOCYTIC LEUKEMIA	-	-	-	-	-	-	-	1
LYMPHOMA	2	4	1	8	4	1	2	1

KEY: GROUP 1 = CONTROL

GROUP 2 = 15 MG/KG/DAY

GROUP 3 = 45 MG/KG/DAY

GROUP 4 = 135/270 MG/KG/DAY

Studies in Mice

3.2.4. Fourteen-Week Oral Range Finding Toxicity Study in Mice

Study Facility: MSD Research Laboratories, West Point, PA

Study No: TT #90-058-0

Study Dates: 3/12/90- 7/13/90

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Male and female CrI:CD-1 (ICR) BR mice (39 days old at initiation of study).

Drug Administration: Losartan (Lot # 005H010) was dissolved in deionized water and administered orally by gavage.

Dose Levels: 0 (vehicle), 50, 250 and 500 mg/kg/day (15/sex/dose group)

Observations/Measurements: Mice were observed daily for mortality and clinical signs of toxicity. Body weights were measured prior to treatment, once during week 1 of treatment and twice weekly, thereafter. Food consumption was measured weekly. Urine was collected from mice during week 13 of treatment for urinalysis. At termination of the study, surviving mice were anesthetized with ether and blood was withdrawn from the vena cava for hematological and serum biochemical analyses. All animals were examined for gross pathology; sections of major organs and tissues from control and high dose animals were sectioned, fixed on slides and examined microscopically.

Results: One high dose (500 mg/kg/day) female mouse died on day 3 of treatment. Food consumption was decreased by 10% in high dose females; there was no effect on food consumption in male mice. Body weight gain was significantly lower in high dose males and females and in mid dose males compared to controls.

TABLE 3.2.4.1
EFFECT ON BODY WEIGHT AND BODY WEIGHT GAIN IN MALE MICE

Dose (mg/kg/day)	Starting Weight (gm)	Terminal Weight (gm)	% Difference from Final Control Weight	% Difference from Control Weight Gain
0	29.6	40.4		
50	29.1	38.3	-5.2	-16
250	28.1	35.5	-12.1	-31*
500	29.6	36.6	-9.4	-35*

*Indicates statistically significant difference from control

TABLE 3.2.4.2
EFFECT ON BODY WEIGHT AND BODY WEIGHT GAIN IN FEMALE MICE

Dose (mg/kg/day)	Starting Weight (gm)	Terminal Weight (gm)	% Difference from Final Control Weight	% Difference from Control Weight Gain
0	23.5	30.3		
50	22.9	29.9	-1.3	+3
250	23.8	29.9	-1.3	-10
500	23.8	28.8	-5.0	-25*

*Indicates statistically significant difference from control

Mean erythrocyte, hemoglobin and hematocrit values were decreased from concurrent control by 8% to 10% in high dose females. These erythroid parameters were generally unaffected by 50 or 250 mg/kg/day doses of losartan.

Serum urea nitrogen values in mid and high dose females, respectively, were 25% and 154% higher than concurrent control values. Serum urea nitrogen in high dose males was only 10% above control. Other serum biochemical parameters were unaffected by treatment.

Urinalysis revealed a decrease in urine volume in high dose females compared to control (0.8 ml vs. 1.9 ml) as well as an increase in specific gravity (1.032 vs. 1.020). These effects were not seen in male mice or in lower dose female groups. No other urinalysis parameter was affected by treatment.

Treatment-related decreases in absolute and relative heart weights were observed with mid and high dose males and females. There were no gross or microscopic changes to account for these decreases in heart weights.

TABLE 3.2.4.3
EFFECT ON ABSOLUTE AND RELATIVE HEART WEIGHT

Dose Group (mg/kg/day)	% Difference from Control Absolute (Relative) Heart Weight	
	Males	Females
50	-2 (+4)	-7 (-4)
250	-16 (-4)	-14 (-13)
500	-20 (-12)	-14 (-9)

Microscopic examination revealed treatment related renal effects which consisted of hyperplasia of the juxtaglomerular apparatus and focal basophilia of the renal tubules. The incidence of these renal effects are as follows.

TABLE 3.2.4.4
RENAL HISTOPATHOLOGIC EFFECTS

Effect	Incidence							
	Control		Low Dose		Mid Dose		High Dose	
	M	F	M	F	M	F	M	F
JG Hyperplasia	0	0	0	2	7	7	13	11
Tubular Focal Basophilia	2	0	0	1	5	5	11	11

No other gross or microscopic effects were associated with losartan treatment.

3.2.5. Ninety-Two Week Oral Carcinogenicity Study in Mice

Study Facility: MSD Research Laboratories, West Point, PA

Study No: TT #90-133-0

Study Dates: 8/20/90 - 5/20/92

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Male and female Crl:CD-1(ICR)BR mice (22.6-32.7 gm males, 17.7-27.0 gm females; 36 days old; housed 2-3/cage)

Drug Administration: Losartan (Batch # 086-00511-010 and 086-00511-019) was dissolved in deionized water and administered orally by gavage once daily.

Dose Levels:

Vehicle Control 1		50M, 50F
Vehicle Control 2		50M, 50F
Losartan 20 mg/kg/day	(Low Dose)	50M, 50F
Losartan 100 mg/kg/day	(Mid Dose)	50M, 50F
Losartan 300/200 mg/kg/day	(High Dose, Males)	50M
Losartan 500/300/200 mg/kg/day	(High Dose, Females)	50F

Note: Due to treatment-related decreases in body weight gain and increases in mortality, the dosage level for the high dose females was lowered from 500 to 300 mg/kg/day in Drug Week 28 and the dosage level for the high dose males and females was lowered from 300 to 200 mg/kg/day in Drug Week 43. An additional 5/sex/group were used as replacement animals for mice that died of causes unrelated to treatment, such as dosing accidents, during the first 8 weeks of the study. After 8 weeks, the remaining animals in these groups were discarded.

Observations/Measurements: Mice were observed daily for mortality and weekly for clinical signs of toxicity. The animals were palpated for masses every 4 weeks beginning in Drug Week 26. Body weights were measured pretest, once in Drug Week 1, twice weekly in Drug Weeks 2 through 13, and once weekly thereafter. Ophthalmoscopic examinations were conducted on all animals prior to treatment and in Drug Weeks 52 and 89. At scheduled sacrifice, mice were anesthetized with ether and venous blood was obtained from the vena cava for hematologic examination. Caval blood samples were obtained at unscheduled necropsies to aid in the diagnosis of leukemias and lymphomas. All animals were necropsied and sections of major organs and tissues were fixed on slides for microscopic examination. The incidences of various tumor types were analyzed for statistically significant trend ($P < 0.05$) with adjustments made for variations in mortality.

Results:

Mortality and Survival: A higher than expected occurrence of early deaths/early sacrifices (due to gastrointestinal lesions or to undetermined causes) was noted among high dose females prior to Drug Week 28 and in high dose males prior to Drug Week 43, prompting the sponsor to reduce the dosage levels for high dose males and females. At study termination, the number of male and female control and high dose mice which died or were killed were similar. The incidences of early sacrifices (ES) and early deaths (ED) among low and mid dose treated mice were lower than control.

TABLE 3.2.5.1.
INCIDENCE OF EARLY SACRIFICES/EARLY DEATHS

Dose Group	No. of Early Sacrifices/Early Deaths	
	Females	Males
Control 1	26	30
Control 2	29	30
Low Dose	16	23
Mid Dose	21	25
High Dose	33	29

TABLE 3.2.5.2.
GI AND UNDETERMINED CAUSES OF EARLY SACRIFICES/EARLY DEATHS

Dose Group	No. of Early Sacrifices/Early Deaths				
	GI Lesions		Undetermined		Total
	F	M	F	M	
Control 1	0	0	0	0	0
Control 2	0	1	0	0	1
Low Dose	0	1	0	0	1
Mid Dose	0	2	0	2	4
High Dose	5	4	4	7	20

Physical Signs: Dyspnea, decreased locomotor activity, weakness, pallor and abdominal distension were observed in several mid and high dose animals prior to early death or early sacrifice. These signs were often associated with treatment-related gastrointestinal effects (intestinal distension, gastritis and ulcers).

Body Weight: Statistically significant ($P < 0.05$) reductions in body weight gain, as compared to the average of combined concurrent control values, were observed after 91 weeks of treatment in high dose males and in females of all dose groups. Body weights and body weight gains in high dose females were reduced after Drug Weeks 27 and 42 and in high dose males after Drug Week 42. These body weight decreases, in conjunction with the increase in early mortalities and GI toxicity, prompted the lowering of the dosage level for the high dose animals.

TABLE 3.2.5.3.
EFFECT ON BODY WEIGHT AND BODY WEIGHT GAIN

Dose Group	Sex	Percent Change from Control Wt. (Wt. Gain)		
		27 Weeks	42 Weeks	91 Weeks
Low Dose	M	0	0	-4
	F	-6	-8	-4 (-10)
Mid Dose	M	-1	-2	0
	F	-6	-10	-9 (-22)
High Dose	M	-5 (-12)	-8 (-23)	-6 (-22)
	F	-13 (-39)	-15 (-40)	-13 (-34)

*Average of 2 concurrent control group values used in calculating change.

Ophthalmoscopic Effects: No treatment-related ocular effects were observed.

Hematological Effects: There were no treatment-related effects on hematologic parameters in animals that died or those sacrificed at termination of the study.

Gross Pathology: Except for the gastrointestinal lesions (gastric fundic erosions, ulceration, or hemorrhage of the small and/or large intestine) observed primarily in high dose animals that died or were sacrificed prior to study termination, no treatment-related gross pathology was seen at necropsy.

Microscopic Pathology:

Neoplastic Lesions: There were no significant differences in the number of mice with neoplasms or total neoplasms between losartan-treated groups and concurrent controls.

TABLE 3.2.5.4.
SUMMARY OF NEOPLASMS IN MALE MICE

	Number or Incidence				
	Control 1	Control 2	Low Dose	Mid Dose	High Dose
# Mice with Neoplasms					
Malignant	8	11	16	9	15
Benign	19	19	14	22	16
Malignant or Benign	25	23	25	28	26
Total # of Neoplasms					
Malignant	8	12	17	11	20
Benign	25	22	18	29	19
Malignant or Benign	33	34	35	40	39

TABLE 3.2.5.5.
SUMMARY OF NEOPLASMS IN FEMALE MICE

	Number or Incidence				
	Control 1	Control 2	Low Dose	Mid Dose	High Dose
# Mice with Neoplasms					
Malignant	12	12	8	11	7
Benign	14	16	18	11	7
Malignant or Benign	23	26	23	20	13
Total # of Neoplasms					
Malignant	14	14	10	11	7
Benign	15	18	20	13	9
Malignant or Benign	29	32	30	24	16

A statistically significant ($P < 0.05$) increased trend in the incidence of lung adenocarcinomas was seen in male mice. No statistically significant increased trend in the incidence of lung adenocarcinomas was seen in female mice and no increase was observed in either sex for lung adenomas.

TABLE 3.2.5.6.
INCIDENCE (%) OF PULMONARY ADENOMAS AND ADENOCARCINOMAS

	Percent Incidence				
	Control 1	Control 2	Low Dose	Mid Dose	High Dose
<u>Male Mice</u>					
Adenoma	14	12	18	18	12
Adenocarcinoma	4	6	6	6	16
Adenoma or Adenocarcinoma	18	18	24	24	28
<u>Female Mice</u>					
Adenoma	20	10	14	14	10
Adenocarcinoma	6	8	2	0	4
Adenoma or Adenocarcinoma	26	18	16	14	14

Although the incidence of lung adenocarcinoma in high dose males was significantly increased above concurrent control, the sponsor dismisses this finding based on the fact that this incidence is within their range of historical control values. In the 9 most recent carcinogenicity studies from the same laboratory (studies of similar duration with 18 control groups of 50 male mice/group), the sponsor has observed the following mean incidences and ranges for pulmonary neoplasms (individual study results shown in Appendix II).

TABLE 3.2.5.7
HISTORICAL INCIDENCE OF PULMONARY TUMORS IN MALE MICE

	Mean	Median	Range
Adenoma	15%	20%	8-34%
Adenocarcinoma	6.6%	6.0%	0-24%

There was no statistically significant increased trend in the incidence of neoplasms in any other organs or tissues in this study (Appendix III).

Non-Neoplastic Lesions: As previously described, treatment-related gastrointestinal (GI) lesions were observed in several mice of both sexes, primarily in the high dose group but also in some males in the mid dose group. The types and incidences of GI lesions observed are as follows:

TABLE 3.2.5.8
TREATMENT-RELATED GASTROINTESTINAL LESIONS

GI Effect	Incidence (# mice)										
	C-1		C-2		Low		Mid		High		
	F	M	F	M	F	M	F	M	F	M	
Stomach											
Distension	0	0	0	0	0	0	0	0	1	1	
Necrotizing Gastritis	0	0	0	0	0	0	0	0	1	0	
Sm. Intestine											
Distension	0	0	0	1	0	0	0	3	5	3	
Ulcer	0	0	0	0	0	1	1	2	1	2	
Lge. Intestine											
Distension	0	0	0	0	0	0	0	1	3	1	
Ulcer	0	0	0	0	0	0	0	0	0	2	

A dose-related occurrence of renal juxtaglomerular (JG) cell hyperplasia was seen in all losartan-treated groups. The lesions were characterized by an increase in the number and size of these specialized cells comprising the wall of the afferent arteriole of the glomeruli. A slightly higher incidence of chronic nephritis was seen in mid and high dose females and in high dose males.

TABLE 3.2.5.9
RENAL EFFECTS

Pathology		Incidence (# mice)				
		C-1	C-2	Low	Mid	High
JG Cell Hyperplasia	F	0	0	10	22	24
	M	0	0	8	15	32
Chronic Nephritis	F	24	31	29	43	42
	M	30	34	28	36	42

Appendix II

Historical Incidence of Benign and Malignant Pulmonary Tumors in Control Male CD-1 (ICR)BR Mice from Nine Recently Conducted Carcinogenicity Studies

Study	Group	Malignant Adenocarcinoma		Benign Adenoma	
		Incidence*	% Incidence	Incidence*	% Incidence
1	C-1	0/50	0	11/50	22
	C-2	0/50	0	8/50	16
2	C-1	12/50	24	4/50	8
	C-2	7/49	14	8/49	16
3	C-1	0/50	0	10/50	20
	C-2	0/50	0	6/50	12
4	C-1	1/50	2	9/50	18
	C-2	2/50	4	8/50	16
5	C-1	5/50	10	17/50	34
	C-2	6/50	12	10/50	20
6	C-1	5/50	10	8/50	16
	C-2	7/50	14	9/50	18
7	C-1	3/50	6	8/50	16
	C-2	3/50	6	12/50	24
8	C-1	2/50	4	11/50	22
	C-2	4/50	8	10/50	20
9	C-1	1/50	2	11/50	22
	C-2	1/47	2	10/47	21

All groups on study for 92 weeks except groups from study #7 which were on study for 73 weeks. *Represents # mice with tumor/# mice necropsied

Appendix III

Primary Neoplasms in Mice

LOGARDAN: 92-WEEK ORAL CARCINOGENICITY STUDY IN MICE. TT #90-133-0
SUMMARY OF PRIMARY NEOPLASMS

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5		GROUP 6	
	F	M	F	M	F	M	F	M	F	M	F	M
NUMBER NECROPSIED	50	50	50	50	50	50	50	50	-	50	50	-
STOMACH												
NONGLANDULAR MUCOSA, PAPILLOMA	-	-	-	-	1	-	-	-	-	-	-	-
SMALL INTESTINE												
ADENOCARCINOMA	-	-	-	-	-	-	1	-	-	-	-	-
HEMANGIOMA	-	-	-	1	-	-	-	-	-	-	-	-
POLYP	-	-	1	1	-	-	-	1	-	-	-	-
LARGE INTESTINE												
ANUS, SQUAMOUS CELL CARCINOMA	-	-	-	-	-	-	1	-	-	-	-	-
LIVER												
HEMANGIOMA	-	-	3	-	1	-	-	-	-	-	-	-
HEMANGIOSARCOMA	-	1	-	1	-	1	-	-	-	-	-	-
HEPATOCELLULAR ADENOMA	-	6	1	3	1	2	-	5	-	6	-	-
HEPATOCELLULAR CARCINOMA	2	3	-	6	-	8	-	4	-	7	-	-
PANCREAS												
ISLET, ADENOMA	-	-	-	1	-	-	-	-	-	-	-	-
ADRENAL												
CORTEK, ADENOMA	-	2	-	1	-	1	-	-	-	-	-	-
MALIGNANT PHEOCHROMOCYTOMA	1	-	-	-	-	-	-	-	-	-	-	-
BENIGN SPINDLE CELL TUMOR	1	-	-	-	-	-	1	-	-	-	1	-
PITUITARY												
ADENOMA	2	-	-	-	-	-	1	1	-	-	-	-
THYROID												
FOLLICULAR CELL, ADENOMA	-	2	-	1	-	-	1	-	-	1	-	-
KIDNEY												
PELVIC EPITHELIUM, TRANSITIONAL CELL CARCINOMA	-	-	-	-	-	-	1	-	-	-	-	-
OVARY												
PAPILLARY ADENOMA	-	-	-	-	1	-	-	-	-	-	-	-
BENIGN GRANULOSA CELL TUMOR	-	-	1	-	-	-	1	-	-	-	-	-
MALIGNANT GRANULOSA CELL TUMOR	-	-	-	-	1	-	-	-	-	-	-	-

KEY: GROUP 1 = CONTROL 1

GROUP 5 = 300/200 MG/KG/DAY

GROUP 2 = CONTROL 2

GROUP 6 = 500/300/200 MG/KG/DAY

GROUP 3 = 20 MG/KG/DAY

GROUP 4 = 100 MG/KG/DAY

L-158,086 (CONTINUED): 92-WEEK ORAL CARCINOGENICITY STUDY IN MICE. TT #90-133-0
SUMMARY OF PRIMARY NEOPLASMS

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5		GROUP 6	
	F	M	F	M	F	M	F	M	F	M	F	M
SKELETAL MUSCLE												
HEMANGIOSARCOMA	-	-	-	-	-	1	-	-	-	-	-	-
RHABDOMYOSARCOMA	1	-	-	-	-	-	1	-	-	-	-	-
NERVE												
MALIGNANT SCHWANNOMA	-	-	-	-	-	-	-	-	-	1	-	-
EYE												
HARDERIAN GLAND, ADENOMA	-	5	2	5	3	5	1	10	-	5	2	-
PRIMARY SITE UNDETERMINED												
HISTIOCYTIC SARCOMA	1	-	1	1	-	1	1	-	-	1	1	-
MYELOID LEUKEMIA	-	-	-	-	-	1	-	-	-	-	-	-
LYMPHOMA	1	-	3	-	5	2	4	3	-	2	2	-
MALIGNANT PLASMA CELL MYELOMA	-	-	-	-	-	-	1	-	-	-	-	-

KEY: GROUP 1 = CONTROL 1

GROUP 2 = CONTROL 2

GROUP 3 = 20 MG/KG/DAY

GROUP 4 = 100 MG/KG/DAY

GROUP 5 = 300/200 MG/KG/DAY

GROUP 6 = 500/300/200 MG/KG/DAY

Studies in Dogs**3.2.6. One Month Oral Toxicity Study in Dogs**

Location of Data: Vol. 13, Tab B-5

Testing Facility: Toxicology Section, Experimental Station, Pharmaceuticals and Biotechnology R & D Division, E. I. du Pont de Nemours and Company, Medical Products Department, Wilmington, DE.

Study No.: 88-7-3

Study Dates: Initiated: July 26, 1988
Terminated: August 26, 1988

GLP Compliance: Studies were done in accordance with GLP regulations.

Animals: Beagle dogs (both sexes, approximately 9-13 months of age, 7.1 to 11.7 kg)

Drug Administration: Losartan (Lot # INE-3340-15) was prepared fresh daily as an aqueous solution in sterile water for injection and administered orally by gastric intubation.

Dose Levels: 0 (vehicle), 15, 45, and 135 mg/kg (4/sex/dose).

Observations/Measurements: All dogs were observed once daily for mortality and clinical signs of toxicity. Body weights were measured twice before treatment, on study day 1 prior to dosing and twice weekly during the dosing period. A final body weight was measured prior to scheduled sacrifice. Food consumption was measured daily one week before commencement of treatment and daily throughout the dosing period. Stool samples were analyzed for occult blood for approximately one week before treatment and then daily during the dosing period. Body temperatures and respiratory rates were recorded and neurologic reflexes evaluated during the pretest period, and within two hours after dosing during the last week of the study. Electrocardiographic tracings were recorded pretest and predose and within two hours after dosing just prior to termination of the study. Ophthalmoscopic examinations were performed once pretreatment and during the last week of the dosing period. Blood for hematology and clinical chemistry measurements was collected from all dogs twice pretest and once after approximately two weeks of dosing. Urinalysis was performed on urine collected from all dogs pretest and after 4 weeks of dosing. The concentration of losartan in plasma was determined from blood samples collected from all dogs approximately 45 min after dosing on dose days 1, 14, and 30. Necropsy was performed on all animals at the end of treatment. Liver, heart, kidneys, testes, adrenals and brain from all animals were weighed and organ-to-terminal body weight ratios calculated. Major tissues/organs collected from all animals were fixed for histopathological evaluation.

Results: No treatment-related deaths occurred. There was one non-scheduled kill in the high dose group. Within one hour after receiving its fifth dose, the high dose male became ataxic, displayed reduced motor activity, increased salivation and shortly later, red material was observed in the animal's vomitus. Within 90 min of dosing, the animal was prostrate and had labored breathing, cyanotic membranes and no pupillary response. The animal was sent to necropsy as a moribund kill. This animal had moderate hemorrhage, congestion, necrosis and edema of the lungs.

The most prominent clinical findings, observed at all dose levels were adverse gastrointestinal effects, as evidenced by emesis, mucoidal, soft or watery stool, and red material under the cage (not otherwise described). These signs were considered to be losartan-induced effects since they were not seen in control animals. The frequency and severity of these observations were dose-dependent and considered to be dose-limiting in the high dose group. These clinical observations occurred sporadically and were relatively mild in nature in low dose group animals. In the 45 mg/kg/day dosage group, the onset for these effects ranged from study day 2 to study day 21. At 135 mg/kg/day, these clinical signs generally occurred as soon as study day 1, shortly after dosing. The total number of occurrences or frequency of all but one clinical sign (soft stool) was 1.3- to 4.6-fold greater for the high dose group than for the mid-dosage group. Fecal occult blood was infrequently observed for all low dosage group animals. However, repeated (for at least three consecutive days) occurrences of fecal occult blood in animals from both mid and high dosage groups suggests a dosage dependent relationship between gastrointestinal effects and losartan administration.

There were no treatment-related effects on body weight gain, food consumption or ophthalmoscopic and E.C.G. examinations. Slight but statistically significant differences (from control) in group mean serum chemistry parameters (including aspartate aminotransferase, alanine aminotransferase, sodium and inorganic phosphorus) were observed sporadically at various dosage levels during the study period. These changes were not considered to be treatment-related since they were minor and non-dose dependent. There were no treatment-related effects on urinalysis profiles or organ weights for any of the dose groups. Gross and histopathological examination revealed no treatment-related abnormalities. The numerous occurrences of emesis might suggest an irritation of gut mucosa, but histopathological findings did not indicate that losartan was irritating to the mucosal wall.

In conclusion, clinical signs suggestive of gastrointestinal effects were the most prominent findings at all dose levels. The severe emetic episodes that occurred in animals receiving losartan at 135 mg/kg/day were considered to be dose limiting.

Plasma concentrations of losartan increased dose-dependently but not in proportion to the dose administered as shown in Table 3.2.6.1.

TABLE 3.2.6.1
PLASMA CONCENTRATIONS ($\mu\text{g/ml}$)[@] OF LOSARTAN FREE ACID. STUDY # 88-7-3.

Dose (mg/kg/day)		Day 1	Day 14	Day 30
15	M	2.63 $\pm$ 1.83	2.88 $\pm$ 1.63	2.76 $\pm$ 1.69
	F	2.14 $\pm$ 0.76	2.23 $\pm$ 0.97	2.47 $\pm$ 0.30*
45	M	6.54 $\pm$ 3.16	8.74 $\pm$ 3.83	7.62 $\pm$ 3.81
	F	4.00 $\pm$ 2.90	12.46 $\pm$ 4.19	8.51 $\pm$ 2.46
135	M	10.54 $\pm$ 5.30	25.17 $\pm$ 10.40*	19.86 $\pm$ 10.79*
	F	22.38 $\pm$ 8.36	31.47 $\pm$ 10.28	27.54 $\pm$ 12.84

Values: Mean $\pm$ S.D. (n=4); @: measured 45 min after dosing; *: mean data from three animals.

3.2.7. Three Month Oral Toxicity Study in Dogs

Location of Data: Vol. 13, Tab B-6

Testing Facility: Toxicology Section, Experimental Station, Pharmaceuticals and Biotechnology R & D Division, E. I. du Pont de Nemours and Company, Medical Products Department, Wilmington, DE.

Study No.: 89-5-6

Study Dates: Initiated: May 31, 1989
Terminated: September 1, 1989

GLP Compliance: Studies were done in accordance with GLP regulations.

Animals: Beagle dogs (Males, 8.2 - 11.4 kg; Females, 6 - 10.7 kg) were approximately 9-13 months of age at initiation of treatment.

Drug Administration: Losartan (Lot # INE-3340-19M) was prepared fresh daily as an aqueous solution in sterile water for injection and administered via liquid-filled gelatin capsules.

Dose Levels: 0 (vehicle), 5, 25, and 125 mg/kg (5/sex/dose).

Observations/Measurements: All dogs were observed once daily for mortality and clinical signs of toxicity. Body weights were measured before treatment and twice weekly during the dosing period. A final body weight was measured prior to scheduled sacrifice. Food consumption was measured daily and stool samples were analyzed for occult blood for one week before commencement of treatment and daily throughout the dosing period. Body temperatures and respiratory rates were recorded and neurologic reflexes evaluated during the pretest period, and once monthly during the dosing period. Electrocardiographic tracings were recorded twice during the pretest period, prior to dosing and approximately two hours after

dosing during study weeks 1, 4, 7-8, and 13. Ophthalmoscopic examinations were performed pretreatment and during the last week of the dosing period. Blood and urine samples were collected from all dogs twice pretest and once at approximate monthly intervals during the dosing period for hematology and blood chemistry, and urinalysis. The concentration of losartan in plasma was determined from blood samples collected from all dogs approximately 45 min after dosing on dose days 1, 7, 31, 59, and 84. Necropsy was performed on all animals at the end of treatment. Liver, heart, kidneys, testes, adrenals, pituitary and brain from all animals were weighed and organ-to-terminal body weight ratios calculated. Major tissues/organs collected from all animals were fixed for histopathological evaluation.

Results: No deaths occurred. The most prominent clinical findings observed in high dose animals were vomiting, increased salivation and fecal abnormalities, which included positive fecal occult blood. With the exception of emesis, the onset and total incidence of these signs were similar among both sexes of the high dose group. Emesis, however, occurred with a greater frequency in (all) high dose female dogs following dosing on study day 1 and continued to be observed throughout the study. The onset of emesis was within 15 minutes of dosing. In the high dose males, the onset of the emetic response to losartan was not observed until study day 12, with 4 of 5 males vomiting during the study period. The total frequency (days) of emesis observed with each of the dogs ranged from 24 to 32 days for females and 5 to 15 days for the males during the 3-month study period. In the 25 mg/kg/day group, the clinical sign profile suggested a trend toward increased salivation, and increased incidence of emesis. However, the incidences are not considered to be of toxicological significance due to their relatively mild and sporadic occurrence. Fecal abnormalities, including abnormal consistency and/or color of the stool(s) were observed at a much greater frequency in the high dose group. Four of 5 high dose males and 3 of 5 high dose females tested positive for fecal occult blood (at least three consecutive days) five or more times during the study. Animals from other dose groups including control did not test positive for fecal occult blood for at least three consecutive days.

There were no treatment-related effects on body weight gain, food consumption or ophthalmoscopic and E.C.G. examinations. A slight but statistically significant increase in the serum creatinine level for the 125 mg/kg/day female group (relative to concurrent control) was observed at the two month sampling interval. However, the elevation was considered to be minor, of no biological significance, and unrelated to losartan treatment. Also noted in the high dose males was a slight decrease in erythroid parameters (RBC, hematocrit, and hemoglobin) at the one- and two-month intervals when compared to control. This too was not considered by the sponsor to represent a biologically adverse effect of treatment.

A statistically significant decrease in the mean absolute adrenal weight was found for the 5 and 25 mg/kg/day male groups. However, the mean absolute adrenal weight for males receiving 125 mg/kg/day was comparable with that of the control male group. There were no other significant differences in organ weights between vehicle control and losartan treated groups. The only histopathological finding of note was moderate lymphocytic infiltration of the gastric mucosa of a 125 mg/kg/day female dog, which was compatible with gastric

irritation. The emetic response induced by losartan may be attributed, in part, to a direct irritation of the gastric mucosa. Similarly, the fecal abnormalities observed were consistent with a treatment-induced irritation of the gastrointestinal tract. The no observable effect level was 5 mg/kg/day.

The plasma concentrations of losartan increased dose-dependently and appeared to increase in proportion to the dose administered in both male and female dogs. Losartan concentration and variabilities were similar in both male and female dogs at each dosage level.

TABLE 3.2.7.1
PLASMA CONCENTRATIONS ($\mu\text{g/ml}$)[@] OF LOSARTAN FREE ACID. STUDY #89-5-6.

Dose (mg/kg/day)		Day 1	Day 7	Day 31	Day 59	Day 84
5	M	0.79 $\pm$ 0.56 ⁴	1.02 $\pm$ 0.17 ²	0.27 $\pm$ 0.39	0.57 $\pm$ 0.37 ⁴	0.50 $\pm$ 0.72 ²
	F	0.70 $\pm$ 0.42 ⁴	0.71 $\pm$ 0.43 ⁴	0.45 $\pm$ 0.42 ³	0.66 $\pm$ 0.44 ⁴	0.72 $\pm$ 0.47 ⁴
25	M	3.57 $\pm$ 2.59	5.37 $\pm$ 4.64	3.89 $\pm$ 3.13	3.28 $\pm$ 1.94	4.21 $\pm$ 2.05
	F	4.05 $\pm$ 2.04	5.98 $\pm$ 3.24	2.16 $\pm$ 0.96	4.29 $\pm$ 2.42	3.02 $\pm$ 1.14
125	M	17.90 $\pm$ 8.45	21.98 $\pm$ 4.60	18.00 $\pm$ 6.70	19.27 $\pm$ 5.18	18.89 $\pm$ 3.50
	F	9.81 $\pm$ 5.66	18.94 $\pm$ 7.74	18.67 $\pm$ 6.33	16.09 $\pm$ 6.07	26.05 $\pm$ 7.08

Values: Mean $\pm$ S.D; @ measured 45 min after dosing; N=5 unless otherwise specified by a superscript number which denotes the sample size for a given interval of time and dose.

3.2.8. Fifty-Three-Week Oral Toxicity Study in Dogs with a 27-Week Interim Necropsy

Location of Data: Vol. 14, Tab B-7

Testing Facility: Department of Safety Assessment, Merck Sharp & Dohme Research Laboratories, Merck & Co., Inc., West Point, PA

Study No.: TT #90-028-0

Study Dates: Initiated: February 26, 1990
Interim necropsy: August 27 and 28, 1990
Terminal necropsy: February 25 and 26, 1991

GLP Compliance: Studies were done in accordance with GLP regulations.

Animals: Beagle dogs (32 Males, 8.9-14.9 kg; 32 Females, 6.9-16.2 kg) were 32-59 weeks of age at initiation of treatment.

Drug Administration: Losartan (Lot # 010) was prepared fresh daily as an aqueous solution in

deionized water and administered by orogastric gavage (5 ml/kg).

Dose Levels: 0 (vehicle), 5, 25, and 125 mg/kg, (8/sex/dose).

Observations/Measurements: All dogs were observed once daily for mortality and clinical signs of toxicity. Body weights were measured before treatment and once weekly during the dosing period. Food consumption was measured daily (4 days/week) through drug week 27 and then every fourth week (4 days/week) thereafter and drug weeks in which hematological, serum biochemical, and urinalysis parameters were evaluated. Ophthalmic and electrocardiographic examinations were performed pretreatment and in drug weeks 12, 24 or 25, 39, and 52. Blood for hematological and biochemical examinations was collected from the jugular vein of each animal (fasted) pretest and on all surviving animals during drug weeks 4, 12, 25, 39, and 51. In addition, alkaline phosphatase, ALT, and AST were determined on all dogs in drug week 17. Urinalyses were performed pretest and during drug weeks 12, 25, 39, and 51.

Four dogs/sex from the control and the 5 and 125 mg/kg/day dose groups and 3 females and 4 males from the 25 mg/kg/day dose group were sacrificed in drug week 27. The remaining animals were sacrificed in drug week 53. At both the interim and terminal necropsies, detailed gross examinations were performed on all dogs, including one mid dose female dog that died of an intubation accident in drug week 6. The weights of brain, spleen, heart, kidney, liver, adrenal, pituitary, thyroid, lung, testes, prostate, ovary and uterus were recorded. Major tissues/organ samples collected from all animals were preserved in appropriate solutions. Histopathological evaluations were performed on all control and high dose group dogs as well as the mid dose female dog which did not survive to scheduled necropsy. In addition, specimens of all gross lesions (from all dogs) were examined.

Results: No treatment-related deaths occurred. A female dog from the 25 mg/kg/day group died in drug week 6 due to an intubation accident. Mild, transient, treatment-related predose and/or postdose hypersalivation was observed frequently at the high dose and infrequently at the mid and low doses and not at all in control animals. Post dose hypersalivation generally lasted 10-30 minutes. Occasional treatment-related emesis and changes in stool consistency (unformed or loose) and color (yellow) were more frequently observed in high dose dogs compared to control animals. However, these signs were not considered significant given their mild and sporadic nature and the lack of histomorphologic changes in the gastrointestinal tract. The incidence of emesis in dogs given 5 and 25 mg/kg/day was not appreciably greater than that observed with control animals.

There were no treatment-related effects on body weight gain, food consumption, ophthalmoscopic and E.C.G. examinations, or hematologic and urinalysis parameters. Throughout the study, there were recurrent increases in serum ALT values for one mid dose male dog, and two female and one male high dose dogs when compared to pretest and historical control values (Table 3.2.8.1). However, the magnitude of the increases was not dose- or time-dependent and there was no histomorphological evidence of hepatic injury in

these animals. The recurrent increases in ALT as noted in this study are, nevertheless, attributed to treatment.

There were no organ weight or histopathologic findings that could be attributed to treatment.

TABLE 3.2.8.1
INDIVIDUAL SERUM ALT (U/L) VALUES. STUDY #90-028-0

Dose mg/kg/day	Pretest -1 week	Drug week					
		4	12	17	25	39	51
25/Male	28	34	73*	83*	99*	-	-
125/Female	36	41	46	49*	167*	86*	199*
125/Female	27	88*	91*	25	37	-	-
125/Male	31	26	43	32	32	49*	46*

* Values outside 95% limits for 3 year control values
- = Sacrificed at interim necropsy

In conclusion, with the exception of mild clinical signs of gastrointestinal toxicity and sporadic, isolated increases in serum ALT in one mid and three high dose dogs, oral administration of losartan at dosages levels up to 125 mg/kg/day for 53 weeks was well tolerated.

Studies in Monkeys

3.2.9. 14-Week Oral Toxicity Study in Monkeys

Study Facility: MSD Research Laboratories, West Point, PA

Study No: 90-193-0

Study Dates: 12/13/90 - 3/14/91

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Rhesus monkeys (16M, 16F; 2.3-3.3 kg)

Drug Administration: Losartan (Lot # 10) was dissolved in deionized water and administered orally once daily by nasogastric tube.

Dose Levels: 0, 20, 100 and 300 mg/kg/day (4/sex/dose group)

Observations/Measurements: Animals were observed daily during treatment for clinical signs of toxicity and mortality. Body weights were measured pretest and weekly during the study. Ophthalmoscopic exams were performed pretest and in weeks 5 and 11 of treatment. Blood was obtained via a femoral vein pretest and in weeks 4, 8 and 11 of treatment for hematology and serum biochemistry analyses. Urine was collected pretest and in weeks 2, 4, 8 and 11 of treatment for urinalysis. Prior to scheduled sacrifice and 24 hours after dosing, blood was obtained from all control and high dose animals for measurement of plasma angiotensin II levels. Blood samples were also obtained from 3 losartan-treated females/group during Drug Week 13 at 0.25, 0.5, 1, 2, 4, 6, 8 and 24 hours after dosing for measurement of parent drug and carboxylic acid metabolite levels. Monkeys were sacrificed at termination of the study and examined for gross pathology. Sections of major organs and tissues were fixed on slides for histopathologic examination.

Results:

Mortality: There were no treatment-related deaths. One mid dose male was killed for humane reasons in Drug Week 3 due to a fracture of the right humerus, with associated soft-tissue damage.

Clinical Signs: No clinical signs of toxicity were observed.

Body Weight: No treatment-related effects on body weights were observed.

Ophthalmoscopy: No treatment-related changes were seen on ophthalmologic examinations.

Hematology: Slightly lower (up to 5%) erythroid parameters (erythrocyte count, hematocrit and hemoglobin concentrations) compared to control occurred in monkeys given 300 mg/kg/day in weeks 8 and 11 of treatment.

Serum Biochemistry: No treatment-related effects were seen in the biochemical parameters measured. Angiotensin II levels in the high dose group (49.6 pg/ml) were approximately 5-fold higher than in the control group (11.8 pg/ml) 24 hours after losartan administration.

Urinalysis: No treatment-related effects on urinalysis parameters were observed.

Organ Weights: There were no treatment-related differences in organ weights.

Gross Pathology: Tarry intestinal contents and small depressed, reddened foci were noted in the stomachs and/or intestines in 4 high dose monkeys.

Histopathology: No microscopic effects related to losartan treatment were observed. No gastrointestinal lesions were observed in the high dose monkeys to correlate with the reddened foci noted during gross examination.

Plasma Drug Levels: Parent compound was detected in monkey plasma in only a few sampling periods after oral dosing at 20 mg/kg/day during Drug Week 13. Female monkeys did not extensively metabolize losartan to its acid metabolite or to its N2-tetrazole glucuronide. The acid metabolite was not detected in any sample after the 20 mg/kg/day dose and plasma samples were consistently less than 1.3 ug/ml for the 100 to 300 mg/kg/day dosage groups. Also, systemic exposure (AUC) to the acid metabolite increased in a near dose-proportional manner in the 100 and 300 mg/kg/day range and represented less than 20 percent of the systemic exposure to drug.

TABLE 3.2.9.1
LOSARTAN AND ACID METABOLITE PHARMACOKINETICS AFTER ORAL LOSARTAN IN FEMALE MONKEYS *

Dose Group (mg/kg/day)	AUC ₀₋₂₄ (ug.hr/ml)	Losartan C _{max} (ug/ml)	T _{max} (hr)	Acid Metabolite AUC ₀₋₂₄ (ug.hr/ml)
20	ND	0.29-0.65	0.5-2.0	ND
100	6.55	1.8	0.5	1.05
300	28.1	5.0	3.0	3.76

*N=3. ND= Drug not detected in sufficient number of intervals to calculate AUC value.

3.3. GENOTOXICITY

3.3.1. Bacterial Reverse Mutation Assay (Ames Test) #1

Study Facility: Haskell (du Pont) Laboratory, Newark, NJ

Study Number: 88-4-8

Study Dates: 7/06/88 -8/16/88

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Bacterial Strains: *Salmonella typhimurium* strains TA97, TA98, TA100 and TA1535.

Procedure: Losartan (Lot#E-3340-14) was dissolved in distilled-deionized water and added directly to the plate medium at concentrations of 0 (vehicle), 50, 100, 500, 1000 and 5000 ug/plate in the presence and absence of metabolic activation with S-9 fraction obtained from livers of Aroclor 1254-treated rats. Sodium azide, 2-aminoanthracene, 2-nitrofluorene and acridine (concentrations not stated) were used as positive controls. The numbers of revertant colonies per plate were determined for controls (vehicle and positive) and losartan-treated plates. Each strain was tested in 2 experiments, each using 2 plates/dose group. The criteria for a positive mutagenic effect required (1) an increase (at least 2X or greater) in the average number of revertant colonies at one or more drug concentrations over the average number of revertant colonies in the solvent control and (2) that the drug-related increase in revertant colonies be dose-related.

Results: In each of the four tester strains, losartan did not significantly increase the number of revertant bacterial colonies above vehicle control, either in the presence or absence of metabolic activation. The positive controls that were included in each test showed consistent positive mutagenic effects.

TABLE 3.3.1.1
MICROBIAL MUTAGENESIS ASSAY WITH S. TYPHIMURIUM

Treatment (µg/plate)	S-9	Mean # Revertants/plate			
		TA97	TA98	TA100	TA1535
Vehicle	-	125	30	114	19
	+	142	31	134	22
Losartan 50	-	127	20	123	16
	+	153	30	132	17
100	-	142	19	124	20
	+	149	32	121	15
500	-	137	19	119	21
	+	150	33	137	19
1000	-	141	24	135	16
	+	165	31	127	16
5000	-	143	21	126	14
	+	138	28	119	12
NAAZ	-			969	695
2-AA	+	1708	2106	2193	349
ACR	-	2184			
2-NF	-		1508		

NAAZ= Sodium azide; 2-AA= 2-aminoanthracene; ACR=acridine; 2-NF= 2-nitrofluorene

3.3.2. Bacterial Reverse Mutation Assay #2

Study Facility: MSD Research Laboratories, West Point, PA

Study Number: 90-8011

Study Dates: 5/16/90 - 5/18/90

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Bacterial Strains: *Escherichia coli* strains WP2, WP2 *uvrA*, WP2 *uvrA* pKM101

Procedure: Losartan (Lot# 005H010) was dissolved in DMSO and added directly to the plate medium at concentrations of 0 (vehicle), 100, 300, 1000, 3000 and 10,000 µg/plate in the presence and absence of metabolic activation with S-9 fraction obtained

from livers of Aroclor 1254-treated rats. Methyl methanesulfonate (2ug/plate), 2-aminoanthracene (2, 5, 10 ug/plate), and hydrazine sulfate (500 and 1000 ug/plate) were used as positive controls. The number of revertant colonies per plate were determined for controls (vehicle and positive) and losartan-treated bacterial plates. Losartan was tested in triplicate against each bacterial strain. The criteria for a positive mutagenic effect required 1) an increase (at least 2X or greater) in the average number of revertant colonies at one or more drug concentrations over the average number of revertant colonies in the solvent control and 2) that the drug-related increase in revertant colonies be dose-related.

Results: In each of the 3 bacterial strains, losartan did not significantly increase the number of revertant bacterial colonies above vehicle control, either in the presence or absence of metabolic activation. The positive controls that were included in each test showed consistent positive mutagenic effects.

TABLE 3.3.2.1
MICROBIAL MUTAGENESIS ASSAY WITH E. COLI

Treatment (µg/plate)	S-9	Mean # Revertants/plate		
		WP2	WP2uvrA	WP2uvrApK
Vehicle	-	32	10	63
	+	36	13	80
Losartan 100	-	35	13	61
	+	33	11	82
300	-	35	10	65
	+	35	16	86
1000	-	32	11	65
	+	30	9	81
3000	-	26	8	65
	+	38	11	82
10000	-	36	11	60
	+	34	10	85
MMS, 2 µl	-	14x*	45x*	33x*
2AA 5 µg	+		31	585
	+		37	739
HS 500 µg	+	206		
	+	369		

*Indicates the fold increase from vehicle (0) control.

MMS=methyl methanesulfonate; 2-AA= 2-aminoanthracene; HS= hydrazine sulfate

3.3.3. Bacterial Reverse Mutation Assay #3

Study Facility: MSD Research Laboratories, West Point, PA

Study Number: 92-8086 and 92-8088 (replicate test)

Study Dates: 11/30/92 - 3/01/93

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Bacterial Strains: *Salmonella typhimurium* strains TA97, TA98, TA100 and TA1535.
Escherichia coli strains WP2, WP2 uvrA, WP2 uvrA pKM101

Procedure: Losartan (Lot# 005H019) was dissolved in DMSO and added directly to the plate medium at concentrations of 0 (vehicle), 100, 300, 1000, 3000 and 10,000 ug/plate in the presence and absence of metabolic activation with S-9 fraction obtained from livers of Aroclor 1254-treated rats. Methyl methanesulfonate (2ug/plate), sodium azide (1.5u g/plate) and daunomycin (5 ug/plate) were used as positive controls for the *Salmonella* strains; hydrazine sulfate (500 and 1000 ug/plate) was used for *E. coli* WP2 strain and 2-aminoanthracene (2, 5 and 10 ug/plate) was used for *Salmonella* and *Escherichia* strains. The numbers of revertant colonies per plate were determined for controls (vehicle and positive) and losartan-treated bacterial plates. Losartan was tested in triplicate against each bacterial strain. The criteria for a positive mutagenic effect required 1) an increase (at least 2X or greater) in the average number of revertant colonies at one or more drug concentrations over the average number of revertant colonies in the solvent control and 2) that the drug-related increase in revertant colonies be dose-related.

Results: Losartan, up to the highest tested concentration of 10000 ug/plate did not produce any two-fold or greater increases in revertant colonies above vehicle control in any of the tester strains, either with or without metabolic activation. The positive controls that were included in each test showed the expected strain-dependent, positive mutagenic effects.

TABLE 3.3.3.1
MICROBIAL MUTAGENESIS ASSAY WITH S. TYPHIMURIUM AND E. COLI

Treatment (µg/plate)	S-9	Mean # Revertants/plate						
		TA97	TA98	TA100	TA1535	WP2	WP2uvrA	WP2 uvrApK
Vehicle	-	136	18	100	12	37	31	66
	+	144	21	100	16	33	24	59
Losartan 100	-	130	15	112	16	30	30	72
	+	150	26	100	13	33	30	55
300	-	134	16	96	13	32	27	57
	+	148	21	101	20	34	24	58
1000	-	124	19	105	13	36	28	66
	+	144	18	96	15	26	25	57
3000	-	130	15	96	10	33	23	70
	+	164	16	98	16	35	22	68
10000	-	103	14	113	13	31	27	57
	+	144	17	93	13	34	30	59
2AA 10 ug	+	1360	1332	1796	218		67	363
HS 1000 ug	+					241		
NAAZ 1.5ug	-			4.8x*	43x*			
MMS 2 ul	-	2.4x*	2.1x*	15x*	8.1x*	9.6x*	21x*	22x*

*Indicates the fold increase from vehicle (0) control.

2-AA= 2-aminoanthracene; HS= hydrazine sulfate; NAAZ=sodium azide; MMS= methyl methanesulfonate

3.3.4. Bacterial Reverse Mutation Assay with Primary Metabolite (L-158,641)

Study Facility: MSD Research Laboratories, West Point, PA

Study Number: 92-8021

Study Dates: 7/25/90 - 7/27/90

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Bacterial Strains: *Salmonella typhimurium* strains TA97, TA98, TA100 and TA1535.
Escherichia coli strains WP2, WP2 uvrA, WP2 uvrA pKM101

Procedure: L-158,641 (Lot# 002X001) was dissolved in DMSO and added directly to the plate medium at concentrations of 0 (vehicle), 100, 300, 1000, 3000 and 10,000 ug/plate in the presence and absence of metabolic activation with S-9 fraction obtained from livers of Aroclor 1254-treated rats. Methyl methanesulfonate (2ug/plate), sodium azide (1.5u g/plate) and daunomycin (5 ug/plate) were used as positive controls for the *Salmonella* strains; hydrazine sulfate (500 and 1000 ug/plate) was used for *E. coli* WP2 strain and 2-aminoanthracene (2, 5 and 10 ug/plate) was used for *Salmonella* and *Escherichia* strains. The number of revertant colonies per plate were determined for controls (vehicle and positive) and L-158,641-treated bacterial plates. L-158,641 was tested in triplicate against each bacterial strain. The criteria for a positive mutagenic effect required 1) an increase (at least 2X or greater) in the average number of revertant colonies at one or more drug concentrations over the average number of revertant colonies in the solvent control and 2) that the drug-related increase in revertant colonies be dose-related.

Results: L-158,641 up to the highest tested concentration of 10000 ug/plate did not produce any two-fold or greater increases in revertant colonies above vehicle control in any of the tester strains, either with or without metabolic activation. The positive controls that were included in each test showed the expected strain-dependent, positive mutagenic effects.

TABLE 3.3.4.1
MICROBIAL MUTAGENESIS ASSAY WITH S. TYPHIMURIUM AND E. COLI

Treatment (µg/plate)	S-9	Mean # Revertants/plate						
		TA97	TA98	TA100	TA1535	WP2	WP2uvrA	WP2 uvrApK
Vehicle	-	175	22	172	39	33	11	134
	+	188	25	195	36	30	11	97
L-158,641	-	193	20	166	40	31	9	123
	+	194	28	198	31	36	13	90
300	-	178	23	170	34	28	9	148
	+	174	21	198	36	28	9	87
1000	-	167	23	176	40	35	7	138
	+	188	26	188	30	35	9	94
3000	-	170	22	169	41	34	10	140
	+	198	20	191	30	28	9	103
10000	-	162	23	171	34	36	10	139
	+	156	22	224	50	28	7	108
2AA 5 µg	+	1359	1439	1832	209		40	901
HS 500 µg	+					201		
NAAZ 1.5µg	-			2.8x*	9.3x*			
MMS 2 µl	-	2.6x*	2.6x*	8.9x*	2.2x*	11x*	51x*	17x*

*Indicates the fold increase from vehicle (0) control.

2-AA=2-aminoanthracene; HS=hydrazine sulfate; NAAZ= sodium azide; MMS= methyl methanesulfonate.

3.3.5. Chinese Hamster Lung Cell Forward Mutation Assay:

Study Facility: MSD Research Laboratories, West Point, PA

Study Number: 91-8501

Study Dates: 1/23/91 - 2/08/91

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Procedure: This assay measures forward mutations at the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus as resistance to the purine analog 6-thioguanine (6-TG). Cells that have lost functional activity of the salvage enzyme

HGRPT are resistant to 6-TG and form mutant colonies. This assay measures forward mutations such as deletions, nonsense, missense, base-pair substitutions or frame shift mutations. Losartan (Lot# 005H010) was dissolved in DMSO and added to the Chinese hamster lung cell culture at concentrations of 0 (vehicle), 0.05, 0.1, 0.5, 1, and 2 mM (in duplicate) with and without metabolic activation using S-9 fraction obtained from the livers of Aroclor 1254-treated rats. 3-Methylcholanthrene (37.3uM) and 1-methyl-1-nitrosourea (100uM) were used as positive controls. Cells were exposed to compound for 3 hours at 37°C. The drug medium was replaced with growth medium, cells were incubated for 6-7 days for expression and then treated with 6-TG for mutant selection. The number of mutant colonies were counted for each concentration and compared to vehicle control. The criteria for a positive mutagenic effect required 1) an increase in the mutant frequency of 2.21X the standard deviation of the vehicle control frequency, 2) an increasing mutant frequency trend over 3 concentrations of drug and 3) positive mutagenic effects observed in a replicate assay.

Results:

TABLE 3.3.5.1
CHINESE HAMSTER LUNG MUTAGENESIS ASSAY

Treatment	S-9	Mean Mutant Fraction	Significance Level
Vehicle	-	2.32	
	+	2.32	
Losartan 0.05 mM	-	-	N.S.
	+	1.42	
0.1 mM	-	1.98	N.S.
	+	1.50	N.S.
0.5 mM	-	2.43	N.S.
	+	1.50	N.S.
1.0 mM	-	1.27	N.S.
	+	1.96	N.S.
2.0 mM	-	2.75	N.S.
	+	-	
3-MC*	+	54.06	p<0.0001
1-M-1-N*	-	54.63	p<0.0001

*3-MC = 3 methylcholanthrene, 1-M-1-N = 1 methyl-1-nitrosourea

At non-cytotoxic concentrations (80% cytotoxicity was noted with losartan concentrations >1 mM with S-9 and >2 mM without S-9), losartan did not induce

mutations in Chinese hamster lung cells in the presence or absence of metabolic activation.

Note: In replicate study (# 92-8558), losartan up to the same maximum concentrations produced no mutagenic effects in Chinese hamster lung cells.

3.3.6. Alkaline Elution/Rat Hepatocyte Genotoxicity Assay

Study Facility: MSD Research Laboratories, West Point, PA

Study Number: 90-8311; 92-8516 and 92-8531 (replicate assays)

Study Dates: 2/27/90 - 2/28/90 (Study # 90-8311) 11/04/92 - 12/3/92 (Study # 92-8516 and 92-8531)

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Procedure: This assay measures drug-induced DNA strand breaks in cultured rat hepatocytes. The assay sensitively detects small changes in molecular weight by measuring the rate at which single alkali-denatured strands of DNA elute through 2 μ pore filters. Measurements by alkaline sucrose gradients show that low molecular weight DNA elutes first, followed by DNA of successively higher molecular weight. The amount of DNA in each elution fraction is measured fluorometrically. Losartan (Lot #005H009) was dissolved in DMSO and added to the hepatocyte cell culture plates at concentrations of 0 (vehicle), 1.0, 1.7, 2.4, 3.1 and 3.8 mM in Study # 90-8311 and 0, 0.6, 1.2, 1.8, 2.4, 3.0 and 3.6 mM (2 plates/conc.) in the replicate assays. These concentrations were selected from prior cytotoxicity tests; concentrations producing less than 70% relative cell viability were not used for mutagenicity assessment. Aflatoxin B1 (1 μ M) was used as the positive control. The cells were incubated with drug or vehicle for 3 hours, removed from the culture plates, tested for cell viability by trypan blue exclusion and then prepared for elution. For each drug concentration/plate, a 5 ml aliquot of cell suspension (approx. 1×10^6 cells) was placed on a 2 μ polycarbonate filter and lysed with a lysing solution. An alkaline solution (pH 12.1) was added to the DNA held on the filter and 3 fractions of 3-hrs elution time were collected. The DNA from each fraction was trapped on other (0.2 μ) polycarbonate filters and the amount of DNA on each filter was measured as the fluorescent product of 3,5-diaminobenzoic acid and deoxyribose. The rate of elution was calculated from a semi-log plot of the fraction of DNA retained against the time of elution. The mean slope of the plotted line from 3 to 9 hrs of elution was taken as the elution rate. The criteria used for defining a positive genotoxic effect are 1) induction of an elution slope (treatment slope-negative control slope) which is equal to or greater than 0.034 and 2) relative cytotoxicity $<30\%$ (i.e. relative cell viability $>70\%$) because DNA strand breaks are also produced as a result of cytotoxicity and cell death.

Results:

TABLE 3.3.6.1
RAT HEPATOCYTE GENOTOXICITY ASSAY

Treatment	Assay #	Relative Cell Viability (%)	Mean Elution Slope
Vehicle	1	100	0.001
Losartan			
1.0 mM		90	0.002
1.7 mM		80	0.002
2.4 mM		64	0.024
3.1 mM		42	0.070
3.8 mM		15	N.D.*
Aflotoxin B1		98	0.051
Vehicle	2	100	0.006
Losartan			
0.6 mM		84	0.006
1.2 mM		80	0.005
1.8 mM		41	0.01
2.4 mM		61	0.032
3.0 mM		33	0.054
3.6 mM		17	0.087
Aflotoxin B1	99	0.149	
Vehicle	3	100	0.004
Losartan			
0.6 mM		94	0.004
1.2 mM		90	0.002
1.8 mM		92	0.010
2.4 mM		83	0.048
3.0 mM		60	0.111
3.6 mM		34	0.188
Aflotoxin B1	97	0.129	

*N.D. = Not determined due to extreme cytotoxicity.

Losartan did not induce an elution slope equal to or greater than 0.034 at concentrations that did not affect cell survival except in one assay (Study # 92-8516) in which a concentration of 2.4 mM of losartan induced an increase in the elution slope (0.048) although the relative cell viability at this concentration was 83% and did not satisfy the exclusion criteria. However, this concentration produced higher levels (>30%) of cytotoxicity in the other two assays (Study # 90-8311 and 92-8531) and produced elution slopes less than the required 0.034 for acceptance as positive mutagenic activity. At concentrations of 3.0 mM and higher, the mean elution slopes were above the minimum criteria of 0.034; however, these concentrations were

associated with appreciable cytotoxicity. It is concluded that losartan is not mutagenic in this assay.

3.3.7. Alkaline Elution/Rat Hepatocyte Genotoxicity Assay with Metabolite L-158,641

Study Facility: MSD Research Laboratories, West Point, PA

Study Number: 90-8317 and 90-8319 (replicate assay)

Study Dates: 3/14/90 - 3/27/90

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Procedure: L-158,641 (Lot #002X001) was dissolved in DMSO and added to the hepatocyte cell culture plates at concentrations of 0 (vehicle), 1.6, 2.3, 3.0, 3.7, 4.4 and 5.1 mM in Study # 90-8317 and 0, 5, 6, 7, 8 and 9 mM (2 plates/conc.) in the second assay. These concentrations were selected from prior cytotoxicity tests; concentrations producing less than 70% relative cell viability were not used for mutagenicity assessment. Aflatoxin B1 (1uM) was used as the positive control. The cells were incubated with drug or vehicle for 3 hours, removed from the culture plates, tested for cell viability by trypan blue exclusion and then prepared for elution. For each drug concentration/plate, a 5 ml aliquot of cell suspension (approx. 1×10^6 cells) was placed on a 2 u polycarbonate filter and lysed with a lysing solution. An alkaline solution (pH 12.1) was added to the DNA held on the filter and 3 fractions of 3-hrs elution time were collected. The DNA from each fraction was trapped on other (0.2 u) polycarbonate filters and the amount of DNA on each filter was measured as the fluorescent product of 3,5-diaminobenzoic acid and deoxyribose. The rate of elution was calculated from a semi-log plot of the fraction of DNA retained against the time of elution. The mean slope of the plotted line from 3 to 9 hrs of elution was taken as the elution rate. The criteria used for defining a positive genotoxic effect are 1) induction of an elution slope (treatment slope-negative control slope) which is equal to or greater than 0.034 and 2) relative cytotoxicity <30% (i.e. relative cell viability >70%) because DNA strand breaks are also produced as a result of cytotoxicity and cell death.

Results: L-158,641 did not induce an elution slope equal or greater than 0.034 at any of the concentrations tested. It is concluded that the losartan metabolite L-158,641 is not mutagenic in this assay.

TABLE 3.3.7.1
RAT HEPATOCYTE GENOTOXICITY ASSAY

Treatment	Assay #	Relative Cell Viability (%)	Mean Elution Slope
Vehicle	1	100	0.002
L-158,641			
1.6 mM		93	0.006
2.3 mM		90	0.006
3.0 mM		94	0.007
3.7 mM		97	0.006
4.4 mM		93	0.008
5.1 mM		92	0.007
Aflotoxin B1		96	0.067
Vehicle	2	100	0.002
L-158,641			
5 mM		92	0.005
6 mM		90	0.006
7 mM		93	0.012
8 mM		88	0.006
9 mM		83	0.005
Aflotoxin B1			101

3.3.8. Chromosomal Aberrations in Chinese Hamster Ovary Cells:

Study Facility: MSD Research Labs, West Point, PA

Study Number: 90-8622 and 90-8629 (replicate assay)

Study Dates: 3/01/90 - 6/11/90

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Cell Culture: Chinese hamster ovary cells

Procedure: This mammalian cell assay measures breaks or rearrangements in chromatids or chromosomes in post-treatment metaphase cells *in vitro* as a means of assessing genotoxicity. Losartan (lot #005H010) was dissolved in DMSO and added to the cell culture at concentrations of 0 (vehicle), 0.125, 0.25, 0.5, 1, 2, 4, 6, 8 and 10 mM (Study # 90-8622) and 0, 1, 1.5, 2.25, 2.5, 2.75, 3, 3.25 and 2.5 mM (Study #90-8629) and incubated for a period of 3 hours in the presence and absence of metabolic activation with S-9 fraction obtained from the livers of Aroclor 1254-treated

rats. Cyclophosphamide (2.5 and 5 μM) and mitomycin-C (0.25, 0.35 and 0.5 μM) were used as positive controls. After treatment the cells were washed free of drug and incubated for 17 hours to permit cell division. Cells were then fixed on slides and 200 metaphase spreads per treatment were scored for chromosomal aberrations (gaps, deletions, exchanges and translocations). Cells exposed to low concentrations of drug were examined by inverted microscope before harvest for frequency of mitotic cells and were not scored if they appeared healthy with no apparent reduction in mitotic frequency. A significant increase ($p < 0.05$) in chromosomal aberrations at two or more dose levels with less than 50% cytotoxicity was judged to be a positive effect. A positive result at one dose level was considered equivocal until repeated in another assay.

Results: The concentrations of losartan scored for aberrations in Study #90-8622 were 1 and 2 mM with and without S-9. Doses above 2 mM were cytotoxic (> 50%). Losartan, with or without metabolic activation, did not cause a significant increase in the proportions of cells with chromosomal aberrations above concurrent solvent controls. The concentrations tested in the second assay were chosen to provide a range between concentrations that caused little cytotoxicity and those that produced severe cytotoxicity (>50%). There were no significant increases at losartan concentrations of 2.5 mM or less. At a concentration of 3 mM with and without metabolic activation, losartan caused significant increases in chromosomal aberrations. Cytotoxicity at this concentration (3 mM) was 47% and 49% (very close to the exclusion level of 50%) with and without S-9, respectively. At a slightly higher concentration of 3.25mM, losartan was extremely cytotoxic (64%-85%); thus, significant increases in chromosomal aberrations were not seen at two or more dose levels for losartan to satisfy the criteria for a positive effect. Therefore, losartan is judged as negative in this chromosomal aberration assay.

TABLE 3.3.8.1
CHROMOSOMAL ABERRATIONS IN CHO CELLS (TEST #1)

Treatment	S-9	Cell Viability (% control)	Chromosomal Aberrations/100 Cells
Vehicle	-	100	2.5
	+	100	2.0
Losartan	-	99	N.D.
	+	114	
0.125 mM	-	86	N.D.
	+	121	
0.25 mM	-	88	N.D.
	+	124	
0.50 mM	-	103	2.5
	+	84	
2.0 mM	-	85	1.0
	+	75	
4.0 mM	-	22	N.S.
	+	21	
6.0 mM	-	19	N.S.
	+	13	
8.0 mM	-	24	N.S.
	+	11	
10.0 mM	-	25	N.S.
	+	N.D.	
Cyclophosphamide	-	-	-
	+	-	
2.5 µM	+	82	11.5*
	+	63	23.0*
Mitomycin C	-	90	14*
	-	N.D.	7*
0.50	-	82	N.D.

*Statistically significant ($P < 0.05$) increase compared to vehicle control

N.D. = Not done

N.S. = Not scored due to excessive toxicity

TABLE 3.3.8.2.
CHROMOSOMAL ABERRATIONS IN CHO CELLS (TEST #2)

Treatment	S-9	Cell Viability (% control)	Chromosomal Aberrations/100 Cells
Vehicle	-	100	2.0
	+	100	2.5
Losartan 1.0 mM	-	93	N.D.
	+	78	N.D.
1.5 mM	-	88	N.D.
	+	83	N.D.
2.0 mM	-	75	N.D.
	+	78	N.D.
2.25 mM	-	87	3.0
	+	62	2.5
2.5 mM	-	69	1.5
	+	56	4.0
2.75 mM	-	67	N.D.
	+	42	N.S.
3.0 mM	-	51	10.0*
	+	53	14.5*
3.25 mM	-	36	N.S.
	+	15	N.S.
3.5 mM	-	27	N.S.
	+	29	N.S.
Cyclophosphamide			
	+	78	15*
5.0 µM	+	73	48*
Mitomycin C			
	-	94	N.D.
	-	N.D.	11.0*
0.50 µM	-	91	19.0*

*Statistically significant ($P < 0.05$) increase compared to vehicle control

N.D. = Not done

N.S. = Not scored due to excessive cytotoxicity

3.3.9. Chromosomal Aberration Assay with Losartan Metabolite (L-158,641) in Chinese Hamster Ovary Cells

Study Facility: MSD Research Labs, West Point, PA

Study Number: 90-8628

Study Dates: 3/13/90 - 3/20/90

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Cell Culture: Chinese hamster ovary cells

Procedure: This mammalian cell assay measures breaks or rearrangements in chromatids or chromosomes in post-treatment metaphase cells *in vitro* as a means of assessing genotoxicity. L-158,641 (Lot #002X001) was dissolved in DMSO and added to the cell culture at concentrations of 0 (vehicle), 0.125, 0.25, 0.5, 1, 1.5, 2, 2.5, and 3 mM in the presence of metabolic activation (S-9 fraction obtained from the livers of Aroclor 1254-treated rats) and concentrations of 0, 1, 1.5, 2, 2.5, 3, and 3.5 mM without metabolic activation. Cyclophosphamide (2.5 and 5 μ M) and mitomycin-C (0.25, 0.35 and 0.5 μ M) were used as positive controls. Following 3 hours of drug exposure, the cells were washed free of drug and incubated to permit cell division. Cells were then fixed on slides and 200 metaphase spreads per treatment were scored for chromosomal aberrations (gaps, deletions, exchanges and translocations). Cells exposed to low concentrations of drug were examined by inverted microscope before harvest for frequency of mitotic cells and were not scored if they appeared healthy with no apparent reduction in mitotic frequency. A significant increase ($p < 0.05$) in chromosomal aberrations at two or more dose levels with less than 50% cytotoxicity was judged to be a positive mutagenic effect. A positive result at one dose level was considered equivocal until repeated in another assay.

Results: L-158,641 formed a fine precipitate at concentrations of 1.5 mM and higher with S-9; therefore, the top concentration level scored for chromosomal aberrations with S-9 was 1.0 mM. L-158,641 did not cause a significant increase above vehicle control in the number of Chinese hamster ovary cells with chromosomal aberrations. Cyclophosphamide and mitomycin-C elicited the expected positive genotoxic effects.

TABLE 3.3.9.1
CHROMOSOMAL ABERRATIONS IN CHO CELLS

Treatment	S-9	Chromosomal Aberrations (% cells)
Vehicle (DMSO)	-	1.5
	+	2.5
L-158,641	-	N.D.
	+	2.5
0.125 nM	-	N.D.
	+	2.5
0.25 mM	-	N.D.
	+	3.0
0.5 mM	-	N.D.
	+	2.5
1.0 mM	-	N.D.
	+	2.0
1.5 mM	-	N.D.
	+	N.S.
2.0 mM	-	N.D.
	+	N.S.
2.5 mM	-	2.0
	+	N.S.
3.0 mM	-	1.0
	+	N.S.
3.5 mM	-	3.0
	+	N.S.
Mitomycin C	-	
	+	
0.25 µM	-	8.0*
	+	21.0*
0.50 µM	-	
	+	
Cyclophosphamide	-	
	+	
2.5 µM	-	
	+	10.5*
5.0 µM	-	
	+	40.0*

* Statistically significant ($P < 0.05$) increase compared to vehicle control

N.D. = Not done

N.S. = Not scored due to precipitate

3.3.10. Chromosomal Aberrations in Male Mouse Bone Marrow

Study Facility: MSD Research Labs, West Point, PA

Study Number: 90-8635

Study Dates: 5/15/90 - 6/07/90

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Male Crl:CD-1 [ICR] BR mice (20-29 gm)

Procedure: This mammalian cell assay measures chromosomal aberrations from treated mice by examining mitotically active cells from the marrow of the femurs which have been arrested at metaphase. Chromosomal aberrations, such as structural changes and rearrangements, can be observed microscopically and serve as possible indicators of mutagenic potential of test compounds. Losartan (Lot # 005H010) was dissolved in water and administered to mice orally by gavage at doses of 0 (vehicle), 150, 500 and 1500 mg/kg (24/dosegroup for low and mid dose; 30/high dose and 36/vehicle group). The high dose is approx 2/3 of the LD₅₀. Mitomycin-C (3.5 mg/kg and 1 mg/kg; 4 and 8/dose, respectively) was used as the positive control. One-third of vehicle and losartan-treated mice were sacrificed at 6, 24 and 48 hours after treatment. Mice treated with the positive control were sacrificed 24 hours after treatment. Mice were dosed with colchicine 2 mg/kg 2.5-3.5 hours prior to sacrifice to arrest cells in metaphase. Both femurs of each animal were removed, the bone marrow harvested and marrow cells fixed on slides for measurement of mitotic activity and chromosomal aberrations. In this assay, at least 50 metaphase spreads per animal are scored with the aim of achieving at least 300 metaphases/dose group. Chromosomes and chromatids are scored for gaps, deletions, exchanges and translocations. The assay is considered positive if a significant increase in aberration frequencies ($p < 0.05$) above vehicle control occurs at a minimum of two dose levels; either two at a given sacrifice time or one dose at each of two sacrifice times. A significant increase at a single dose level at one sacrifice time would be considered equivocal and would require replication in a repeat assay.

Results: Five of 30 mice treated with 1500 mg/kg died within 5 hours after treatment. Losartan caused no significant increases in chromosomal aberrations above vehicle control with any dose tested (150 - 1500 mg/kg) or after any sacrifice time.

**TABLE 3.3.10.1.
CHROMOSOMAL ABERRATIONS IN MALE MOUSE BONE MARROW**

Treatment	Hours Postdose	Chromosomal Aberrations (% cells)
Vehicle	6	0.50
Losartan		
150 mg/kg	6	0.00
500 mg/kg	6	0.00
1500 mg/kg	6	0.50
Vehicle	24	0.83
Losartan		
150 mg/kg	24	0.50
500 mg/kg	24	1.00
1500 mg/kg	24	1.00
Mitomycin C		
1 mg/kg	24	2.21
3.5 mg/kg	24	46.50 **
Vehicle	48	0.67
Losartan		
150 mg/kg	48	1.32
500 mg/kg	48	0.52
1500 mg/kg	48	0.25

** Statistically significant ($P < 0.001$) increase compared to vehicle control

3.3.11. Chromosomal Aberrations in Female Mouse Bone Marrow

Study Facility: MSD Research Labs, West Point, PA

Study Number: 93-8601

Study Dates: 1/21/93 - 4/15/93

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Female Crl:CD-1 [ICR] BR mice (17.6 - 25 gm)

Procedure: This mammalian cell assay measures chromosomal aberrations from treated mice by examining mitotically active cells from the marrow of the femurs which have been arrested at metaphase. Chromosomal aberrations, such as structural changes and rearrangements, can be observed microscopically and serve as possible indicators of mutagenic potential of test compounds. Losartan (Lot # 005H009) was

dissolved in water and administered to mice orally by gavage at doses of 0 (vehicle), 150, 500 and 1500 mg/kg (24/dosegroup for low and mid dose; 30/high dose and 36/vehicle group). The high dose is approx 2/3 of the LD₅₀. Mitomycin-C (3.5 mg/kg and 1 mg/kg; 4 and 8/dose, respectively) was used as the positive control. One-third of vehicle and losartan-treated mice were sacrificed at 6, 24 and 48 hours after treatment. Mice treated with the positive control were sacrificed 24 hours after treatment. Mice were dosed with colchicine 2 mg/kg 2.5-3.5 hours prior to sacrifice to arrest cells in metaphase. Both femurs of each animal were removed, the bone marrow harvested and marrow cells fixed on slides for measurement of mitotic activity and chromosomal aberrations. In this assay, at least 50 metaphase spreads per animal are scored with the aim of achieving at least 300 metaphases/dose group. Chromosomes and chromatids are scored for gaps, deletions, exchanges and translocations. The assay is considered positive if a significant increase in aberration frequencies ($p < 0.05$) above vehicle control occurs at a minimum of two dose levels; either two at a given sacrifice time or one dose at each of two sacrifice times. A significant increase at a single dose level at one sacrifice time would be considered equivocal and would require replication in a repeat assay.

Results: Three of 30 female mice treated with 1500 mg/kg of losartan died within 24 hours after treatment. Losartan caused no significant increases in chromosomal aberrations above vehicle control with any dose tested (150 - 1500 mg/kg) or after any sacrifice time.

TABLE 3.3.11.1
CHROMOSOMAL ABERRATIONS IN FEMALE MOUSE BONE MARROW

Treatment	Hours Postdose	Chromosomal Aberrations (% cells)
Vehicle	6	0.67
Losartan		
150 mg/kg	6	0.25
500 mg/kg	6	0.75
1500 mg/kg	6	0.50
Vehicle	24	1.33
Losartan		
150 mg/kg	24	0.00
500 mg/kg	24	1.25
1500 mg/kg	24	1.25
Mitomycin C		
1 mg/kg	24	3.5*
3.5 mg/kg	24	41.6*
Vehicle	48	1.5
Losartan		
150 mg/kg	48	0.00
500 mg/kg	48	1.75
1500 mg/kg	48	0.25

* Statistically significant ($P < 0.01$) increase compared to vehicle control

3.4. REPROTOXICITY

3.4.1. Oral Fertility Study in Male Rats

Location of Data: Vol 18, Tab C-1

Testing Facility: 1

Study No.: TT #90-9807

Study Dates: Initiated: May 8, 1990
Terminated: August 15, 1990

GLP Compliance: Studies were done in accordance with GLP regulations.

Animals: Sprague-Dawley (CrI:CD BR) rats from Charles River Laboratories; Males were approximately 8 weeks of age and weighed 270-339 gm at initiation of the study.

Methods and Observations: Dosage levels of 25, 50, and 150 mg/kg/day were given orally by gavage daily to three groups of 25 males each for 70 days prior to and during cohabitation with untreated mature females of the same strain until confirmation of mating. An additional group of 25 males received the vehicle (water) at a dosing volume of 5 ml/kg and served as the control. The mating period was limited to 12 nights. On day 20 of gestation, females were sacrificed and their reproductive status was recorded. Fetuses were weighed, sexed, and examined for external abnormalities. After necropsy of females, all males were sacrificed and examined for gross abnormalities of the thoracic and abdominal viscera.

Results: There were no treatment-related deaths or physical signs of toxicity observed in males. The average body weight gains between dosing days 1 and 8 were significantly ($P \leq 0.05$) lower in the 50 (12%) and 150 (16%) mg/kg/day dose groups than in the control group. The body weights in treated groups between days 8 and 70 were comparable to or greater than that of controls.

No drug-related gross changes were observed in males at necropsy. Reproductive performance of mated males, as evidenced by time to mating, mating index (mean of $1/(\text{time to mating})$) for mated females and zero for females that did not mate), incidence of mating (percent mated females/females cohabited), and fecundity (percent pregnant females/mated females) and fertility (percent pregnant females/female cohabited) indices, was not affected by drug treatment. Also, there was no effect on the reproductive status of pregnant females or on the average body weight of live fetuses. No drug-related external abnormalities were observed in fetuses. In conclusion, losartan administered to male rats at dosage levels up to 150 mg/kg/day for 70 days prior to mating and throughout mating had no effects on reproductive

performance and fertility, and the prenatal development of the F₁ generation.

3.4.2. Oral Fertility Study in Female Rats

Location of Data: Vol 18, Tab C-2

Testing Facility: Department of Safety Assessment, Merck Sharp & Dohme Research Laboratories, Merck & Co., Inc., West Point, PA

Study No.: TT #90-708-0

Study Dates: Initiated: February 19, 1990
Terminated: July 28, 1990 (date of last F₁ necropsy)

GLP Compliance: Studies were done in accordance with GLP regulations.

Animals: Sprague-Dawley (CrI:CD BR) rats from Charles River Laboratories; Females were approximately 11 weeks of age and weighed 224-292 gm at initiation of the study.

Mode of Administration/Dosage Levels: Dosage levels of 25, 100, and 300/200 mg/kg/day were given orally by gavage daily to three groups of 40 females each (the high dose was initially 300 mg/kg/day and was lowered to 200 mg/kg/day at the start of mating due to excessive toxicity as reflected in severe loss of body weight). An additional group of 40 females received the vehicle (water) at a dosing volume of 5 ml/kg and served as the control. The females were given either water or test drug for 15 days prior to mating, during mating (with untreated mature males of the same strain), and through days 0 to 19 of gestation (cesarean-sectioned animals) or through day 20 of lactation (natural delivery females).

Observations/Measurements: All animals were observed for physical signs once daily (1-5 hr postdosing) from initiation to sacrifice. Body weights were recorded on days 1, 8, and 15 of the pre-mating period, weekly during mating and on days 0, 6, 12, 16, 18, 20, 22, 24 of gestation and on days 0, 3, 7, 10, 14, 17 and 21 of lactation. Food consumption was recorded on days 1 to 5 and 8 to 12 of the pre-mating period, days 1 to 5, 8 to 12, and 15 to 19 of gestation, and days 1 to 5 and 8 to 12 of lactation.

Females killed on day 20 of gestation (19-20/group) were examined for reproductive status, corpora lutea and implants were counted and the latter were classified as live fetus, dead fetus, or resorption. All fetuses were weighed, sexed, and examined externally. One-third of the fetuses from each litter were given a visceral examination, and heads of these fetuses were fixed in Bouin's solution for examination by free-hand coronal sectioning. All except two fetuses were fixed, cleared, and stained with alizarin red for subsequent skeletal examinations. One fetus from control and another from the 100 mg/kg/day group were submitted for histological analysis of the perineal region.

Females assigned for natural delivery were observed for parturition from day 21 until completion of delivery. Dams were killed between days 23 and 27 postpartum and the uterus of each female was examined to count metrial glands. A gross examination of thoracic and abdominal viscera was also performed. The F₁ pups were counted, examined externally, and sexed on postnatal day 0. All litters were reduced to 4 males and 4 females on lactation day 3. Two male and two female pups from each litter were examined for surface righting reflex on postnatal days 2, 4, and 6 and auditory response on postnatal days 11, 13, and 15. These pups were separated from dams on postnatal days 23 to 26 and housed individually until mating. They were observed daily for mortality and twice weekly for physical signs. Body weights were recorded once a week until breeding (in females) or sacrifice (in males). Testicular descent was recorded on postnatal day 39 and preputial separation on postnatal days 39, 43 and 47. Vaginal canalization was recorded on postnatal days 31, 34, and 37. Tests for behavioral assessment (open field activity and swimming maze) were performed on 1 male and 1 female animal from each litter during postnatal days 54-71. One female and one male of the same dose group but of different litters were mated between postnatal weeks 10 and 12. F₁ females which mated were weighed on days 0, 7, 14, and 20 of gestation, and after natural delivery on day 0 of postpartum. Approximately half of the F₁ males and females that were not needed for mating were sacrificed and discarded (without further examination) prior to F₁ mating. All F₁ males used for mating were killed after most females had completed delivery, and only the testes and epididymides were examined for gross changes. Histomorphologic examination was performed on testes and epididymides from the control and 300/200 mg/kg/day groups. F₁ females which delivered were killed within 1 week after delivery and the uterus of each animal was examined to count metrial glands. No gross necropsy was done.

The F₂ pups were counted, weighed, sexed, examined for external malformations on day 0 postpartum. All pups were killed within 3 days of delivery and discarded without further examination.

Results: There were no treatment-related deaths or physical signs in the F₀ females. Two animals (from 100 and 300/200 mg/kg/day groups) died as a result of intubation accidents during pre-mating or gestation intervals. Two females (both in the high dose group) were sacrificed in the postpartum interval because they had no live pups remaining.

In the pre-mating period of days 1 to 15 there was a significant treatment-related 84% decrease in mean body weight gain in the 300 mg/kg/day group when compared to control. Due to this excessive toxicity the dose of this group was lowered to 200 mg/kg/day prior to mating. There was a further significant treatment-related 7.4% decrease in mean body weight gain from days 0 to 20 of gestation (Table 3.4.2.1). In this same group, average food consumption was significantly lower than control consumption for the entire pre-mating period, day 19 of gestation and day 12 of lactation (Table 3.4.2.2). There were no significant effects either on mean body weight gain or on food consumption in other groups.

TABLE 3.4.2.1
AVERAGE MATERNAL BODY WEIGHT CHANGES (GRAMS) OF F₀ FEMALES. TT #90-708-0

TREATMENT GROUP:	CONTROL	25 MG/KG/DAY	100 MG/KG/DAY	300/200 MG/KG/DAY
<u>PREMATING PERIOD</u>				
DAY 1 TO 8	14 (40)	12 (40)	14 (39)	6 (40)
DAY 8 TO 15	10	8	9	-1
DAY 1 TO 15	25	20	23 ^{NS}	4 ^S
<u>GESTATIONAL PERIOD</u>				
DAY 0 TO 12	64 (32)	67 (34)	64 (32)	63 (32)
DAY 12 TO 16	24	30	26	23 (31)
DAY 16 TO 20	60 (31)	61	56	52
DAY 0 TO 20 ^a	148	158	145 ^{NS}	137 ^S
<u>LACTATIONAL PERIOD</u>				
DAY 0 TO 7	21 (15)	18 (18)	28 (18)	20 (18) ^{NS}
DAY 7 TO 14	17 (16)	19	17	27 (17) ^{NS}
DAY 14 TO 21	-20	-21	-15	-17 (16) ^{NS}
DAY 0 TO 21	18 (15)	16 ^{NS}	30 ^S	29 ^S

(N) = Group size and appears only if different from previous n. See individual table for exclusions.

NS = Trend not statistically significant through indicated dose ($p > 0.05$).

S = Trend statistically significant through indicated dose ($p \leq 0.05$).

a = Trend analysis was performed with an adjustment for day 0 weights.

TABLE 3.4.2.2
AVERAGE MATERNAL FOOD CONSUMPTION (GRAMS/DAY) OF F₀ FEMALES. TT #90-708-0

TREATMENT GROUP:	CONTROL	25 MG/KG/DAY	100 MG/KG/DAY	300/200 MG/KG/DAY
<u>PREMATING PERIOD*</u>				
DAY 5	22 (40) ^a	22 (40)	21 (40) ^{ns}	19 (40) ^s
DAY 12	21	21	21 (39) ^{ns}	20 ^s
<u>GESTATIONAL PERIOD*</u>				
DAY 5	26 (32)	27 (34)	26 (32)	27 (32) ^{ns}
DAY 12	28	30	29	29 (31) ^{ns}
DAY 19	29	31	29 ^{ns}	28 (30) ^s
<u>LACTATIONAL PERIOD*</u>				
DAY 5	40 (16)	36 (16)	47 (18)	36 (16) ^{ns}
DAY 12	63	63 (17)	60 (17) ^{ns}	53 (17) ^s

a: Indicated day denotes end of 4 day interval.

n: Group size and appears only if different from previous n. See individual table for exclusions.

ns: Trend not statistically significant through indicated dose ($p > 0.05$).

s: Trend statistically significant through indicated dose ($p \leq 0.05$).

There were no treatment-related gross lesions found at necropsy in F₀ females sacrificed at the end of the study. Incidental findings included one mid and one high dose female with uterine distention with fluid, and one high dose female with pyometra.

There were no treatment-related effects on reproductive performance as assessed by mating index (mean of $1/(\text{time to mating})$) for mated females and zero for females that did not mate), incidence of mating (percent mated females/females cohabited), fecundity index (percent pregnant females/mated females), fertility index (percent pregnant females/females cohabited), percent females with live pups/pregnant females, and mean length of gestation. In the 300/200 mg/kg/day c-sectioned group, there were significantly ($P \leq 0.05$) fewer corpora lutea/female (-12.3%), implants/female (-17.6%) and live fetuses/female (-18%). In the 100 mg/kg/day group there was a slight but significant effect on number of corpora lutea/pregnant female (-11%) (Table 3.4.2.3). There was no effect on preimplantation loss in these groups. Postimplantation loss increased with dose (from 1.9 to 3.76 times control) but did not attain significance at any dose level.

Lower live female (5.5% below control, $P < 0.05$) and male fetal weights (4.2% below control, $P > 0.05$) observed in the high dose c-sectioned group were considered by the sponsor as treatment-related since the finding was consistent with the dose-related reduction in birth weights of pups of the natural delivered groups (see Table 3.4.2.4). External examination of fetuses showed one fetus in the low dose group with polydactyly, one fetus in the mid dose

TABLE 3.4.2.3
SUMMARY OF LAPAROTOMY DATA FROM F, FEMALES. TT #90-708-0

TREATMENT GROUP:	CONTROL	25 MG/KG/DAY	100 MG/KG/DAY	300/200MG/KG/DAY
FEMALES				
TOTAL FEMALES	20	19	19 ^c	20
LIVE PREGNANT	16	17	15	14
LIVE NOT PREGNANT	3	2	3	5
DEAD PREGNANT	0	0	0	1
NOT BRED	1	0	1	0
LENGTH OF GESTATION (DAYS)	22.3	22.1	22.3	22.4 ^{NS}
MATING INDEX ^d	0.87	0.93	0.89	0.92 ^{NS}
MATED FEMALES/FEMALES COHABITED, %	98	100	97	100 ^{NS}
FECUNDITY INDEX	82	90	87	85 ^{NS}
FERTILITY INDEX	80	90	85	85 ^{NS}
CORPORA LUTEA				
CORPORA LUTEA	288	289	240	221
CORPORA LUTEA/PREGNANT FEMALE	18.0	17.0 ^{NS}	16.0 ^S	15.8 ^S
% PREIMPLANTATION LOSS (LM)	10.9	6.8	10.9	14.0 ^{NS}
IMPLANTS				
IMPLANTS	264	270	223	191
IMPLANTS/PREGNANT FEMALE	16.5	15.9	14.9 ^{NS}	13.6 ^S
RESORPTIONS AND DEAD FETUSES				
RESORPTIONS	9	15	4	10
DEAD FETUSES	0	0	0	0
% (RESORP+DEAD FET)/IMP (LM)	2.9	5.6	8.5	10.9 ^{NS}
LIVE FETUSES				
LIVE FETUSES (M/F)	255 (120/135)	255 (127/128)	219 (98/121)	181 (92/89)
LIVE FETUSES/PREGNANT FEMALE	15.9	15.0	14.6 ^{NS}	12.9 ^S
LIVE FETAL WEIGHT (GM, LM), M ^a /F ^b	3.60/3.48	3.60/3.48	3.60/3.41 ^{NS}	3.45 ^{NS} /3.29 ^S

% preimplantation loss = ((no. corpora lutea - no. implants) / no. corpora lutea) x 100.

L.M = Litter mean. NS = Trend not statistically significant through indicated dose ($p > 0.05$). S = Trend statistically significant through indicated dose ($p \leq 0.05$). a = Trend analysis was performed with an adjustment for time of sacrifice. b = Trend analysis was performed with an adjustment for time of sacrifice and litter size. c = One additional female excluded which died prior to mating due to intubation accident. d = Mating index = Mean of $1/(\text{time to mating})$ for mated females and zero for females that did not mate.

TABLE 3.4.2.4
SUMMARY OF STATUS OF F₁ GENERATION PRIOR TO WEANING. TT #90-708-0

	CONTROL	25 MG/KG/DAY	100 MG/KG/DAY	300/200 MG/KG/DAY
PARENTAL FEMALES, F ₀ (A)	16	19	18	19
IMPLANTS PER FEMALE	14.8	14.8	15.3	14.9 ^{NS}
% POSTIMPLANTN. SURVIVAL (L.M.)	96.5	89.9	94.5	85.8 ^{NS}
FEMALES WITH LIVE PUPS PND 0	16	18	18	18
FEMALES WITH LIVE PUPS PND 21	16	18	18	16
TOTAL PUPS (FEMALES/MALES)	232 (120/112)	275 (142/133)	270 (141/129)	266 (143/122)
LIVE PUPS ON POSTNATAL DAY 0	230 (118/112)	267 (136/131)	260 (134/126)	257 (138/119)
DEAD PUPS ON POSTNATAL DAY 0	2 (2/0)	8 (6/2)	10 (7/3)	9 (5/3)
LIVE PUPS/ LITTER, L.M. (% LIVE PUPS)	14.4 (99.0)	14.8 (97.4)	14.4 (96.1)	14.3 ^{NS} (96.7)
LIVE PUPS AFTER CULLING (PND 3)	128	144	144	143
PUP DEATHS (L.M.) ^a (% PUP DEATHS)				
POSTNATAL DAYS 0-3 ^b	2 (0.8)	4 (2.5)	7 (2.7) ^{NS}	17 (7.7) ^S
POSTNATAL DAYS 4-7	0 (0.0)	2 (1.4)	0 (0.0)	24 (17.2)
POSTNATAL DAYS 8-14	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.1)
POSTNATAL DAYS 15-21	0 (0.0)	0 (0.0)	0 (0.0)	6 (4.2)
POSTNATAL DAYS 4-21	0 (0.0)	2 (1.4)	0 (0.0) ^{NS}	33 (23.4) ^S
LIVE PUP WEIGHT (GM) (L.M.), M/F	M/F	M/F	M/F	M/F
POSTNATAL DAY 0 ^c	6.5/6.2	6.7 ^{NS} /6.2	6.3 ^S /6.0 ^{NS}	6.3 ^S /5.9 ^S
POSTNATAL DAY 7 ^d	18.8/18.0	17.8 ^{NS} /16.7 ^{NS}	17.6 ^S /16.4 ^S	16.3 ^S /15.1 ^S
POSTNATAL DAY 14 ^d (% CHANGE)	38.5/37.3	35.8 ^S (7.0)/34.4 ^S (7.8)	35.2 ^S (8.6)/33.5 ^S (10.2)	33.5 ^S (13.0)/30.4 ^S (18.5)
POSTNATAL DAY 21 (% CHANGE)	62.8/60.7	59.2 ^S (5.7)/56.5 ^S (6.9)	52.5 ^S (16.4)/49.5 ^S (18.5)	50.4 ^S (9.8)/46.0 ^S (24.3)

Total includes pups for which sex could not be determined. (A) = Excludes any females not surviving past day 20 of gestation. (L.M.) = Litter mean. M = Male. F = Female. PND = Postnatal day. NS = Trend not statistically significant through indicated dose ($p > 0.05$).

S = Trend statistically significant through indicated dose ($p \leq 0.05$).

a = Excludes pups born dead day 0.

b = Includes only deaths in day 0 pups which died after weighing.

c = Statistical analysis was performed with an adjustment for length of gestation and number of live pups per litter on postnatal day 0.

d = Statistical analysis was performed with an adjustment for length of gestation.

group with a perineal malformation and anasarca, microcardia, a reduced atrium, an enlarged ductus arteriosus and a displaced testes, and another fetus in the mid dose group with an azygos vein variation. Since these incidences are low in number, the sponsor considers them as spontaneous events unrelated to treatment. There was a slight increase in the percent of high dose fetuses with variations or sites of incomplete ossification (40.4% of high dose fetuses *versus* 31.7% of control fetuses). The increase in sites of incomplete ossification was the result of a non-dose related increase in incompletely ossified sternebra.

There were no effects of the test drug on % postimplantation survival or live pups/litter in the natural delivery groups. However, significant increases in pup mortality in the high dose group from postnatal days 0-3 (7.7%) and from days 4 to 21 (23.4%) were considered treatment-related (Table 3.4.2.4). The pup deaths were associated with decreased pup weights. There were significant treatment-related decreases in pup weights during lactation in all dose groups. In general, these decreases were dose and postnatal age-dependent with female pups being more severely affected than male pups. Similar percent decreases in weights of day 20 fetuses and day 0 pups in the high dose group suggests that these effects are due to late gestation and lactation exposure to losartan and it could be secondary to maternal toxicity. There was no evidence of treatment-related external malformations or variations in F₁ pups.

There was no effect of treatment on surface righting or testes descent in F₁ pups. In the female pups, there was a significant treatment-related delay in the estimated mean day of occurrence of the auditory startle reflex in the 100 and 300/200 mg/kg/day groups (0.44 and 0.47 days, respectively). There was also a delay of 1.2 days in the estimated mean day of vaginal canalization in the high dose group animals. According to the sponsor, these delays are considered to be related to the significantly decreased body weights in these groups and are secondary to generalized immaturity of the pups rather than a specific effect of losartan on developmental maturation. In the males from high dose group, the mean day of occurrence for preputial separation was significantly increased by 1.3 days compared to control. Treatment-related significant decreases in open field activity in male offspring in the mid and high dose groups (11 and 15.5%, respectively, compared to control) were observed. There was no effect of treatment on swim maze activity in F₁ rats.

From weaning (postnatal day 21) until postnatal day 25 there were pup deaths in the mid (4 of 143) and high dose (5 of 108) groups. These deaths were considered by the sponsor as unusual and were regarded as treatment-related. There were no physical signs of toxicity among weaned F₁ rats. The postweaning weight changes among males and females in all drug treated groups were different. In females, from postweaning weeks 1 to 9 there were slight but significant decreases in mean body weight gain of 4.3, 5.6 and 5.2% in the 25, 100 and 300/200 mg/kg/day groups, respectively, when compared to control. For the entire 14 week postweaning period the average weight gain of females in all treatment groups was within 2% of control.

Losartan had no adverse effects upon the reproductive capacity of the F₁ generation at any dose level tested (Table 3.4.2.5). There was no effect of treatment on mortality, weight or

TABLE 3.4.2.5
SUMMARY OF REPRODUCTIVE PERFORMANCE OF F₁ FEMALES AND STATUS OF F₂ GENERATION AT PARTURITION. TT #90-708-0

	CONTROL	25 MG/KG/DAY	100 MG/KG/DAY	300/200MG/KG/DAY
FEMALES COHABITED	16	18	17	15
MALES COHABITED	15	18	17	15
MATED FEMALES	16	15	15	14
PREGNANT FEMALES	15	15	14	12
DIED OR SACRIFICED PRIOR TO DAY 20	0	0	0	0
FEMALES WITH LIVE PUPS	15	15	14	12
TIME TO MATING (4-DAY PERIODS)	1.25	1.20	1.47	1.43 ^{NS}
MATED FEMALES/FEMALES COHABITED, %	100	83	88	93 ^{NS}
FECUNDITY INDEX (PREGNANT FEMALES/MATED FEMALES, %)	94	100	93	86 ^{NS}
FERTILITY INDEX (PREGNANT FEMALES/FEMALES COHABITED, %)	94	8	382	80 ^{NS}
FEMALES WITH LIVE PUPS/PREGNANT FEMALES, %	100	100	100	100
LENGTH OF GESTATION (DAYS)	22.2	22.6	22.3	22.5 ^{NS}
IMPLANTS PER FEMALE	17.8	16.7	16.6	16.8 ^{NS}
% POSTIMPLANTATION SURVIVAL (L.M.)	91.4	86.5	93.9	88.6
FEMALES WITH LIVE PUPS DAY 0 POSTPARTUM	15	15	14	12
TOTAL PUPS (FEMALES/MALES)	249 (130/119)	232 (125/105)	222 (118/104)	185 (92/93)
LIVE PUPS ON POSTNATAL DAY 0	244 (128/116)	217 (118/99)	218 (116/102)	179 (89/90)
DEAD PUPS ON POSTNATAL DAY 0	5 (2/3)	15 (7/6)	4 (2/2)	6 (3/3)
LIVE PUPS PER LITTER (%)	16.3 (98.1)	14.5 (93.8)	15.6 (98.2)	14.9 ^{NS} (96.7)
LIVE PUP WEIGHT (GM) (L.M.) ON DAY 0 ^a , M/F	6.7/6.3	7.0/6.6	6.6/6.3	6.9/6.4 ^{NS}

Total includes pups for which sex could not be determined.

(L.M.) = Litter mean. NS = trend not statistically significant through indicated dose ($p > 0.05$).

a = Statistical analysis was performed with an adjustment for length of gestation and number of live pups per litter.

external morphology of the F₂ pups.

In conclusion, there was no evidence of teratogenicity in any dose group in the F₁ or F₂ generation. Developmental toxicity was observed in all dose groups based on decreased F₁ pup weight gain and mortality (in both lactation and postweaning periods and dose and time-dependent). Females had more severe weight gain reductions than males. In addition, developmental signs were adversely affected. The toxicity observed may be due to late gestation/lactation drug exposure. This study has failed to establish a no observed effect dose.

3.4.3. Oral Developmental Toxicity Study in Rats

Location of Data: Vol 19, Tab C-6

Testing Facility: Department of Safety Assessment, Merck Sharp & Dohme Research Laboratories, Merck & Co., Inc., West Point, PA

Study No.: TT #90-702-0

Study Dates: Initiated: April 9, 1990
Terminated: May 3, 1990

GLP Compliance: Studies were done in accordance with GLP regulations.

Animals: Female Sprague-Dawley (CrI:CD BR) rats from Charles River Laboratories were 11 weeks of age and weighed 223-346 gm at initiation of the study.

Mode of Administration/Dosage Levels: Doses of 50, 100, and 200 mg/kg/day were given orally, by gavage, to three groups of 25 mated females each on gestational days 6 through 17. An additional group of 25 mated females received the vehicle (water) at a dosing volume of 5 ml/kg and served as the control. The dosage levels were selected based on an oral range-finding study (#90-702-1) in pregnant rats in which treatment-related decreases ($P \leq 0.05$) in mean maternal body weight gain were observed in the 225 (18.1%) and 300 (28.2%) mg/kg/day groups from days 6 through 18 of gestation.

Observations/Measurements: All animals were observed for physical signs once daily on day 0 and on days 6 through 20 of gestation. Body weights were recorded on days 0, 6, 8, 10, 12, 14, 16, 18, and 20 of gestation. Food consumption was measured on every third day beginning on day 3 of gestation. Females were killed on day 20 of gestation, uterus was examined to determine reproductive status and the number of corpora lutea were counted. A gross examination of thoracic, pelvic, and abdominal viscera was done on all sacrificed females. All fetuses were weighed, sexed, and examined externally. One third of the fetuses in each litter and all externally malformed fetuses were examined for visceral alterations. All fetuses were examined for skeletal alterations.

Results: There were no treatment-related physical signs, deaths, abortions or gross lesions observed at necropsies. There was no effect on average maternal body weight gain in the 50 and 100 mg/kg/day groups. In the 200 mg/kg/day group there was a significant ($P \leq 0.05$) 21.4% treatment-related decrease in average maternal body weight gain from gestational day 6 to gestational day 18. In the postdosing interval of days 18 to 20 of gestation there was a significant ($P \leq 0.05$) increase (13.5%) in average maternal body weight gain. There was no evidence of developmental toxicity based on postimplantation survival, fetal weight, and external, visceral, or skeletal examination.

The no-observed-effect dose level in this study for maternal toxicity was 100 mg/kg/day, and for developmental toxicity was >200 mg/kg/day.

3.4.4. Oral Developmental Toxicity Study in Rats With Postweaning Evaluation

Location of Data: Vol 19, Tab C-7

Testing Facility: Department of Safety Assessment, Merck Sharp & Dohme Research Laboratories, Merck & Co., Inc., West Point, PA

Study No.: TT #91-727-0

Study Dates: Initiated: September 16, 1991
Terminated: January 7, 1992

GLP Compliance: Studies were done in accordance with GLP regulations.

Animals: Female Sprague-Dawley (CrI:CD BR) rats from Charles River Laboratories were 10 weeks of age and weighed 220-299 gm at initiation of the study.

Mode of Administration/Dosage Levels: Doses of 5, 20, and 100 mg/kg/day were given orally, by gavage, to three groups of 20 mated females each on gestational days 6 to 15. An additional group of 20 mated females received the vehicle (water) at a dosing volume of 5 ml/kg and served as the control.

Observations/Measurements: All animals were observed for physical signs once daily on gestation day 0, from gestation day 6 through end of gestation, and on days 0, 3, 7, 10, 14, and 17 of lactation. Body weights were recorded on days 0, 6, 8, 10, 12, 14, 16, 18, 20 and 22 of gestation and days 0, 3, 7, 10, 14, 17 and 21 of lactation. Food consumption was measured gestation days 3-5, 6-8, 9-11, 12-14, 15-17, 18-20, and lactation days 1-5, 8-12, 12-16 and 16-20. Females which delivered were killed between days 23 and 27 postpartum, uterine metrial glands were counted, and gross necropsies (limited to thoracic and abdominal viscera) performed.

All F₁ pups were counted, examined externally for malformations, weighed and sexed on

postnatal day 0. On postnatal day 3, litters were reduced to 4 males and 4 females. Selected pups from each litter (2 males and 2 females) were tested on postnatal days 2, 4, and 6 for surface righting reflex and on postnatal days 11, 12, and 13 for auditory startle reflex. Approximately on postnatal days 23 to 27, the same animals, when possible, were removed and housed separately for postweaning examinations. They were observed daily and body weights were recorded once a week from weaning until breeding or termination. Testicular descent was recorded on postnatal day 39 and preputial separation on postnatal days 39, 43, and 47. Vaginal canalization was recorded on postnatal days 31, 34, and 37. Behavioral tests (swimming maze on days 61 to 70 and open field motor activity on days 82 to 84) were performed on one male and one female animal from each litter. Of 1140 live F₁ pups examined externally, 238 pups were necropsied. One male and one female per litter from 10 litters in each group were necropsied on postnatal days 0 to 3 (9 litters were examined in 5 mg/kg/day group), 21 and 86 of life for gross and histological examination of the kidneys. Animals used in postweaning studies were sacrificed at 13 weeks of age.

Results: There were no treatment-related physical signs, deaths, abortions or gross lesions observed at necropsy of the F₀ females. There was no effect on average maternal body weight gain or food consumption during gestation or lactation. There were no treatment-related effects on reproductive performance as assessed by mean implants/female or live pups/litter. However, there was a very slight but statistically significant ($P \leq 0.05$) decrease (5.8%) in postimplantation survival in the high dose group (Table 3.4.4.1). The decrease is in part due to one female which had 7 pups and 12 metrial glands (a 58.3% postimplantation survival). This slight decrease, according to the sponsor, is not considered treatment-related because similar decreases were not observed in two previous studies in rats (see section # 3.4.2 and 3.4.3). There was no effect of treatment on F₁ pup survival, physical signs, body weights, or malformations based on external examinations. There was no treatment-related effect on developmental signs or behavioral tests. Also no drug-related gross or microscopic kidney pathology was observed in F₁ rats examined on days 0-3, 21 or 86 of life.

In conclusion, treatment of rats with up to 100 mg/kg/day of losartan from day 6 to day 15 of gestation had no adverse effects on the dams during gestation and lactation and no effect on the F₁ generation as assessed by mortality, physical signs, weight gain, external examinations, developmental signs, behavioral tests and gross or microscopic kidney morphology.

TABLE 3.4.4.1

REPRODUCTIVE PERFORMANCE OF F₀ FEMALES AND SUMMARY OF STATUS OF F₁ GENERATION PRIOR TO WEANING. TT #91-727-0

	CONTROL	5 MG/KG/DAY	20 MG/KG/DAY	100 MG/KG/DAY
PARENTAL FEMALES, F ₀	19	19	18	20
IMPLANTS PER FEMALE	16.4	15.6	17.7	15.6 ^{NS}
% POSTIMPLANTATION SURVIVAL (L.M.)	93.4	95.3	90.4 ^{NS}	88.0 ^S
FEMALES WITH LIVE PUPS DAY 0 POSTPARTUM	19	19	18	20
FEMALES WITH LIVE PUPS DAY 21 POSTPARTUM	19	19	18	20
TOTAL PUPS (FEMALES/MALES)	297 (146/150)	284 (144/140)	293 (158/135)	278 (133/145)
LIVE PUPS ON POSTNATAL DAY 0	292 (144/148)	283 (143/140)	289 (156/133)	276 (131/145)
DEAD PUPS ON POSTNATAL DAY 0	5 ^a (2/2)	1 (1/0)	4 (2/2)	2 (2/0)
LIVE PUPS PER LITTER (% LIVE, L.M.)	15.4 (98.1)	14.9 (99.7)	16.1 (98.5)	13.8 ^{NS} (99.3)
LIVE PUPS AFTER CULLING ON POSTNATAL DAY 3	152	152	144	160
PUP DEATHS (% PUP DEATHS) (L.M.)				
POSTNATAL DAYS 1-3	4 (1.2)	1 (0.4)	2 (0.7)	1 (0.3) ^{NS}
POSTNATAL DAYS 4-7	0 (0.0)	0 (0.0)	2 (1.4)	0 (0.0)
POSTNATAL DAYS 8-14	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
POSTNATAL DAYS 15-21	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
POSTNATAL DAYS 4-21	0 (0.0)	0 (0.0)	2 (1.4)	1 (0.6) ^{NS}
LIVE PUP WEIGHT (GM) (L.M.), M/F				
POSTNATAL DAY 0 ^b	6.4/6.1	6.8 ^{NS} /6.4	6.9 ^S /6.4 ^{NS}	7.1 ^S /6.6 ^S
POSTNATAL DAY 7 ^b	18.4/17.5	19.3/18.3	18.8/17.7	19.5 ^{NS} /18.2 ^{NS}
POSTNATAL DAY 14 ^c	37.4/36.2	39.1/37.3	37.7/36.2	38.3 ^{NS} /36.2 ^{NS}
POSTNATAL DAY 21 ^c	60.2/57.9	63.7/60.9	61.5/58.9	63.6 ^{NS} /59.6 ^{NS}

Total includes pups for which sex could not be determined

(L.M.) = Litter Mean

NS = Trend not statistically significant ($p > 0.05$) through indicated dose.S = Trend statistically significant ($p \leq 0.05$) through indicated dose.^a = Includes one pup that was dead before delivery was complete and was then missing on day 0 of lactation.^b = Statistical analysis was performed with an adjustment for length of gestation and number of the live pups per litter on postnatal day 0.^c = Statistical analysis was performed with an adjustment for length of gestation.

3.4.5. Oral Late Gestation and Lactation Study in Rats

Location of Data: Vol 21, Tab C-16

Testing Facility: Department of Safety Assessment, Merck Sharp & Dohme Research Laboratories, Merck & Co., Inc., West Point, PA

Study No.: TT #90-727-0

Study Dates: Initiated: August 13, 1990
Terminated: January 5, 1991

GLP Compliance: Studies were done in accordance with GLP regulations. Animals: Female Sprague-Dawley (CrI:CD BR) rats from Charles River Laboratories were 10 weeks of age and weighed 218-313 gm at initiation of the study.

Mode of Administration/Dosage Levels: Dosage levels of 10, 25, and 100 mg/kg/day were given orally, by gavage, to three groups of 20 females each from gestation day 15 to lactation day 20. An additional group of 20 females received the vehicle (water, 5 ml/kg) and served as the control.

Observations/Measurements: All animals were observed for physical signs once daily on gestation days 0, 7 and 15 through sacrifice. Body weights were recorded on gestation days 0, 7, 15, 16, 18, 20 and 22; and lactation days 0, 3, 7, 10, 14, 17 and 21. Food consumption was measured on gestation days 8-12 and 15-19; and lactation days 1-5 and 8-12. Females which delivered were killed between lactation days 23 and 27, uterine metrial glands were counted, and gross necropsies (limited to thoracic and abdominal viscera) performed.

All F₁ pups were counted, examined externally for malformations, weighed and sexed on postnatal day 0. On postnatal day 3, litters were reduced to 4 males and 4 females. Two pups per sex from each litter were tested on postnatal days 2, 4 and 6 for surface righting reflex and on postnatal days 11, 12 and 13 for auditory startle reflex. The same animals, when possible, were used for postweaning examinations. They were observed daily for mortality and twice weekly for physical signs. Body weights were recorded once a week from weaning until breeding or termination. Testicular descent was recorded on postnatal day 39 and preputial separation on postnatal days 39, 43, and 47. Vaginal canalization was recorded on postnatal days 31, 34, and 37. Behavioral tests (swimming maze on days 61 to 69 and open field motor activity on days 75 to 79) were performed on one male and one female animal from each litter.

During postweaning week 9, one female and one male per litter were caged together for a maximum of 16 nights for mating. Non-selected pups were euthanized and discarded without further examination. All males used for mating were sacrificed after most females had completed delivery and the testes and epididymides were examined for gross changes and

weighed. Histomorphologic examination was performed on testes and epididymides from the control and high dose groups. All F₁ females which mated were weighed on gestation days 0, 7, 14, 20, and after natural delivery on lactation day 0. F₁ females which delivered were euthanized between lactation day 0 and 5 and the uterine metrial glands counted. The F₂ pups were counted, weighed, sexed, examined for external malformations, and mortality noted on postnatal day 0. All pups were killed within 5 days thereafter and discarded without further examination.

Results: There were no treatment-related physical signs, deaths, abortions or gross lesions observed at necropsy of the F₀ females. There was no effect of treatment on average maternal body weight gain from gestation day 15 to gestation day 20 or during lactation in the 10 and 25 mg/kg/day groups. However, in the 100 mg/kg/day group, average maternal body weight gain from gestation day 15 to gestation day 20 was 16.7% below control ($P \leq 0.05$) and weight gain during lactation was 20.6% below control ($P \geq 0.05$). Effects on food consumption were limited to the 100 mg/kg/day group, for which average food consumption on days 9 to 12 of lactation was 12.1% below control ($P \leq 0.05$). There were no treatment-related effects on reproductive performance of F₀ females (Table 3.4.5.1).

A significant treatment-related increase in pup mortality was observed in the 100 mg/kg/day group on postnatal days 1 to 3 (Table 3.4.5.1). There were statistically significant ($P \leq 0.05$) treatment-related decreases in pup weights during lactation in all dose groups which were, in general, time and dosage dependent and considered treatment-related. Table 3.4.5.1 gives both actual body weight and percent decrease in weights compared to controls. The magnitude of the difference from control in the 25 and 100 mg/kg/day groups is similar to that observed in a previous (female) fertility study (see section 3.4.2) at the same doses. No explanation was, however, advanced for the weight decrease being more severe in the 10 mg/kg/day group than in the 25 mg/kg/day group.

There were no treatment-related malformations or variations in F₁ pups. From weaning until postnatal day 27, there were four deaths of F₁ rats in the 100 mg/kg/day group. All of these rats had lower body weight than littermates at or near the time of death. This incidence of postweaning mortality (2.8%) is similar to that observed in a previously conducted fertility study in female rats (2.7%) at this dosage level (see section 3.4.2). The sponsor attributes these deaths to treatment. During the postweaning weeks 1-8, there were no treatment-related effects on average F₁ body weight gain in the 10 and 25 mg/kg/day groups. In the 100 mg/kg/day group, there was a treatment-related significant difference in body weight gain for both males and females. At postweaning week 1, both male and female F₁ rats had 17-18% lower average body weight than controls. During the next seven weeks, body weight of males but not females in the 100 mg/kg/day group caught up to body weight of controls. During postweaning weeks 9-13, there was no significant effect on average body weight gain in both males and females. There was no effect of treatment on physical and behavioral development. The reproductive performance of the F₁ generation was not significantly different from the control. There were no effects of treatment on F₂ mortality, weight, or external appearance.

TABLE 3.4.5.1
SUMMARY OF STATUS OF F₁ GENERATION PRIOR TO WEANING. TT #90-727-0

	CONTROL	10 MG/KG/DAY	25 MG/KG/DAY	100 MG/KG/DAY
PARENTAL FEMALES, F ₀	20	20	20	20
LENGTH OF GESTATION (DAYS)	22.1	21.9	22.2	22.2 ^{NS}
IMPLANTS PER FEMALE	16.5	15.6	16.1	14.8
% POSTIMPLANTATION SURVIVAL	93.6	97.3	94.0 ^{NS}	89.3 ^S
FEMALES WITH LIVE PUPS DAY 0 POSTPARTUM DAY 21 POSTPARTUM	20 20	20 19	20 20	20 19
TOTAL PUPS (FEMALES/MALES) LIVE PUPS ON PND 0 DEAD PUPS ON PND 0	315 (170/145) 310 (167/143) 5 (3/2)	305 (155/150) 302 (154/148) 3 (1/2)	309 (142/167) 303 (141/162) 6 (1/5)	274 (129/145) 265 (123/142) 9 (6/3)
LIVE PUPS PER LITTER, L.M. (% LIVE PUPS)	15.5 (98.5)	15.1 (99.1)	15.2 ^{NS} (98.1)	13.2 ^S (95.4)
LIVE PUPS AFTER CULLING ON PND 3	160	160	160	152
PUP DEATHS, L.M. (% PUP DEATHS) POSTNATAL DAYS 1-3 POSTNATAL DAYS 4-7 POSTNATAL DAYS 8-14 POSTNATAL DAYS 15-21 POSTNATAL DAYS 4-21	1 (0.3) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0)	4 (1.2) 9 (5.6) 8 (5.0) 0 (0.0) 17 (10.6)	4 (1.2) ^{NS} 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0)	6 (6.4) ^S 3 (2.0) 3 (2.0) 2 (1.3) 8 (5.3) ^{NS}
LIVE M/F PUP WEIGHT (GM), (L.M.), (%) ^c POSTNATAL DAY 0 ^a POSTNATAL DAY 7 ^a (%) ^f POSTNATAL DAY 14 ^b POSTNATAL DAY 21 ^b	6.5/6.2 18.1/17.4 37.0/35.7 59.6/57.5	6.5/6.2 16.5 ^S (8.9)/15.7 ^S (9.8) ^S 33.6 ^S (9.2)/32.3 ^S (9.6) ^S 53.9 ^S (9.6)/51.4 ^S (10.7) ^S	6.8 ^{NS} /6.5 ^{NS} 17.4 ^S (3.9)/16.7 ^S (4.1) 35.4 ^S (4.4)/34.1 ^S (4.5) 56.4 ^S (5.4)/54.5 ^S (5.3)	6.6 ^S (1.6) ^S /6.2 ^S (0) ^{S,c} 16.2 ^S (10.5)/15.7 ^S (9.8) 32.2 ^S (13.0)/31.2 ^S (12.7) 47.9 ^S (19.7)/46.4 ^S (19.4)

(L.M.) = Litter Mean. M = Male. F = Female. PND = Postnatal day.

NS = Trend not statistically significant ($p > 0.05$) through indicated dose. S = Trend statistically significant ($p \leq 0.05$) through indicated dose.

a = Statistical analysis was performed with an adjustment for length of gestation and number of the pups/litter on postnatal day 0. b = Statistical analysis was performed with an adjustment for length of gestation. c = % Decrease in body weight compared to controls.

% Postimplantation survival = live pups on postnatal day 0/metrial glands x 100.

In conclusion, maternal toxicity was limited to the 100 mg/kg/day group and was expressed as decreased average body weight gain during gestation and lactation and decreased food consumption during lactation. Developmental toxicity was expressed in F₁ pups as decreased body weights in all dose groups from lactation day 7 to lactation day 21. There was also a slight but significant increase in pup deaths on postnatal days 1 to 3 in the high dose group and a treatment-related increase in deaths postweaning in this group. The body weight gain in the 100 mg/kg/day group during the postweaning period (weeks 1 to 8) was significantly less than control. The observations made in this study (i.e. decreased pup weights and increased pre and postweaning deaths in the high dose groups) are comparable to those observed earlier with the segment I study (see section 3.4.2). This indicates that the effects observed in the fertility study were due to exposure during late gestation and/or lactation.

3.4.6. Fostering/Cross-Fostering Study in Rats

Location of Data: Vol 21, Tab C-17

Testing Facility: Department of Safety Assessment, Merck Sharp & Dohme Research Laboratories, Merck & Co., Inc., West Point, PA

Study No.: TT #91-710-0

Study Dates: Initiated: March 10, 1991
Terminated: July 16, 1991

GLP Compliance: Studies were done in accordance with GLP regulations.

Animals: Female Sprague-Dawley (CrI:CD BR) rats from Charles River Laboratories were 12 weeks of age and weighed 228-353 gm at initiation of the study.

Mode of Administration/Dosage Levels: Since the previous study documented developmental toxicity, the present study was designed to further evaluate the association of treatment of F₀ females during late gestation and lactation or lactation only on growth, development, and behavior of the F₁ generation. Losartan was administered by oral gavage to a group of 50 mated females from day 15 of gestation to day 20 of lactation at a dose of 100 mg/kg/day. An additional group of 50 females received the vehicle (water), at a dosing volume of 5 ml/kg and served as the control. As soon after delivery as possible: 15 litters of control pups were fostered by control dams (CxC) and 15 litters were fostered by drug-treated dams (CxT); 15 litters of pups from drug-treated dams were fostered by control dams (TxC) and 15 litters were fostered by drug-treated dams (TxT).

Observations/Measurements: All animals were observed for physical signs once daily on gestation days 0 to 15 and twice daily during dosing from gestation day 15 to sacrifice. Body weights were recorded on gestation days 0, 7, 15, 16, 18, 20, 22 and 24, and lactation days 0, 3, 7, 10, 14, 17 and 21. Food consumption was not measured. Dams which delivered pups but

could not be used for cross fostering and dams that did not deliver were sacrificed on postnatal day 0 and gestation days 19 to 23, respectively. Females which were used to rear fostered litters were sacrificed between postnatal days 24 and 27 and numbers of metrial glands were recorded. All dams were given a gross examination of the thoracic and abdominal viscera. Excess litters were sacrificed and discarded on postnatal day 0 after litter weights were recorded.

The F₁ pups were counted, examined externally, weighed and sexed on postnatal day 0. On postnatal day 3, litters were sexed again and reduced to 4 males and 4 females. Body weights were recorded on postnatal days 7, 14 and 21. Two pups per sex from each litter were tested on postnatal days 2, 4 and 6 for surface righting reflex and on postnatal days 11, 12 and 13 for auditory startle reflex. On postnatal day 21, the same animals were removed and housed separately for postweaning examinations. Remaining pups were euthanized on the same day and one male and one female/litter from 10 litters per group were necropsied. Terminal body weights and heart weights were recorded for all pups. The study pups were observed daily for mortality and twice weekly for physical signs. Body weights were recorded once a week from weaning until termination. Testicular descent was recorded on postnatal day 39 and preputial separation on postnatal days 39, 43, and 47. Vaginal canalization was recorded on postnatal days 31, 34, and 37. Behavioral tests (swimming maze on days 56 to 64 and open field motor activity on days 70 and 71) were performed on one male and one female from each litter. F₁ adults were sacrificed at approximately 90 days of age. One male and one female per litter from 10 litters in each of the 4 treatment groups were necropsied. Body, brain and heart weights were recorded and kidneys were taken for histologic examination. Rest of the animals were discarded without further examination.

Results: There were no treatment-related physical signs, deaths or abortions in F₀ females. There was a significant treatment-related decrease (-9%) in average maternal body weight gain from gestation day 15 to gestation day 20 as compared to controls. However, there were no treatment-related effects on mean body weight gain during lactation. There were no treatment-related effects on reproductive performance of F₀ females, on pup survival, externally visible malformations or variations, or pup weights prior to cross-fostering on postnatal day 0.

A significant treatment-related increase in pup deaths was observed on postnatal days 1 to 3 in the groups treated with losartan (i.e., CxT and TxT) (Table 3.4.6.1). Treatment-related effects on survival were not observed between postnatal days 4 and 21. One male rat in the TxC group was found dead on postnatal day 39, and that death was considered related to treatment. On postnatal day 7 there was a statistically significant ($P \leq 0.05$) treatment-related decrease in pup body weights associated with postnatal treatment (i.e., CxT and TxT) for males (approximately 8.9%) and females (approximately 8.2%)(Table 3.4.6.1). There was a statistically significant, treatment-related effect of pre and postnatal administration of losartan to dams on the response of female pups in the surface righting test. Female pups of dams treated with losartan prenatally (TxC and TxT) had an earlier estimated day of occurrence (4.27 versus 4.9) than those from dams not treated during the prenatal period (CxC and CxT).

TABLE 3.4.6.1
SUMMARY OF STATUS OF F1 GENERATION PRIOR TO WEANING. TT #91-710-0

FOSTERING/CROSS-FOSTERING GROUPS⇒	CONTROL/ CONTROL ¹	CONTROL/ 100 MG/KG/DAY ²	100 MG/KG/DAY/ CONTROL ³	100 MG/KG/DAY/ 100 MG/KG/DAY ⁴
PARENTAL FEMALES	15	15	15	15
FEMALES WITH LIVE PUPS DAY 0 POSTPARTUM FEMALES WITH LIVE PUPS DAY 21 POSTPARTUM	15 15	15 15	15 15	15 14
TOTAL PUPS (FEMALES/MALES) LIVE PUPS ON POSTNATAL DAY 0 DEAD PUPS ON POSTNATAL DAY 0	150 (78/72) 150 (78/72) 0 (0/0)	150 (76/74) 150 (76/74) 0 (0/0)	147 (71/76) 147 (71/76) 0 (0/0)	147 (75/72) 147 (75/72) 0 (0/0)
LIVE PUPS PER LITTER ^a	10.0	10.0	9.8	9.8
% LIVE PUPS (L.M.)	100.0	100.0	100.0	100.0
LIVE PUPS AFTER CULLING ON POSTNATAL DAY 3	120	120	119	119
PUP DEATHS, L.M. (% PUP DEATHS) POSTNATAL DAYS 1-3 POSTNATAL DAYS 4-7 POSTNATAL DAYS 8-14 POSTNATAL DAYS 15-21 POSTNATAL DAYS 4-21	2 (1.0) ^{NS} 2 (1.7) 0 (0.0) 1 (0.8) 3 (2.5) ^{NS}	3 (11) ^{S(b)} 8 (6.7) 0 (0.0) 0 (0.0) 8 (6.7) ^{NS}	0 (0.0) ^{NS} 7 (5.8) 2 (1.7) 1 (0.8) 10 (8.3) ^{NS}	6 (2.6) ^{S(b)} 13 (11.1) 4 (3.3) 0 (0.0) 17 (14.4) ^{NS}
LIVE PUP WEIGHT (GM, L.M.) (M/F) POSTNATAL DAY 7 POSTNATAL DAY 14 POSTNATAL DAY 21	17.1 ^{NS} /16.1 ^{NS} 34.6 ^{NS} /33.2 ^{NS} 57.5 ^{NS} /55.4 ^{NS}	15.8 ^{S(b)} /14.8 ^{S(b)} 33.9 ^{NS} /32.1 ^{NS} 56.2 ^{NS} /52.8 ^{NS}	16.8 ^{NS} /16.1 ^{NS} 34.2 ^{NS} /32.4 ^{NS} 51.1 ^{S(a)} /49.2 ^{S(a)}	15.1 ^{S(a)} /14.5 ^{S(b)} 33.1 ^{NS} /31.6 ^{NS} 51.9 ^{S(a)} /49.1 ^{S(b)}

1: control pups fostered by control dams; 2: control pups fostered by drug-treated dams; 3: pups from drug-treated dams fostered by control dams;

4: pups from drug-treated dams fostered by dams receiving drug. (L.M.) = litter mean

a = difference from the control group is not statistically significant ($p > 0.05$) based on the analysis defined in the text and appendix.

Ns = difference from the control group is not statistically significant ($p > 0.05$) based on the analysis defined in the text and appendix.

S^(a) = statistically significant ($p \leq 0.05$) Prenatal effect.

S^(b) = statistically significant ($p \leq 0.05$) Postnatal effect.

Females pups from dams treated with losartan during lactation (CxT and TxT) also had an earlier estimated day of occurrence (4.23 versus 4.93) than those from dams not treated during lactation (CxC and TxC). There was a statistically significant, treatment-related postnatal effect of losartan on the auditory startle response of the female pups. Female pups fostered to drug-treated dams (CxT and TxT) had a later estimated day of occurrence (13.31) than those with no postnatal treatment (CxC and TxC) (12.98). For the male pups there were no statistically significant treatment effects on surface righting or auditory startle response.

A significant ($P \leq 0.05$) interaction between prenatal and postnatal treatment in preputial separation was observed. Pups from dams which received losartan during gestation displayed preputial separation later (estimated day of occurrence 45.4) if fostered by drug treated dams during lactation (TxT) than if fostered by control females (TxC) (estimated day of occurrence 43.9). This observation was not made in earlier reproduction studies (see sections 3.4.2 and 3.4.5). There were no effects of treatment on vaginal canalization, testes descent, or open field activity. There was a statistically significant ($P \leq 0.05$) prenatal effect on the performance of males in the first swim maze trial. Pups from dams who received losartan during gestation required more trials to perform the first swim maze (7.07) than those whose natural mother received the control treatment (5.35). However, in the second swim maze, there was a statistically significant ($P \leq 0.05$) effect associated with postnatal administration of losartan in that male pups whose foster mothers received losartan during lactation required fewer trials to perform the second test than those fostered by control-treated dams. On the other hand, female pups from the CxT group took more trials to complete the second swim maze (not significant in the performance of the first swim maze) than female pups from the CxC group (see Table 3.4.6.2). The toxicologic significance of these sexually dimorphic effects on swim maze performance with high doses of losartan is not clear though effects on swim maze performance were observed in a previous late gestation and lactation study (section 3.4.5).

There was a decrease in group mean terminal body weights and cardiac weights in 21 day old male and female pups of dams which had been treated with losartan during gestation. The effect was greater when these pups were fostered by drug-treated dams (Table 3.4.6.3). These changes were not observed at 90 days of age.

At necropsy of the F_1 offspring (on postnatal day 21), 4/30 TxC pups (13.3%), and 1/26 TxT pups (3.8%) had unilateral or bilateral dilation of the renal pelvis suggesting that the effect observed here is related to *in utero* exposure rather than to neonatal exposure. Drug-induced medial hypertrophy of intracortical renal arterioles was observed in pups from the TxC (100%) and TxT (90%) groups but not from the CxT group. Electronmicroscopically, the hypertrophied myocytes contained structures compatible with renin granules in greater numbers than in controls. Further, there appeared to be hyperplasia of myocytes in vessels in the absence of an increase in granule content.

Considering the distribution of renin-producing cells in rats of this age, it would appear that the vascular changes noted were the result of drug-induced inhibition of angiotensin II

TABLE 3.4.6.2
SUMMARY OF SWIM MAZE TESTING OF F1 GENERATION. TT #91-710-0

FOSTERING/CROSS-FOSTERING GROUPS ¹ ⇒	CONTROL/CONTROL		CONTROL/ 100 MG/KG/DAY		100 MG/KG/DAY/ CONTROL		100 MG/KG/DAY/ 100 MG/KG/DAY	
	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
DAYS 56 TO 57 POSTNATAL								
NO. ANIMALS TESTED	15	15	15	15	15	15	14	14
MEAN TRIALS TO CRITERION - TEST 1	5.6 ^{NS}	6.2 ^{NS}	5.7 ^{NS}	5.9 ^{NS}	7.0 ^{S(a)}	5.9 ^{NS}	7.9 ^{S(a)}	6.4 ^{NS}
DAYS 63 TO 64 POSTNATAL								
NO. ANIMALS TESTED	15	15	15	15	15	15	14	14
MEAN TRIALS TO CRITERION - TEST 2	5.4 ^{NS}	5.8 ^{NS}	4.3 ^{S(b)}	9.1 ^{S(c)}	5.5 ^{NS}	7.1 ^{S(c)}	3.8 ^{S(b)}	5.9 ^{S(c)}

1: For explanation of groups see footnote in table 3.6.6.1

NS = Difference from the control group is not statistically significant ($p > 0.05$) based on the analysis defined in the text and appendix.

S^(a) = Statistically significant ($p \leq 0.05$) pre-natal effect.

S^(b) = Statistically significant ($p \leq 0.05$) post-natal effect.

S^(c) = Statistically significant ($p \leq 0.05$) for interaction between prenatal and postnatal in effect.

TABLE 3.4.6.3
AVERAGE ORGAN WEIGHTS OF F₁ WEANLINGS. TT #91-710-0

FOSTERING/CROSS-FOSTERING GROUPS ¹ ⇒	CONTROL/CONTROL		CONTROL/100 MG/KG/DAY		100 MG/KG/DAY/CONTROL		100 MG/KG/DAY/100 MG/KG/DAY	
	F	M	F	M	F	M	F	M
SEX								
N	28	29	28	24	24	26	22	24
BODY WEIGHT, GRAMS	56.0	56.9	52.8 ^{NS}	57.2 ^{NS}	50.4 ^S	53.4 ^S	48.8 ^S	52.0 ^S
HEART, GRAMS	0.32	0.32	0.30 ^{NS}	0.32 ^{NS}	0.26 ^S	0.28 ^S	0.26 ^S	0.26 ^S
% B.W.	0.57	0.57	0.58 ^{NS}	0.57 ^{NS}	0.53 ^S	0.53 ^S	0.54 ^S	0.51 ^S

1: For explanation of groups see footnote in table 3.4.6.1

B.W. = Body weight

NS = not statistically significantly different from control/control ($p > 0.05$)

S = statistically significantly different from control/control ($p \leq 0.05$)

resulting in hypertrophy and hyperplasia of renin-producing cells. There was no visible alteration in juxtaglomerular apparatus. Along with the arteriolar change, there were dilation of the renal pelvis (85% incidence of hydronephrosis in TxC and 65% incidence in TxT with a background incidence of about 10% in untreated controls) and edema of the renal papilla (75% incidence in TxC and 85% in TxT) (Table 3.4.6.4). While tubular dilation would be expected in association with the urodynamic alterations which caused hydronephrosis, another tubular degenerative change was also noted, characterized by "swelling" and tinctorial alteration in scattered tubular epithelia. This is a secondary effect related to hemo- and urodynamic effects on the kidney. The sponsor concludes that the vascular myohypertrophy and hyperplasia noted in these rats is related to the pharmacologic effect of losartan on renin-producing cells, but the pathophysiology of the papillary edema, tubular changes, and hydronephrosis remains unclear.

Cardiac and vascular effects disappeared with time in F₁ adults necropsied at 90 days. However, sequelae to intrauterine exposure were present: dilation of renal pelvis persisted in groups which had received prenatal treatment and was present at a much higher incidence than in controls (75-80%, similar to that seen at 21 days); edema of the renal papilla was still present in 50% of TxC and 55% of TxT; cortical tubular degeneration was seen in 5 to 35% of F₁ adults and was similar to that seen at 21 days; tubular mineralization (30% in TxC and 55% in TxT), and inflammation, apparently arising in the renal pelvis and extending centrifugally (Table 3.4.6.4). This nephritis was noted in about 38% of rats born to dams treated during gestation, but not in controls. The lesion progressed in one animal to produce severely damaged kidneys, similar to the diffuse chronic nephritis noted in aged rats.

In conclusion, average maternal body weight gain was significantly lower for treated than for control dams for the gestation day 15 to gestation day 20 period. In fostered/cross fostered F₁ pups there were a number of statistically significant treatment-related effects evident. Prenatal treatment of dams was associated with decreased pup weight on postnatal day 21 and effects on male performance in the first swim maze test. Treatment of dams during lactation increased pup deaths on postnatal days 1-3 and caused decreased pup weights on postnatal day 7. Additionally, decreased performance on the auditory startle test and second swim maze trial were observed in females. Intrauterine exposure to a high dose of losartan caused a decrease in cardiac weight which was slightly exacerbated by continued exposure during suckling. A pharmacologically-induced medial hypertrophy of small intracortical arterioles in the kidneys, as well as dilation of the renal pelvis and edema of the renal papilla, was also produced with *in utero* exposure. Further, while the cardiac and vascular effects disappeared with time, significant renal sequelae (nephritis, etc.) followed intrauterine exposure to losartan. Thus, the study indicates that losartan at a dose of 100 mg/kg/day is associated with adverse effects on pups when administered during late gestation and/or lactation.

N 20386
COZAAR

7 OF 10

Conclusion

The incidence of renal cancer observed with losartan is no greater than that observed in hypertensive patients exposed to EL. However, the incidence rates observed for both are the highest incidence that we have observed in the literature. The mostly likely explanation for the magnitude of the incidence with losartan and EL, is better detection in the study population than occurs in the general population.

 11-3-94

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cc:
HFD-100/Temple
HFD-110/Chen, Granley
HFD-700/O'Neill
HFD-730/Kweder
HFD-733/Burkhart/Chron file
HFD-735/Barash

Bongiovanni

JAN 27 1995

NDA: 20-386

Priority: 1 S

COZAAR® (Losartan Potassium)

Tablets (25, 50 and 100 mg)

SUBMISSION DATES: DEC. 3, 1993

JUNE 17, 1994

AUG. 4, 1994.

OCT 3, 1994

MERCK RESEARCH LABORATORIES.

REVIEWER: Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: Original NME

SYNOPSIS:

The sponsor has adequately studied the pharmacokinetics (single and multiple dose), metabolism and excretion of losartan, a new angiotensin II receptor antagonist, and has established the dose proportionality of losartan to include the dosing range covered in the proposed package insert. Acceptable studies have also been performed to study renal and liver impairment as well as age and gender effects. Drug interaction between the drug and phenobarbital, cimetidine, warfarin, digoxin and hydrochlorothiazide were studied. Food effect was studied. An acceptable in vitro dissolution method has been provided.

RECOMMENDATION:

The Division of Biopharmaceutics recommends that the sponsor's NDA 20-386 be accepted for meeting the Biopharmaceutics requirements provided the comments below (pages 8-10) are satisfactorily addressed by the sponsor.

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Appendix II:

Note: Appendix II contains more data/information such as individual subject data and statistical analyses. This information is being retained in the Division of Biopharmaceutics, and can be obtained upon request.

BACKGROUND: Losartan is a synthetic compound with structure shown in Figure 1.

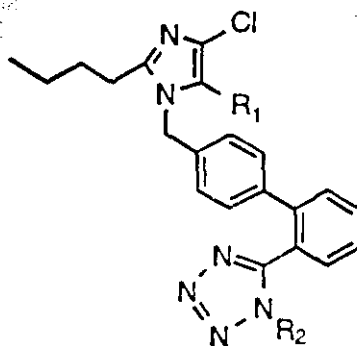
Losartan and its active metabolite block all physiologically relevant actions of angiotensin II by binding to the AT₁ receptor. It is proposed to be used for the treatment of hypertension, and dizziness and orthostatic effects are the major side effects. The sponsor has submitted 18 studies in support of the NDA and the 18 studies were reviewed. The recommended dosing is 50 to 100 mg once a day for up to 3-6 weeks.

Losartan is an acidic polar compound with a solubility of >500 mg/ml in water (resulting pH of 9.7), 2.5 mg/g in acetonitrile, and about 35 mg/g in 2-propanol. The average partition coefficient in octanol-water (phosphate buffer, pH 7; initial aqueous phase concentrations 0.01M and 0.001M) system is 15 ± 1 . The pH of a solution of losartan potassium (1% w/w) in water is about 8.2. The pKa value in aqueous solution containing 1% methanol is 4.1 as determined by ultraviolet spectroscopy using buffers from pH 1 to 13.

Structures of Losartan Potassium and L-158,641

OR
E-3174

(ACTIVE METABOLITE)



	R1	R2	Molecular Formula	Molecular Weight
Losartan potassium	CH ₂ OH	K	C ₂₂ H ₂₂ ClKN ₆ O	461.0
L-158,641	COOH	H	C ₂₂ H ₂₁ ClN ₆ O ₂	436.9

SUMMARY OF BIOAVAILABILITY/PHARMACOKINETICS/PHARMACODYNAMICS

1. BIOAVAILABILITY/BIOEQUIVALENCE:

A. Absolute Bioavailability: With reference to a 30 mg IV bolus dose, the absolute bioavailability of Losartan given as 1 X 100 mg non-market (clinically tested) capsule averaged 24.6% (CV 49.6%) while that of the tablet (used for Phase III studies) averaged 22.9% (CV 43.1%) (Study # 022). With reference to a 20 mg IV bolus dose, the absolute bioavailability of Losartan given as 1 X 50 mg final market image tablet averaged 32.6% (CV 43.4%) (Study # 074). With reference to a 30 mg IV bolus dose, the absolute bioavailability of Losartan given as 100 mg oral solution averaged 38.9% (CV 37.7%) (Study # 060).

B. Bioequivalence: Bioequivalence was evaluated on log-transformed parameters and 90% confidence intervals were reported. Study #022 compared the 100 mg capsule formulation used for early Phase I and Phase II studies to the 100 mg tablet formulation used for Phase III studies. The two one-sided test procedure on the AUC (0.69 - 1.24), C_{max} (0.55 - 1.32) for losartan, and AUC (0.96 - 1.09), C_{max} (0.93 - 1.23) for the active metabolite show that the clinically tested capsule and 100 mg tablet for Phase III are bioinequivalent with respect to losartan but bioequivalent with respect to the active metabolite. Study #075 compared the 50 mg tablet formulation manufactured by Merck and used for Phase III studies to the 50 mg tablet formulation manufactured by DuPont-Merck Pharmaceutical Corporation (DMPC) for marketing (in USA). The two one-sided test procedure on the AUC (0.89 - 1.07), C_{max} (0.69 - 1.17) for losartan, and AUC (0.91 - 1.05), C_{max} (0.81 - 1.02) for the active metabolite show that the 50 mg Merck and DMPC tablets are bioinequivalent with respect to losartan but bioequivalent with respect to the active metabolite. Study #075 also compared 50 mg losartan capsule formulation (prepared by DMPC) to the Merck Phase III tablet. The two one-sided test procedure on the AUC (0.99 - 1.19), C_{max} (0.92 - 1.56) for losartan, and AUC (1.00 - 1.15), C_{max} (0.97 - 1.22) for the active metabolite show that the 50 mg DMPC Losartan Capsules and 50 mg Merck Losartan Tablets are bioinequivalent with respect to losartan but bioequivalent with respect to the active metabolite.

C. Food effect: The effect of food on the absorption of losartan administered AM as single 1 X 100 mg tablet was evaluated (Study #015). After coadministration of a standard meal (caloric content = 469 Kcal) the T_{max} increased from 1.3 hours to 2.9 hours, C_{max} decreased by 52% and AUC decreased by 18% for losartan; T_{max} increased from 3.1 hours to 4.8 hours, C_{max} decreased by 24% and AUC decreased by 13% for the active metabolite but the T_{1/2} remained unchanged for losartan and the active metabolite.

II PHARMACOKINETICS:

After a single AM 2 X 50 mg capsule dose, the mean C_{max} was 315 ng/ml (CV 40%), the mean AUC_(0-∞) 816 ng*hr/ml (CV 44%), and the mean T_{max}, 1.5 hours (CV 60%) for losartan; the mean C_{max} was 568 (CV 36%), the mean AUC_(0-∞) 3642 ng*hr/ml (CV 30%),

and the mean Tmax, 3.4 hours (CV 24%) for the active metabolite (Study #007). On multiple dose administration of 2 X 50 mg capsules qd for 9 days, the Cmax was 437 ng/ml (CV 71%), the mean AUC_(0-∞) 662 ng*hr/ml (CV 42%), and the mean Tmax, 0.9 hours (CV 56%) for losartan; the mean Cmax was 547 (CV 33%), the mean AUC_(0-∞) 3341 ng*hr/ml (CV 28%), and the mean Tmax, 2.7 hours (CV 33%) for the active metabolite (Study #007). The accumulation factor was 0.81 for losartan; and 0.93 for the active metabolite (Study #007). On multiple dose administration of 2 X 50 mg capsules qd for 9 days, the renal clearance for losartan increased from 74.3 ml/min to 91.9 ml/min but there was no change in the mean renal clearance of the active metabolite (Study #007). The terminal half-life for losartan across studies was consistent and approximately 2 hours. 11.5% of the dose was recovered in the urine on administration of a 30 mg IV dose, and 4.8% after 100 mg oral solution on AM administration; > 92% of the total radioactivity was recovered in urine and feces over 168 hours following IV and oral losartan (Study #060). The volume of distribution was about 47 liters and the systemic clearance was 558.7 ml/minute for losartan; and the renal clearance (74 ml/min) accounts for about 13% of plasma clearance. Following single IV doses (10 - 80 mg) of the active metabolite to healthy volunteers (Study #060, Study #017) across the studies, the systemic clearance was 50 ml/minute, the volume of distribution was 12 liters, the half-life was about 6.6 hours, the renal clearance was 26 ml/minute and about 53% of the dose was recovered from urine over 96 hours.

III. METABOLISM: Metabolic profiling confirms the presence of three major metabolites in urine and feces, the carboxylic acid metabolite (active), ω-1 hydroxylated metabolite and ω-3 hydroxylated metabolite. The three metabolites, together with losartan account for 85% and 87% of radioactivity in urine (28% and 35% of the dose) for oral and IV doses respectively. The percentage of IV or PO losartan dose converted to the active metabolite is 14%. In vitro studies with specific enzyme inhibitors and recombinant isoforms of human cytochrome P450 indicate that both CYP2C9 and CYP3A4 isoforms are involved in the biotransformation of losartan to its metabolites. About 1% (4 out of about 500) subjects have so far been found who are unable to metabolize losartan (the 4 subjects are all caucasians).

IV. DOSE AND DOSAGE FORM PROPORTIONALITY:

The Cmax and AUC of losartan and its active metabolite were dose proportional between 10 mg and 200 mg single oral doses, as determined by linear regression (Study #003).

V. SPECIAL POPULATIONS:

A. Renal Impairment: Renally insufficient patients with creatine clearances ranging from < 10 ml/min (hemodialysis) to ≥ 75 ml/min were administered AM multiple (100 mg QD for 7 days) oral doses of losartan. Cmax increased (854 to 1615 ng/ml for losartan and 681 to 715 for the active metabolite) with decreasing renal function (Study #012). The AUC increased (1109 to 2066 ng*hr/ml for losartan and 4362 to 5012 ng*hr/ml for the metabolite) but there was no significant change in the Tmax and the half-life in patients with Clcr < 10 ml/min as compared with normal renal function (Study #012). Losartan and the active

metabolite do not appear to be cleared by hemodialysis.

B. Hepatic Impairment: Patients with hepatic insufficiency were administered AM single doses of 50 mg losartan tablet, 10 mg losartan IV solution and 10 mg of the active metabolite IV solution (Study #067). Compared to normal subjects (Study #060, #022, #074) systemic clearance decreased from 559 ml/min (Study #060) to 285 ml/min (Study #067) for losartan and from 47 ml/min (Study #060) to 33 ml/min (Study #067) for the active metabolite; the volume of distribution decreased from 47 liters (Study #060) to 20 liters (Study #067) for losartan and from 10 liters (Study #060) to 9 liters (Study #067) for the active metabolite; the AUC following oral administration of losartan increased (about 5-fold for losartan and about 1.7-fold for the active metabolite); the oral bioavailability of losartan increased by about 100%. The fractional conversion of losartan in systemic circulation to the active metabolite was similar in hepatic and healthy subjects (13 and 14% respectively). Adjustment to lower doses of losartan to patients with hepatic insufficiency should be considered.

C. Elderly and Gender: Hypertensive patients (5 males and 5 females) aged 65 - 75 years were administered AM single doses of 50 mg losartan tablet and 10 mg losartan IV solution (Study #063). Compared to young healthy males (Study #007, #015, #022) the AUC of losartan following oral administration in the elderly increased by between 15 - 32% while the AUC of the metabolite increased between 34 - 59%. Compared to young healthy males the volume of distribution decreased from 40 liters (Study #022) to 29 liters in elderly males (Study #067) for losartan. There is no difference in the systemic clearance of losartan between the young healthy males and the elderly but the renal clearance is decreased in the elderly hypertensive males by about 50%. The renal clearance of the active metabolite is about 17% lower in the elderly. The absolute bioavailability of oral losartan increased from 25% in young, healthy males to 34% in elderly male hypertensives.

Gender analysis of the data for the elderly patients shows that there are differences in the AUC (after PO) of losartan (males - 478 ng/ml.hr; females - 1008 ng/ml.hr), AUC of the active metabolite (males - 2477 ng/ml.hr; females - 2887 ng/ml.hr), systemic clearance (males - 597 ml/min; females - 416 ml/min), renal clearance (males - 46.6 ml/min; females - 32.8 ml/min) and absolute bioavailability (males - 33%; females - 49%). There was no significant difference in the mean volumes of distribution (males - 29 liters, females - 30 liters).

VI. DRUG INTERACTIONS:

A. Warfarin: In Study #070 healthy male volunteers were administered losartan, 100 mg/day for 7 days, or placebo, and administered a single 30 mg dose of warfarin on Day 7, with plasma samples collected for measurement of (R) and (S) warfarin and prothrombin time over the next 6 days as losartan or placebo were continued. Losartan did not affect the pharmacokinetics of (R) and (S) warfarin (AUC, C_{max}, T_{max}, T_{1/2}, λ) and the pharmacodynamic response (prothrombin time) to warfarin.

B. Phenobarbital: After chronic administration of phenobarbital (100 mg q.h.s. for 16 days)

followed by a single dose of losartan (100 mg) there was an induction of cytochrome P-450 (Study #072). Although this resulted in an increase in the amount of 6- β -hydroxycortisol excreted in the urine there was a reduction of about 20% each in the AUC for losartan and its active metabolite; and a reduction of about 20% each in the amounts excreted in the urine for losartan and its active metabolite.

C. Cimetidine: The results of Study #024 in which volunteers received single dose of losartan (100 mg) with and without prior and concurrent administration of cimetidine (400 mg) indicated that with co-administration of cimetidine there is an increase of about 23% in AUC and 36% in C_{max} of losartan but no difference in the pharmacokinetics of the active metabolite of losartan.

D. Digoxin: Study #079 was a double-blind, two-period crossover design in which subjects received 50 mg losartan or placebo for 15 days in each period and single 0.5 mg IV (Day 4) and oral (Day 11) doses of digoxin. There were no significant differences in the pharmacokinetics of digoxin after intravenous or oral digoxin with and without losartan.

E. Hydrochlorothiazide (HCTZ): Study #073 was a randomized, three-period crossover design in which subjects received losartan (50 mg), HCTZ (12.5 mg) or losartan/HCTZ (50 mg/12.5 mg) single oral doses for 7 consecutive days on three separate occasions. The pharmacokinetics of losartan and its active metabolite are not significantly altered by HCTZ but the AUC₀₋₂₄ for HCTZ is decreased by about 17% when co-administered with losartan.

VII. PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIP: The nature of the interactions between losartan (a competitive angiotensin II antagonist) and its active metabolite (a non-competitive angiotensin II antagonist) makes it extremely difficult to simply estimate the specific contribution of losartan or E-3174 to the activity of the drug following single dose administration to humans. Following IV administration (Study #006) of single doses of losartan (40, 80, 120 mg), the systolic BP responses (% inhibition) to exogenous angiotensin II and concentration of E-3174 during 9 hours after dosing were fit to a Hill-Sigmoid-Emax model. The 9-hour areas under the E-3174 concentration and inhibition vs. time curve were fit to an Emax model. A plot of supine diastolic blood pressure change versus E-3174 concentration in hypertensive patients dosed with 20 mg IV infusion of E-3174 (Study #069) resulted in an open hysteresis with a somewhat linear portion up to achievement of maximal concentrations, followed by additional decreases in blood pressure as concentration declined. Following oral losartan (0-150 mg/day) to patients with mild to moderate hypertension for 8 weeks (Study #011), both drug concentration (E-3174) and effect increased with increasing dose of losartan but single measurements of drug concentration at peak, or trough are not highly correlated with drug effect after multiple-dose administration of losartan.

VIII. FORMULATION: The three tablet formulations to be marketed (25, 50 and 100 mg) are compositionally proportional. Their compositions are shown in Table 1 (Attached).

IX. **DISSOLUTION:** The proposed dissolution method of USP Appartus II at 50 rpm, in water is acceptable but the specification should be changed from Q = at 45 minutes to Q = at 30 minutes.

X. **ASSAY:** The sponsor used validated HPLC methods to measure losartan and its active metabolite in all the studies. Overall, the analytical validation was satisfactory.

XI. **PLASMA PROTEIN BINDING:** Both losartan and its active metabolite were extensively bound to plasma protein. The unbound fractions of losartan and its active metabolite for human plasma were 1.3% and 0.2% respectively. Binding of the two drugs was concentration-independent over a wide concentration range (0.1-10 µg/ml), and over the pH range 6.95 to 8.58. Studies with purified human serum albumin and α₁-acid glycoprotein revealed that serum albumin is the major component of plasma protein responsible for the binding of both drugs.

XII. **LABELING:** The clinical pharmacology section of the labeling is deficient and the firm has been advised to modify it accordingly (see comments below).

XIII. **INFLUENCE OF RACE:** The pharmacokinetics of losartan and its active metabolite has not been described in various race groups.

GENERAL COMMENTS TO THE MEDICAL OFFICER:

The sponsor has not demonstrated bioequivalence in terms of C_{max} of losartan between (a) the 100 mg capsule used for early Phase I and Phase II studies and the 100 mg tablet used for Phase III studies; ^{and} (b) the 50 mg tablet formulation manufactured by Merck and used for Phase III studies and the 50 mg tablet formulation manufactured by DuPont-Merck Pharmaceutical Corporation for marketing in USA. It was however noted that the tablet formulation for Phase III and to-be-marketed products are identical except for color. Additionally, PK/PD analysis shows C_{max} of losartan to be a less important parameter than AUC and C_{max} of the active metabolite for which bioequivalence has been demonstrated. In the light of these facts the demonstration of bioequivalence in terms of C_{max} of losartan may not be very critical for deciding on the approval of the NDA.

GENERAL COMMENTS TO THE PHARMACOLOGIST:

The pharmacologist is requested to please note that under the "Carcinogenesis, Mutagenesis, Impairment of Fertility" section of the labeling the toxicology data in animals in relation to humans should be related to exposure rather than doses.

COMMENTS TO BE SENT TO THE FIRM:

1. In the analyses of C_{max} and AUC (Study #022, #074, #075) the firm normalized the

Cmax and AUC for losartan and E-3174 to assayed contents of the oral and IV formulations used for the studies. The firm should note that this approach is not acceptable for biostudies; instead the labelled strength of the formulations should be used.

2. DISSOLUTION: Based on the dissolution data submitted by the sponsor, the dissolution specification should be changed from not less than _____ of the labelled amount of losartan potassium dissolved in 45 min to " *not less than _____ of the labelled amount of losartan potassium dissolved in 30 min*"

3. RARE SUBJECTS: Four subjects have been identified as rare subjects because of their inability to metabolize losartan. The sponsor submitted a protocol to evaluate the cytochrome P-450 system in these subjects in March 1993 and through a telephone conversation with the firm (Dr. Bell) the reviewer was informed that the studies are not yet completed. The firm submitted a preliminary information on 2 of the subjects on October 3, 1994. The sponsor is requested to submit to the Agency the full reports on these rare subjects as soon as they are available.

LABELING COMMENTS:

1. The Clinical Pharmacology section of the labeling should be written under the following sub-sections: *Mechanism of Action, Pharmacokinetics - introductory paragraph (with most important pharmacokinetic features), absorption, distribution, metabolism, excretion, special populations, gender, race, renal insufficiency, hepatic insufficiency, drug interactions as shown below:*

Mechanism of Action
As in the labeling.

Pharmacokinetics:

Losartan's activity is primarily due to the parent drug and the carboxylic acid metabolite. Studies with radiolabeled drug have demonstrated that orally administered losartan is well absorbed into the systemic circulation with approximately 92% of the radiolabel recovered in urine and feces. Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6-9 hours, respectively. During once-daily dosing at 100 mg, neither losartan nor its active metabolite accumulate significantly in plasma.

Absorption

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The absolute bioavailability of losartan is approximately 33%. Losartan's low bioavailability is due to its high presystemic first pass metabolism. Mean peak concentrations of losartan and its active

metabolite are reached in 1 hour and in 3-4 hours respectively. Administration of losartan with standardized meal (18.8 g of protein, 53.8 g of carbohydrate, 19.5 g of fat; caloric content = 469 Kcal) showed that AUC decreased by 18%, C_{max} decreased by 52%, and T_{max} increased from 1.3 to 2.9 hours for losartan; AUC decreased by 13%, C_{max} decreased by 24%, and T_{max} increased from 3.1 to 4.8 hours for the active metabolite.

Distribution

The volume of distribution of losartan is approximately 47 liters while that of its active metabolite is approximately 12 liters. Both losartan and its active metabolite are $\geq 99\%$ bound to plasma proteins, primarily albumin. The unbound fractions of losartan and its active metabolite are respectively 1.3% and 0.2%. Plasma protein binding is constant over the concentration range achieved with recommended doses. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Metabolism

Losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, inactive metabolites are formed, including the ω -1 hydroxylated metabolite and ω -3 hydroxylated metabolite, and a minor metabolite, an N-2 tetrazole glucuronide. The active carboxylic acid metabolite has been evaluated along with losartan in receptor binding studies and has a demonstrated potency about 5 to 10 times of the parent drug. About 14% of an intravenous- or orally-administered dose losartan is converted to the active metabolite. Following oral and intravenous administration of ¹⁴C-labeled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and its active metabolite. In vitro studies with specific enzyme inhibitors and recombinant isoforms of human cytochrome P450 indicate that both CYP2C9 and CYP3A4 isoforms are involved in the biotransformation of losartan to its metabolites. Minimal conversion of losartan to the active metabolite (less than 1% of the dose compared to 14% of the dose in normal subjects) was seen in about one percent of individuals studied.

Excretion

Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% of the dose is excreted in urine as active metabolite. Biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following oral dose of ¹⁴C-labeled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the feces. Following an intravenous dose of ¹⁴C-labeled losartan in man, about 43% of radioactivity is recovered in the urine and 50% in the feces. The pharmacokinetics of losartan and its active metabolite are linear with single oral losartan potassium doses up to 200 mg.

Special Populations

Pediatric

Losartan pharmacokinetics have not been investigated in patients < 18 years of age.

Geriatric and Gender

Losartan Pharmacokinetics have been investigated in the elderly (65-75 years). The renal clearance of losartan is decreased by about 50% in elderly male hypertensives when compared to young healthy males. Plasma concentrations of losartan were about 2-fold higher in female hypertensives as compared to male hypertensives. Concentrations of the active metabolite were not different in males and females.

Race

Pharmacokinetic differences due to race have not been identified.

Renal Insufficiency

Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 ml/min. Compared to patients with normal renal function, the AUC of losartan is approximately 2-fold greater in hemodialysis patients. Plasma concentrations of the active metabolite are not significantly altered in patients with renal impairment or in hemodialysis patients. Neither losartan nor its active metabolite can be removed by hemodialysis.

Hepatic Insufficiency

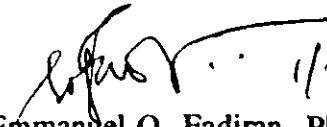
Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were respectively, 5-fold and 1.7-fold greater than those seen in young male volunteers. Compared to normal subjects the volume of distribution of losartan in patients with ~~renal~~ hepatic insufficiency decreased by about 50% but the oral bioavailability increased by about 100%.

Drug Interactions

Losartan did not affect the pharmacokinetics and pharmacodynamics of warfarin. Losartan did not affect the pharmacokinetics of oral or intravenous digoxin. Coadministration of losartan and cimetidine led to an increase of about 23% in AUC of losartan but no difference in the pharmacokinetics of its active metabolite. Coadministration of losartan and phenobarbital led to a reduction of about 20% in the AUC of losartan and that of its active metabolite. There is no interaction between losartan and hydrochlorothiazide.

2. Pharmacodynamics

The following statement should be added to paragraph 4 of the pharmacodynamics section:
" However individual peak or trough concentrations of losartan or the active metabolite do not correlate with antihypertensive effects".

 1/26/95
Emmandel O. Fadiran, Ph.D.
Pharmacokinetics Evaluation Branch

FT Initialed by A. Parekh, Ph.D. Ameeta Parekh 1/27/95
Biopharm Day 9/28/94: Collins, Ludden, Malinowski, Fleischer, Chen, Hepp, Parekh

cc: NDA 20-386, HFD-110, HFD-426 (Fadiran, Fleischer), HFD-427 (M. Chen), Chron,
Drug, Review, FOI (HFD-19), HFD-340 (Vish), DI, F, G, A, RI, PK/PD, H, M

APPENDIX I

METABOLIC PROFILING

STUDY NUMBER: 060-001 **VOLUME:** 1.42 **PAGES:** 1106 - 1360

INVESTIGATOR AND LOCATION:

STUDY PERIOD: June 1992 - July 1992.

OBJECTIVES: (1) To determine the metabolite profiles in plasma and urine after administration of ¹⁴C-losartan to humans; (2) to determine the absorption, distribution, metabolism and elimination of ¹⁴C-losartan when administered by oral and IV routes; (3) to determine if any route of administration-dependent differences in losartan metabolism exists; (4) to determine the fraction of losartan that is metabolized to the active metabolite (E-3174).

FORMULATIONS:

- Radioactive losartan Injection, 30 mg, Formulation # R0954 HSS002A001
- Radioactive losartan Injection, 30 mg (used orally), Formulation # R0954 HSS002A001
- Losartan Injection, 50 mg (used orally), Formulation # 0954 HSS001A001
- E-3174 (Active metabolite) Injection, 50 mg, Formulation # 9519 HSS001A001

STUDY DESIGN:

A randomized, open, three-period cross-over study in 6 healthy volunteers with a washout period of 7 days. ¹⁴C-losartan was administered in the first and third periods as single 100 mg oral (Treatment A) dose (100 μCi) and as a single 30 mg IV (Treatment B) dose (100 μCi). E-3174 (without isotope) was administered as a single 20 mg IV (Treatment C) dose during the second period. For Treatment A, blood samples (11 ml) were collected at 0, .25, .5, .75, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36, and 48 hours; for Treatment B blood samples (11 ml) were collected at 0, 10, 20, 30 minutes, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36, and 48 hours; and for Treatment C blood samples (6 ml) were collected at 0, 10, 20, minutes, 1, 2, 4, 6, 9, 12, 18, 24, 30, and 36 hours. For Treatments A and B urine samples were collected predose (blank) and at 0-2, 2-4, 4-6, 6-8, 8-12, 12-18, 18-24, 24-36, 36-48, 48-72, 72-96 hours; and for Treatment C predose (blank), and at 0-3, 3-6, 6-12, 12-24, 24-36 and 36-48 hours. Feces were collected over 168-hour period following Treatments A and B and fecal samples were assayed radiometrically until negligible radioactivity was observed.

ASSAYS: HPLC with UV detection.

PLASMA SAMPLES - LOSARTAN (MK-954) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curve from 5 to 1000 ng/ml.
Accuracy: Satisfactory. 96.0% at 20 ng/ml, 92.1% at 800 ng/ml for MK-954, and 98.0% at

20 ng/ml, 97.2% at 800 ng/ml for E-3174.

Precision: Satisfactory. %CV - 9.9% at 20 ng/ml, 6.3% at 800 ng/ml for MK-954, and 3.3% at 20 ng/ml, 5.7% at 800 ng/ml for E-3174.

Sensitivity: LOQ - 5 ng/ml.

Specificity: Satisfactory. Chromatograms submitted.

URINE SAMPLES - LOSARTAN (MK-954) AND ACTIVE METABOLTE (E-3174):

Linearity: Satisfactory. Standard curve from 10 to 2000 ng/ml for E-3174 and 20 to 2000 ng/ml for DuP 753..

Accuracy: Satisfactory. 102.0% at 40 ng/ml, 97.6% at 1600 ng/ml for MK-954, and 100.8% at 40 ng/ml, 101.8% at 1600 ng/ml for total E-3174.

Precision: Satisfactory. %CV - 4.2% at 40 ng/ml, 1.0% at 1600 ng/ml for DuP 753, and 1.5% at 40 ng/ml, 2.0% at 1600 ng/ml for E-3174.

Sensitivity: LOQ - 10 ng/ml for E-3174 and 20 ng/ml for MK-954.

Specificity: Satisfactory. Chromatograms submitted.

The assays have been validated over the range of plasma and urine concentrations observed in the study.

DATA ANALYSIS: AUC, Cmax, Tmax, Vdss, λ, CL, CLr, %Dose excreted and bioavailability were calculated.

RESULTS:

Total Radioactivity and Metabolic Profiling (% dose)

	I.V. Losartan 30 mg (100 µCi)		Oral Losartan 100 mg (100 µCi)		
	Urine	Feces		Urine	Feces
Total Radioactivity	43.3 ± 8.4	49.5 ± 13.3		35.2 ± 6.2	57.7 ± 7.9
Metabolic Profile		AN001	AN002		
Losartan	11.4 ± 4.0	12.8	7.77	4.91 ± 2.27	-
L-158,795	9.35 ± 1.73	8.20	8.38	9.09 ± 1.79	-
L-158,641	6.44 ± 2.45	6.92	13.38	6.41 ± 2.22	-
L-158,796	8.24 ± 1.76	7.37	9.44	7.64 ± 1.80	-
L-158,783	0.267 ± 0.109	0.794	1.31	-	-

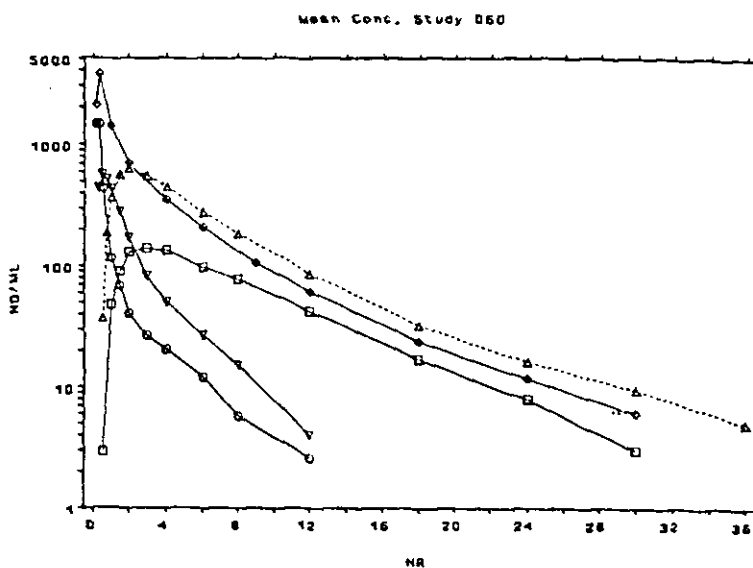
Pharmacokinetics Parameters (mean±S.D.) of Losartan and L-158,641

	Intravenous L-158,641 20 mg	Intravenous Losartan 30 mg (100 µCi)		Oral Losartan (Solution) 100 mg (100 µCi)	
	L-158,641	Losartan	L-158,641	Losartan	L-158,641
C _{20min} , ng/mL	3720.7 ± 342.2	1452.8 ± 636.4	-	-	-
C _{max} , ng/mL	-	-	148.9 ± 78.9	659.1 ± 244.0	652.6 ± 259.1
T _{max} , hr	-	-	4.0 ± 2.1	0.46 ± 0.29	2.33 ± 0.52
AUC _{0-∞} , ng/mL·hr	5969.27 ± 709.03	851.18 ± 234.54	1331.96 ± 490.24	1091.35 ± 397.46	4072.54 ± 1252.91
λ, hr ⁻¹	0.1105 ± 0.0228	0.2181 ± 0.0531	0.1304 ± 0.0501	0.2418 ± 0.0502	0.0881 ± 0.0092
t _{1/2} , hr ^a	6.27 ± 1.36	3.18 ± 0.78	5.32 ± 2.12	2.87 ± 0.57	7.87 ± 0.82
V _{dss} , L	10.33 ± 1.09	46.59 ± 20.50	-	-	-
CL, mL/min	46.93 ± 5.79	558.71 ± 188.01	-	-	-
CL _r , mL/min	25.88 ± 5.59	64.39 ± 25.96	25.25 ± 7.00	64.63 ± 17.28	27.00 ± 6.10
Recovered in Urine (mg)	9.129±1.414	3.020±0.836	1.911±0.616	4.297±1.878	6.516± 2.186
% Dose ^c	55.07 ± 8.95	11.50 ± 3.49	7.59 ± 2.30	4.77 ± 2.08	7.63 ± 2.58
F, % ^b	-	-	-	38.90 ± 14.67	-

^a Harmonic mean and pseudo standard deviation.

^b Oral Bioavailability, geometric mean was 36.47% with 90% confidence interval limits of 26.11% to 50.94%.

^c % dose recovered in the urine as losartan.



Mean Plasma Concentrations of MK-954 and E-3174 in Six Subjects Following the Administration of A Single Intravenous Dose of 30-mg MK-954 (O = MK-954, □ = E-3174), A Single 100-mg Oral Dose of MK-954 (▽ = MK-954, △ = E-3174), and A Single Intravenous Dose of 20-mg E-3174 (○ = E-3174)

CONCLUSION: The study supports the sponsor's labeling claim for the metabolic profiling of losartan following oral or intravenous administration.

DOSE PROPORTIONALITY STUDY (I.V.)

STUDY NUMBER: 013

VOLUME: 1.42

PAGES: 1369 - 1793

INVESTIGATOR AND LOCATION:

OBJECTIVES: To evaluate the safety, tolerability and pharmacokinetics of losartan following administration of the intravenous preparation at several doses.

FORMULATIONS:

Losartan (10 ml fill), Batch No. C-W352, Formulation No. 0954 HSS001A001

Placebo (10 ml fill), Batch No. C-W352, Formulation No. P954 HSS001P001

STUDY DESIGN: Double-blind, randomized, rising-dose, placebo-controlled study in two alternating panels of 9 healthy male subjects per panel. On each study day 6 subjects in each panel received losartan and 3 placebo according to a randomized allocation schedule. Panel I received 1, 10, and 40 mg losartan or placebo and Panel II received 5, and 20 mg losartan or placebo. All doses were administered as a 20-minute infusion with each dose in each subject separated by a 7-day washout period. Plasma samples were drawn at 0, 5, 10, 15, 20, 25, 30, 45, 60, 80, 100 minutes, 2, 3, 4, 5, 6, 8, 10, 16, 24, 30, and 36 hours post-initiation of infusion of losartan. Urine samples were collected at 0-6, 6-12, 12-24, 24-36, and 36-48-hour intervals post-initiation of infusion of losartan.

ASSAYS: HPLC with UV detection.

PLASMA SAMPLES-LOSARTAN (MK-954) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curves from 5 to 1000 ng/ml

Accuracy: Satisfactory. 108.0% at 20 ng/ml, 103.0% at 800 ng/ml for MK-954; and 111.5% at 20 ng/ml, 105.6% at 800 ng/ml.

Precision: Satisfactory. %CV- 6.6% at 20 ng/ml, 4.9% at 800 ng/ml for MK-954; and 4.0% at 20.0 ng/ml, 4.2% at 800 ng/ml.

Sensitivity: LOQ - 5 ng/ml for MK-954 and E-3174.

Specificity: Satisfactory. Chromatograms submitted.

URINE SAMPLES-LOSARTAN (MK-954) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curves from 20 to 2000 ng/ml for MK-954; and

10 to 2000 ng/ml for E-3174.

Accuracy: Satisfactory. 91.0% at 40 ng/ml, 97.8% for 1600 ng/ml for MK-954; and 110.8% at 40 ng/ml, 98.2 % at 1600 ng/ml.

Precision: Satisfactory. %CV- 9.2% at 40 ng/ml, 0.8% at 1600 ng/ml for MK-954; and 11.6% at 40 ng/ml, 0.3% at 1600 ng/ml for E-3174.

Sensitivity: LOQ - 20 ng/ml for MK-954; 10 ng/ml for E-3174.

Specificity: Satisfactory, Chromatograms submitted.

The assays have been validated over the range of plasma and urine concentrations observed in the study.

DATA ANALYSIS: AUC, C_{20min} , $t_{1/2}$, CL, CL_r , V_{dss} , and % Dose excreted in urine were calculated for 10 and 40 doses of losartan.

RESULTS:

Summary of Pharmacokinetic Analysis

Parameter*	Losartan				L-158,641			
	10 mg		40 mg		10 mg		40 mg	
C_{20} (ng/mL)	594	(131)	2501	(564)	—	—	—	—
C_{max} (ng/mL)	—	—	—	—	40	(14)	241	(63)
T_{max} (hr)	—	—	—	—	4.0	(0.9)	2.6	(0.9)
$AUC_{(0-\infty)}$ (ng.hr/mL)	307	(56)	1187	(254)	433	(122)	1786	(369)
$t_{1/2}$ (hr)	2.1	(0.7)	2.2	(0.7)	6.2	(2.3)	6.7	(1.6)
V_{dss} (L)	33	(11)	26	(10)	—	—	—	—
Cl (mL/min)	563	(93)	585	(102)	—	—	—	—
Cl_r (mL/min)	87	(26)	80	(31)	25	(12)	25	(6)
% Dose	15	(2)	16	(4)	5	(1)	7	(1)

* Values are mean (SD) except for $t_{1/2}$ (harmonic mean [pseudo standard deviation])

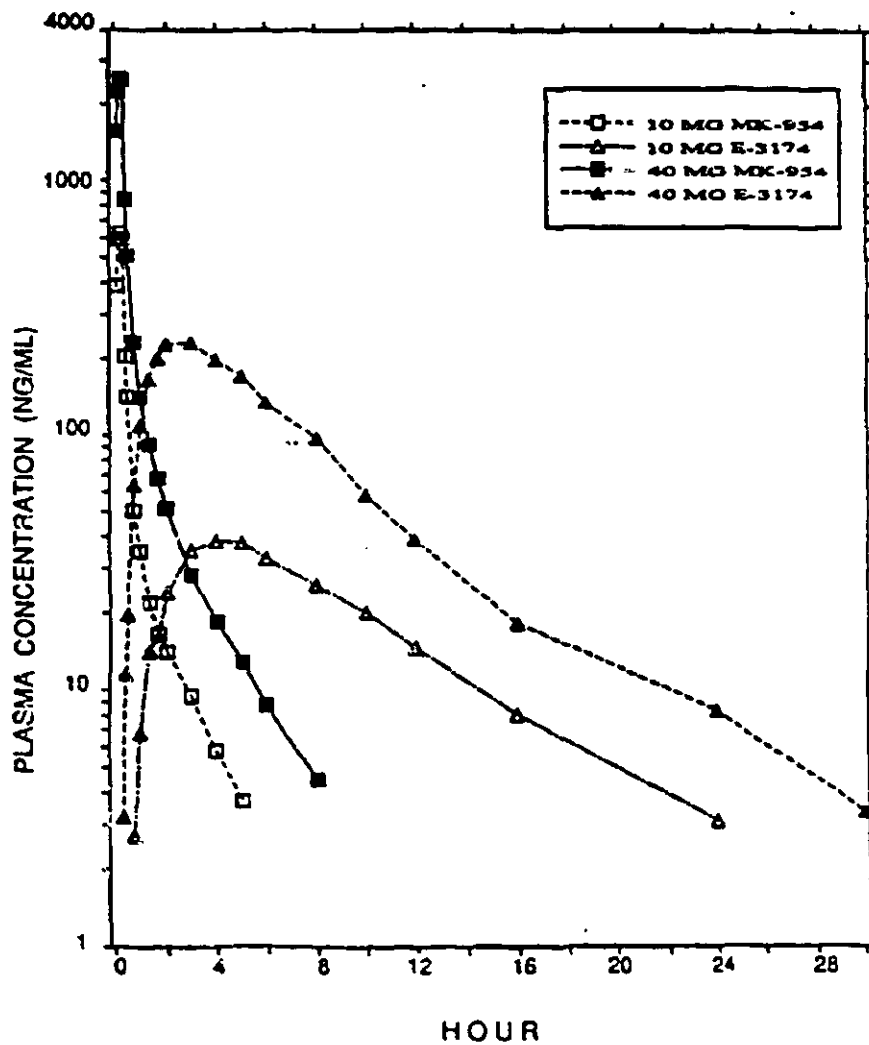
C_{20} = Concentration at end of infusion

Cl = Systemic clearance

Cl_r = Renal clearance

% dose = Percent of dose found in urine (0-48 hours)

Mean Plasma Concentrations of Losartan
and L-158,641 (E-3174) Following 10 mg and 40 mg Losartan (n=6)



CONCLUSION: The study supports the sponsor's claim that the pharmacokinetics of losartan and its active metabolite were dose-independent between the 10- and 40-mg IV doses of losartan.

DOSE PROPORTIONALITY STUDY (METABOLITE)

STUDY NUMBER: 017

VOLUME: 1.43

PAGES: 1794 - 2295

INVESTIGATOR AND LOCATION:

OBJECTIVES: To evaluate the safety, tolerability and pharmacokinetics of E-3174 following administration of the intravenous preparation of E-3174 at several doses.

FORMULATIONS:

E-3174 IV Injection (5 mg/ml; HCl salt), Formulation No. 9519 HSS001a001 (DuPont Lot #901463).

STUDY DESIGN: Double-blind, randomized, rising-dose, placebo-controlled study in two alternating panels of 8 healthy male subjects per panel. On each study day 6 subjects in each panel received E-3174 and 2 placebo according to a randomized allocation schedule. Panel I received 0.1, 1, 10, and 40 mg E-3174 or placebo and Panel II received 0.5, 5, 20, and 80 mg E-3174 or placebo. All doses were administered as a 20-minute infusion with each dose in each subject separated by a 7-day washout period. At doses 1, 5, 10, 20, 40 and 80 mg, plasma samples were drawn at 0, 5, 10, 15, 20, 30, 45, 60, 80, 100 minutes, 2, 3, 6, 9, 12, 16, 24, 30, and 36 hours post-initiation of infusion of E-3174. Urine was collected at 0-6, 6-12, 12-24, 24-36, and 36-48-hour intervals post-initiation of infusion of E-3174.

ASSAYS: HPLC with UV detection.

PLASMA SAMPLES

Linearity: Satisfactory. Standard curve from 5 to 1000 ng/ml.

Accuracy: Satisfactory. 90.0% at 20 ng/ml, 103.8% at 800 ng/ml.

Precision: Satisfactory. %CV - 11.1% at 20 ng/ml, 2.3% at 800 ng/ml.

Sensitivity: LOQ - 5 ng/ml.

Specificity: Satisfactory. Chromatograms submitted.

URINE SAMPLES

Linearity: Satisfactory. Standard curve from 10 to 2000 ng/ml

Accuracy: Satisfactory. 103.5% at 20 ng/ml, 100.8% at 800 ng/ml.

Precision: Satisfactory. %CV - 4.8% at 20 ng/ml, 3.4% at 800 ng/ml.

Sensitivity: LOQ - 10 ng/ml.
 Specificity: Satisfactory. Chromatograms submitted.

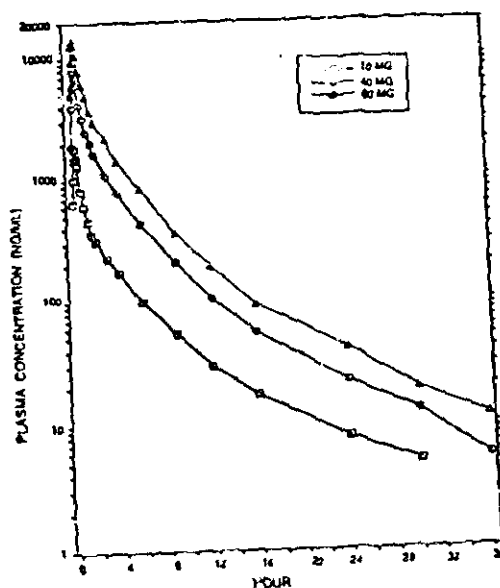
The assays have been validated over the range of plasma and urine concentrations observed in the study.

DATA ANALYSIS: AUC_{∞} , C_{20min} , $t_{1/2}$, CL, CL_r , Vd_{ss} , and % Dose excreted in urine were calculated for 10, 40 and 80 mg doses of E-3174.

RESULTS:

	<u>10 mg</u>	<u>40 mg</u>	<u>80 mg</u>
$C_{20 min}$ (ng/mL)	1818 ± 152	7814 ± 1129	14,305 ± 2676
AUC_{∞} (ng·hr/mL)	2897 ± 407	12,808 ± 2688	24,310 ± 4147
$t_{1/2}$ (hr*)	6.9 ± 5.0	6.5 ± 1.2	6.6 ± 1.2
$v_{d_{ss}}$ (L)	16.4 ± 5.6	10.3 ± 2.4	9.8 ± 1.3
CL (mL/min)	53.0 ± 7.4	48.8 ± 9.5	51.4 ± 11.9
CL_{renal} (mL/min)	27.5 ± 6.1	23.8 ± 4.7	27.9 ± 5.4
% Dose in urine	52.6 ± 2.7	49.2 ± 6.6	54.9 ± 9.7

*Harmonic mean and pseudo standard deviation.



CONCLUSION: The study supports the sponsor's claim that the pharmacokinetics of the active metabolite of losartan were dose-independent between the 10-, 40- and 80-mg IV doses.

DOSE PROPORTIONALITY STUDY

STUDY NUMBER: 003

VOLUME: 1.43 - 1.45

PAGES: 2296 - 3674

INVESTIGATOR AND LOCATION:

STUDY PERIOD: DECEMBER 1989 - MAY 1990.

OBJECTIVES: (i) to determine the safety, tolerability of single doses of losartan (Dup 753) ranging from 10 to 300 mg/day, (ii) to determine preliminary pharmacokinetics, dose proportionality of single doses of DuP 753.

FORMULATIONS:

5 mg losartan capsules, Formulation # DuP 753, lot # 891351

20 mg losartan capsules, Formulation # DuP 753, lot # 891352

50 mg losartan capsules, Formulation # DuP 753, lot # 891353

Placebo capsules lot # 891354

STUDY DESIGN: Single center, double-blind, parallel, placebo-controlled study with 29 male subjects divided into four treatment groups and 7 days washout period between treatments. Each subject received received four single-dose treatments of study drug (three active, one placebo) in rising dose order with respect to active drug and placebo inserted into the sequence according to a random allocation schedule. Group 1 received single doses of 10 mg, 20 mg, and 40 mg; Group 2 received 40 mg, 80 mg, and 120 mg; Group 3 received 120 mg, 150 mg, and 200 mg; and Group 4 received 200 mg, 250 mg and 300 mg. Prior to the start of the active treatment periods, each subject received a single dose of placebo (open label) and blood pressure and ECG recording were measured for a 24-hour period. Blood samples (7ml) were drawn at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 30 hours post dose.

ASSAYS: HPLC with UV detection.

Linearity: Satisfactory. Standard curves from 20 to 1000 ng/ml.

Accuracy: Satisfactory. 99.2% at 83.1 ng/ml, 107.3% at 842.1 ng/ml for DuP 753; and 96.0% at 24.9 ng/ml, 106.52% at 851.3 ng/ml for E-3174.

Precision: Satisfactory. %CV - 2.0% at 83.1 ng/ml, 5.0% at 842.1 ng/ml for DuP 753; and 1.0% at 102.2 ng/ml, 1.9% at 851.3 ng/ml for E-3174.

Sensitivity: LOQ - 20 ng/ml.

Specificity: Satisfactory. Chromatograms submitted.

The assays have been validated over the range of plasma concentrations observed in the study.

DATA ANALYSIS: AUC, $\lambda^{(a)}$, C_{max} , $t_{1/2}$, and T_{max} were calculated.

RESULTS:

Dose (mg)		DuP 763					E-3174				
		C_{max} (ng/mL)	T_{max}^a (hr)	AUC (ng-hr/mL)	$\lambda^{(n)}$ (hr ⁻¹)	$t_{1/2}^b$ (hr)	C_{max} (ng/mL)	T_{max}^a (hr)	AUC (ng-hr/mL)	$\lambda^{(n)}$ (hr ⁻¹)	$t_{1/2}^b$ (hr)
18	Mean	21.1	1.00	94.1	0.4418	1.8	30.3	0.00	434.3	0.0393	17.8
	S.D.	15.9 (0.25-1.50)	NA	NA	NA	NA	15.8 (4.0-8.0)	178.0	NA	NA	
	n	7	5	2	2	2	7	6	6	1	1
20	Mean	71.6	0.50	137.8	0.7437	0.9	68.4	4.00	777.9	0.1266	5.5
	S.D.	35.2 (0.5-2.0)	NA	57.9	0.5327	0.7	35.4 (3.0-6.0)	122.8	0.0182	6.0	
	n	7	7	7	4	4	7	6	6	6	6
40 ^c	Mean	214.8	0.75	391.5	0.4539	1.5	186.7	4.00	1720.8	0.1607	4.3
	S.D.	123.4 (0.5-1.5)	NA	225.5	0.2862	0.7	80.9 (3.0-4.0)	509.2	0.0460	1.3	
	n	15	15	15	14	14	15	14	14	14	14
60	Mean	537.5	0.75	932.7	0.5202	1.1	480.6	3.00	3639.3	0.1669	4.1
	S.D.	226.1 (0.5-1.5)	NA	519.2	0.2269	0.6	181.5 (2.0-4.0)	1451.7	0.0390	1.0	
	n	8	8	8	7	7	8	8	8	8	8
120 ^c	Mean	866.5	1.00	1277.7	0.6111	1.2	987.7	2.00	6333.7	0.1781	3.9
	S.D.	371.3 (0.5-1.5)	NA	572.7	0.2974	0.6	206.2 (1.5-3.0)	1664.1	0.0715	1.6	
	n	15	15	15	15	15	15	15	15	15	15
150	Mean	1141.1	1.00	1678.0	0.4022	1.7	1241.6	1.75	6066.9	0.1610	4.3
	S.D.	364.3 (0.5-2.0)	NA	296.6	0.1194	0.5	236.2 (1.5-3.0)	1735.2	0.0672	1.9	
	n	8	8	8	8	8	8	8	8	8	8
200 ^c	Mean	2177.3	0.75	2371.6	0.4636	1.5	1718.5	1.50	8118.6	0.1454	4.8
	S.D.	826.8 (0.5-1.5)	NA	704.1	0.2471	0.8	452.5 (1.0-3.0)	2110.3	0.0445	1.5	
	n	15	15	15	15	15	15	15	15	15	15
250	Mean	2118.7	1.00	2567.3	0.5410	1.3	2039.9	2.00	9057.8	0.1693	4.1
	S.D.	1442.6 (0.5-2.0)	NA	1862.1	0.5758	1.1	839.3 (1.5-2.0)	2918.9	0.0647	1.0	
	n	7	7	7	7	7	7	7	7	7	7
300	Mean	2870.3	0.50	3492.4	0.5471	1.3	2327.1	2.00	10548.6	0.1426	4.8
	S.D.	1659.8 (0.5-1.0)	NA	1593.8	0.3696	0.9	669.5 (1.5-3.0)	3219.1	0.0233	0.8	
	n	7	7	7	7	7	7	7	7	7	7

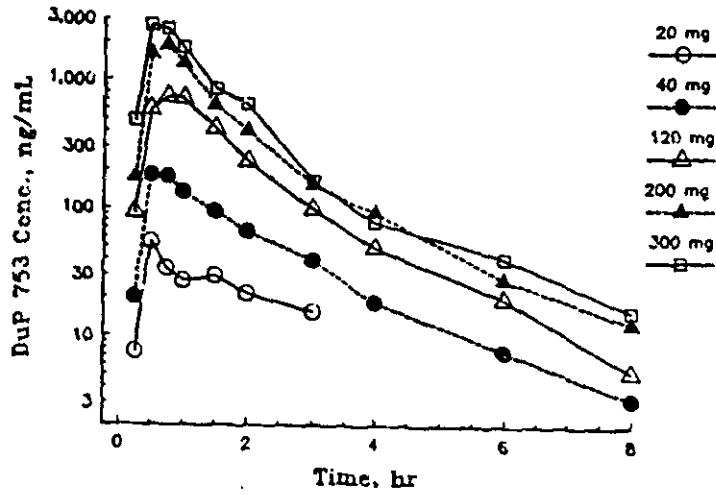
^a Median and range.

^b Harmonic mean and pseudo standard deviation based on the jackknife variance.

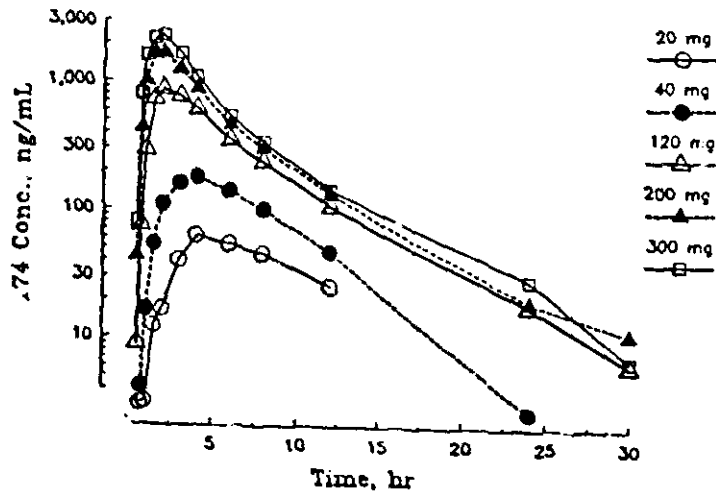
^c Mean and S.D. of all subjects in two groups for this dose.

NA: Not applicable.

Mean Concentration



Mean Concentration



CONCLUSION: The study supports the sponsor's claim that the disposition of losartan (DuP 753) is linear when administered as single, oral doses from 10 - 200 mg to healthy volunteers.

DOSE PROPORTIONALITY STUDY IN PATIENTS

STUDY NUMBER: 004

VOLUME: 1.45 - 1.46

PAGES: 3675 - 4584

INVESTIGATOR AND LOCATION:

STUDY PERIOD: DECEMBER 1989 - JANUARY 1990.

OBJECTIVES: (i) to determine the safety, efficacy, and tolerability of single oral doses of losartan (Dup 753) ranging from 5 to 120 mg/day, (ii) to assess the preliminary pharmacokinetics single doses DuP 753.

FORMULATIONS:

5 mg losartan capsules, Formulation # DuP 753, lot # 891351

20 mg losartan capsules, Formulation # DuP 753, lot # 891352

50 mg losartan capsules, Formulation # DuP 753, lot # 891353

Placebo capsules lot # 891354

STUDY DESIGN: Single center, double-blind, parallel, placebo-controlled study with 20 male patients with mild to moderate essential hypertension divided into two treatment groups and 7 days washout period between treatments. Each patient received received five single-dose treatments of study drug (four active, one placebo) in rising dose order with respect to active drug and placebo inserted into the sequence according to a random allocation schedule. Group 1 received single doses of 5 mg, 20 mg, and 60 and 100 mg; and Group 2 received 10, 40 mg, 80 mg, and 120 mg. all escalations were made in a sequential order relative to the active doses and Group 2 was started three days after Group 1 had started so that the doses were given in a leader follow design. Prior to the start of the active treatment periods, each subject received a single dose of placebo and blood pressure and ECG recording were measured for a 24-hour period. Blood samples (7ml) were drawn at 0, 0.5, 1, 2, 4, 8, 12, and 24 hours post dose.

ASSAYS: HPLC with UV detection.

Linearity: Satisfactory. Standard curves from 15 to 1000 ng/ml.

Accuracy: Satisfactory. 99.2% at 83.1 ng/ml, 107.3% at 842.1 ng/ml for DuP 753; and 96.0% at 24.9 ng/ml, 106.52% at 851.3 ng/ml for E-3174.

Precision: Satisfactory. %CV - 2.0% at 83.1 ng/ml, 5.0% at 842.1 ng/ml for DuP 753; and 1.0% at 102.2 ng/ml, 1.9% at 851.3 ng/ml for E-3174.

Sensitivity: LOQ - 20 ng/ml for DuP 753 and 17 ng/ml for E-3174.

Specificity: Satisfactory. Chromatograms submitted.

The assays have been validated over the range of plasma concentrations observed in the study.

DATA ANALYSIS: $AUC_{0-\infty}$, C_{max} , $t_{1/2}$, CL_o , T_{max} , and $\lambda_{(0)}$ were calculated.

RESULTS:

Pharmacokinetic Parameters

Dose (mg)	Sex	DuP 753						
		Conc (ng/mL)	T_{max}^a (hr)	$AUC_{0-\infty}^b$ (ng·hr/mL)	CL_o (L/min)	$\lambda_{(0)}$ (hr ⁻¹)	$t_{1/2}^c$ (hr)	
5	Mean	12.6	0.75	NA ^d	NA	NA	NA	
	S.D.	17.1	(0.5-3.0)	NA	NA	NA	NA	
	n	10	4	NA	NA	NA	NA	
10	Mean	26.7	0.5	115.3	1.584	NA	NA	
	S.D.	31.1	(0.5-1.0)	41.6	0.574	NA	NA	
	n	8	7	8	8	NA	NA	
20	Mean	124.5	0.5	361.2	1.228	0.500	1.4	
	S.D.	63.8	(0.5-1.0)	345.8	0.784	0.373	0.9	
	n	10	10	7	7	8	8	
40	Mean	308.6	0.5	403.4	1.792	0.498	1.4	
	S.D.	130.3	(0.5-1.0)	143.0	0.472	0.244	0.8	
	n	8	8	8	8	8	8	
80	Mean	571.1	0.5	674.8	1.287	0.677	1.0	
	S.D.	223.1	(0.5-1.0)	280.4	0.353	0.431	0.7	
	n	10	10	10	10	8	8	
100	Mean	471.2	1.0	822.4	1.609	0.558	1.2	
	S.D.	237.8	(0.5-1.0)	212.0	0.478	0.205	0.5	
	n	8	8	8	8	8	8	
120	Mean	643.0	0.75	1323.9	1.267	0.684	1.0	
	S.D.	466.8	(0.5-1.0)	719.4	0.729	0.311	0.3	
	n	10	10	10	10	10	10	

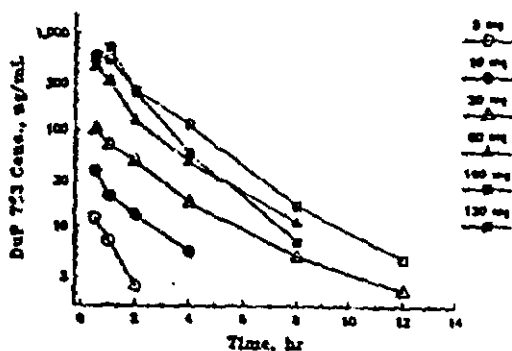
^aMedian ± Range.
^bMean ± SD and pseudo standard deviation based on jackknife variance.
^cNot available.

Pharmacokinetic Parameters

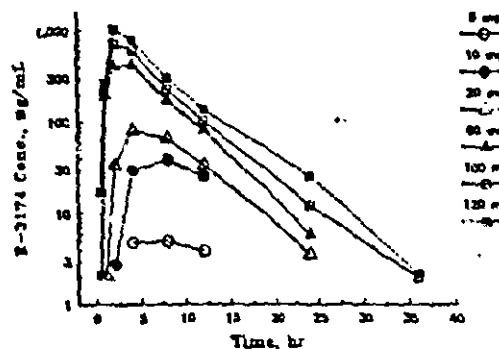
Dose (mg)	Sex	S-3174						
		Conc (ng/mL)	T_{max}^a (hr)	$AUC_{0-\infty}^b$ (ng·hr/mL)	$\lambda_{(0)}$ (hr ⁻¹)	$t_{1/2}^c$ (hr)		
5	Mean	7.2	8.0	288.4	NA ^d	NA		
	S.D.	11.8	(4.0-12.0)	107.4	NA	NA		
	n	10	4	2	NA	NA		
10	Mean	29.5	8.0	529.1	NA	NA		
	S.D.	12.0	(3.0)	123.1	NA	NA		
	n	8	8	7	NA	NA		
20	Mean	89.9	4.0	953.7	0.125	8.5		
	S.D.	64.8	(4.0-8.0)	413.5	0.066	2.8		
	n	10	10	10	8	8		
40	Mean	166.6	4.0	2113.4	0.122	8.2		
	S.D.	100.0	(4.0)	688.0	0.027	1.1		
	n	8	8	8	7	7		
80	Mean	486.5	4.0	2543.0	0.200	3.5		
	S.D.	234.2	(1.0-8.0)	1075.9	0.060	1.0		
	n	10	10	10	8	8		
100	Mean	383.7	4.0	4536.1	0.176	3.8		
	S.D.	237.7	(2.0-4.0)	1260.1	0.047	1.2		
	n	8	8	8	8	8		
120	Mean	636.0	3.0	8056.8	0.209	3.3		
	S.D.	352.3	(1.0-4.0)	1170.0	0.070	1.1		
	n	10	10	10	10	10		

^aMedian and Range.
^bMean ± SD and pseudo standard deviation based on jackknife variance.
^cNot available.

Mean Concentration



Mean Concentration



CONCLUSION: The study supports the sponsor's claim that the disposition of losartan (DuP 753) is linear when administered as single, oral doses from 5 - 120 mg to patients with mild to moderate essential hypertension.

MULTIPLE DOSE PHARMACOKINETICS STUDY

STUDY NUMBER: 007-001 **VOLUME:** 1.46 - 1.47 **PAGES:** 4585 - 5150

INVESTIGATOR AND LOCATION:

STUDY PERIOD: SEPTEMBER 1990 - SEPTEMBER 1990.

OBJECTIVES: To determine whether the pharmacokinetics of losartan change with multiple dosing; to investigate the possibility of drug and/or metabolite accumulation during multiple dose administration, to determine the safety, tolerability, and hemodynamic effects of losartan in normotensive volunteers and to investigate the effects of losartan on renin, angiotensin II, and aldosterone.

FORMULATIONS:

50 mg losartan capsules, lot # C-W166, Formulation # 0954DFC002C003;
Matching Placebo capsules lot # C-166, Formulation # P095DFC001C002.

STUDY DESIGN: Double-blind, parallel, placebo-controlled, three-phase study with 14 male subjects and a placebo run-in day, followed by 1-day single dose phase and a 7-day multiple dose phase. Ten of the subjects received 2x50 mg losartan capsules once daily on Days 1, 3 - 9; while the other four subjects received placebos. Plasma samples were drawn at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 7, 8, 12, 18, 24, 30, and 36 hours post dose; trough predose samples were drawn on Days 5, 7, and 8. Urine was collected at 0-6-, 6-12-, 12-24-, 24-36-, and 36-48-hour intervals on Day 1 and at 0-6-, 6-12- and 12-24-hour intervals on Day 9. Subjects were fasted the nights before Days 1 and 9. Plasma samples for plasma renin activity, angiotensin II, aldosterone, norepinephrine and epinephrine were collected periodically.

ASSAYS: HPLC with UV detection.

PLASMA SAMPLES - LOSARTAN (DuP 753) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curves from 5 to 1000 ng/ml.

Accuracy: Satisfactory. 96.0% at 20 ng/ml, 92.1% at 800 ng/ml for DuP 753, and 98.0% at 20 ng/ml, 97.2% at 800 ng/ml for E-3174.

Precision: Satisfactory. %CV - 9.9% at 20 ng/ml, 6.3% at 800 ng/ml for DuP 753, and 3.3% at 20 ng/ml, 5.7% at 800 ng/ml for E-3174.

Sensitivity: LOQ - 5 ng/ml.

Specificity: Satisfactory. Chromatograms submitted.

URINE SAMPLES - LOSARTAN (DuP 753) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curve from 10 to 2000 ng/ml for E-3174 and 20 to 2000

ng/ml for DuP 753..

Accuracy: Satisfactory. 102.0% at 40 ng/ml, 97.6% at 1600 ng/ml for DuP 753, and 100.8% at 40 ng/ml, 9101.8% at 1600 ng/ml for E-3174.

Precision: Satisfactory. %CV - 4.2% at 40 ng/ml, 1.0% at 1600 ng/ml for DuP 753, and 1.5% at 40 ng/ml, 2.0% at 1600 ng/ml for E-3174.

Sensitivity: LOQ - 10 ng/ml for E-3174 and 20 ng/ml for Dup 753.

Specificity: Satisfactory. Chromatograms submitted.

The assays have been validated over the range of plasma and urine concentrations observed in the study.

DATA ANALYSIS: AUC_{24} , AUC_{∞} , C_{max} , $t_{1/2}$, CL_r , T_{max} , % Dose excreted in urine and accumulation factors for DuP 753 and E-3174 were calculated.

The accumulation factor was calculated for the final dose from:

$$\frac{AUC_{24}(\text{Day9})}{AUC_{24}(\text{Day1})}$$

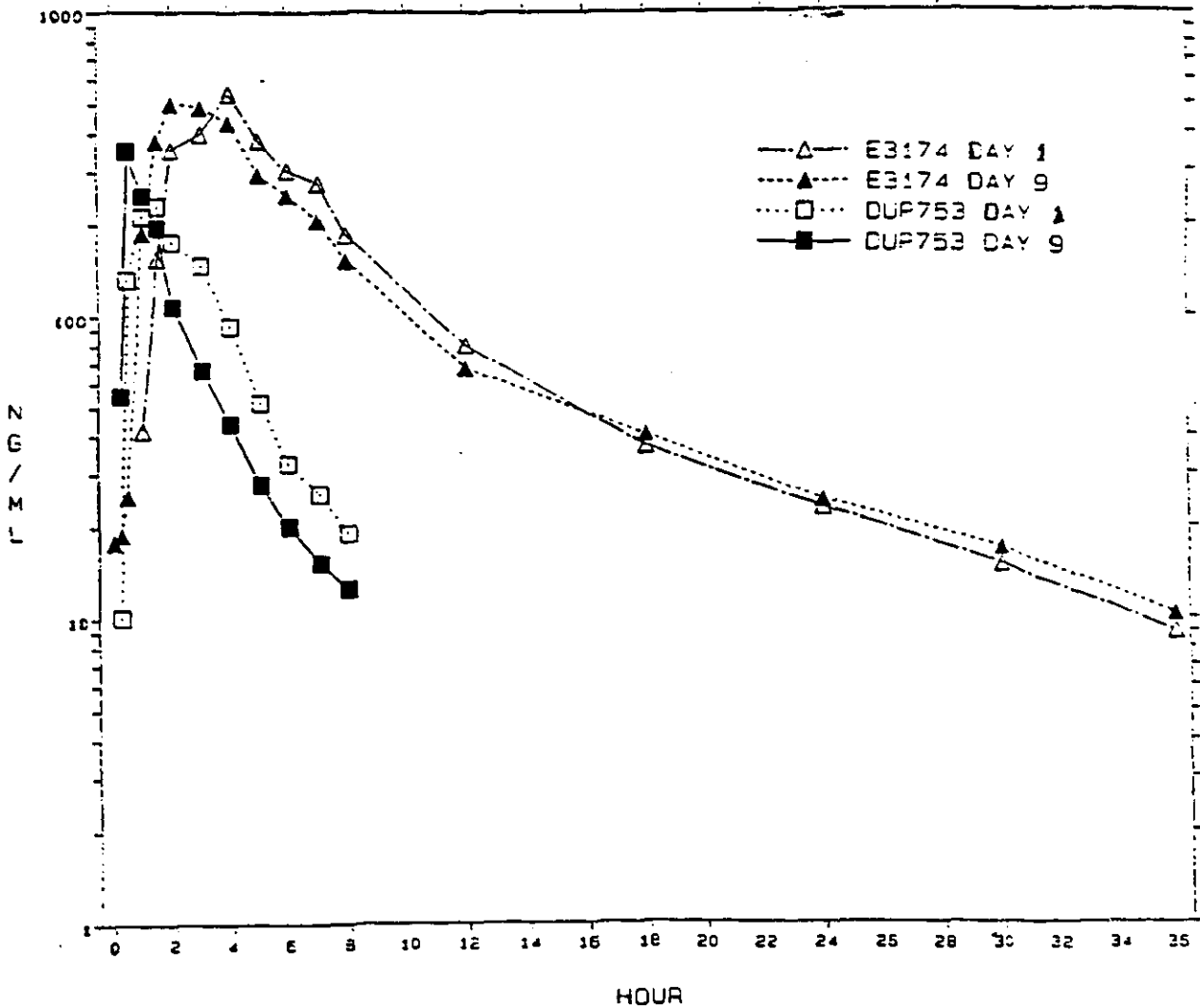
Or

$$\frac{AUC_{24}(\text{Day9})}{AUC_{\infty}(\text{Day1})}$$

RESULTS:

	DuP 753		E-3174	
	Day 1	Day 9	Day 1	Day 9
C_{max} , ng/ml	315 ± 126	437 ± 312	568 ± 205	547 ± 179
T_{max} , hr	1.5 ± 0.9	0.9 ± 0.5	3.4 ± 0.8	2.7 ± 0.9
AUC_{24} , ng·hr/ml	814 ± 355	662 ± 276	3342 ± 1031	3341 ± 924
AUC_{∞} , ng·hr/ml	816 ± 357	—	3642 ± 1105	—
$t_{1/2}$, hr	2.0 ± 0.7	2.2 ± 0.8	9.0 ± 1.7	9.1 ± 1.6
CL_r , ml/min.	74 ± 18	92 ± 24	25 ± 5	27 ± 6
% Dose	3.5 ± 1.0	3.6 ± 1.7	5.6 ± 1.7	5.8 ± 2.1
$\frac{AUC_{24}(\text{Day 9})}{AUC_{24}(\text{Day 1})}$		0.95 ± 0.17*		1.02 ± 0.13
$\frac{AUC_{24}(\text{Day 9})}{AUC_{\infty}(\text{Day 1})}$		0.95 ± 0.17*		0.93 ± 0.11

*Corrected by renal clearances.



CONCLUSION: The study supports the sponsor's labeling claim that during once-daily dosing at 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.

COMMENT:

Losartan renal clearance increased by about 24% upon multiple dose administration and the sponsor corrected for this increase in the calculation of the accumulation factor for losartan. There is no rationale for this correction. Without the correction the accumulation factor for losartan will be 0.81.

ABSOLUTE ORAL BIOAVAILABILITY

STUDY NUMBER: 074

VOLUME: 1.47

PAGES: 5151 - 5423

INVESTIGATOR AND LOCATION:

STUDY PERIOD: SEPTEMBER 1992 - OCTOBER 1992.

OBJECTIVES: (i) to assess the absolute bioavailability of oral losartan using final process biobatch tablets, (ii) to compare the plasma concentration profile of the metabolite L-158,641 (E-3174) following administration of losartan, 50 mg orally and 20 mg intravenously.

FORMULATIONS:

50 mg losartan Tablet, Formulation # 0954FCT017C001

5 mg/ml losartan Injection, Formulation # 0954HSS001A003

STUDY DESIGN: Randomized, open, two-period, crossover study with 12 subjects and a wash period of 7 days. Subjects received a single dose of 50 mg losartan tablet during the first period (Treatment A) and 20 mg losartan solution (20 minute IV infusion, Treatment B) during the second period. Subjects fasted from midnight before and until 3 hours postdose on both study days. Blood samples (8 ml) were collected 0, .25, .5, .75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 30, and 36 hours after the oral administration of losartan; and at 0, 5, 10, 15, 20, 23, 26, 30, 45 and 90 minutes, 2, 3, 4, 5, 6, 8, 12, 18, 24, and 30 hours after IV administration. Urine samples were collected predose (blank) and at 0-3, 3-6, 6-12, 12-36, and 36-48 hours.

ASSAYS: HPLC with UV detection.

PLASMA SAMPLES - LOSARTAN (DuP 753) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curves from 5 to 1000 ng/ml.

Accuracy: Satisfactory. 96.0% at 20 ng/ml, 98.8% at 800 ng/ml for DuP 753; and 105.0% at 20 ng/ml, 105.2% at 800ng/ml for E-3174.

Precision: Satisfactory. %CV - 4.0% at 20 ng/ml, 1.5% at 800 ng/ml for DuP 753; and 4.6% at 20 ng/ml, 3.6% at 800 ng/ml for E-3174.

Sensitivity: LOQ - 5 ng/ml.

Specificity: Satisfactory. Chromatograms submitted.

URINE SAMPLES - LOSARTAN (DuP 753) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curves from 10 to 2000 ng/ml.

Accuracy: Satisfactory. 92.0% at 40 ng/ml, 96.6% at 1600 ng/ml for DuP 753, and 103.0% at 40 ng/ml, 100.7% at 1600 ng/ml for E-3174.

Precision: Satisfactory. %CV - 3.4% at 40 ng/ml, 0.8% at 1600 ng/ml for DuP 753, and 3.4% at 40 ng/ml, 2.7% at 1600 ng/ml for E-3174.

Sensitivity: LOQ - 10 ng/ml .

Specificity: Satisfactory. Chromatograms submitted.

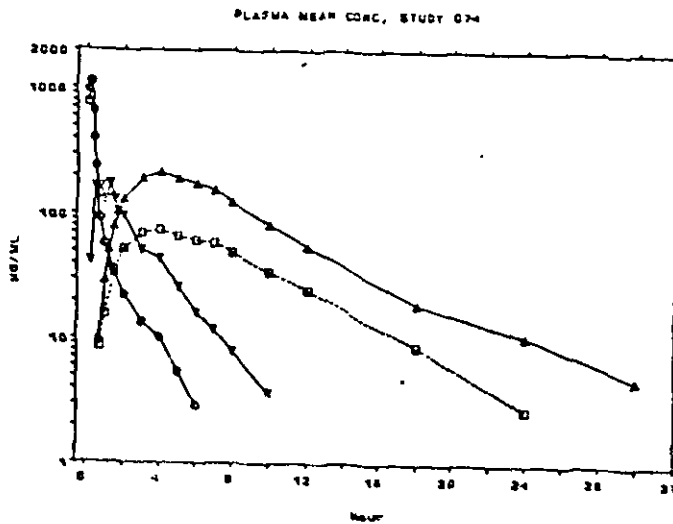
The assays have been validated over the range of plasma and urine concentrations observed in the study.

DATA ANALYSIS: AUC_{∞} , C_{max} , $t_{1/2}$, Cl, CLr, T_{max} , vd_{ss} , %Dose excreted in urine, absolute bioavailability and $\lambda_{(a)}$ were calculated.

RESULTS:

	Losartan 20 mg Intravenous Dose		Losartan 50 mg Oral Dose	
	Losartan	L-158,641	Losartan	L-158,641
C_{max} , ng/mL ^a	--	76.4 ± 30.4	296.4 ± 217.0	249.4 ± 73.7
T_{max} , hr	--	4.17 ± 0.58	1.02 ± 0.52	4.09 ± 1.56
$T_{1/2}$, hr ^b	1.81 ± 0.60	4.55 ± 1.30	2.13 ± 0.54	6.42 ± 2.29
AUC , ng-hr/mL ^a	538.69 ± 94.87	744.40 ± 272.36	475.56 ± 199.55	1915.25 ± 537.82
AUC , ng-hr/mL (geometric mean) ^a	531.1	--	433.6	--
λ , hr ⁻¹	0.3836 ± 0.1253	0.1524 ± 0.0438	0.3260 ± 0.0829	0.1080 ± 0.0379
Vd_{ss} , L	28.36 ± 13.61	--	--	--
CL, mL/min	635.95 ± 107.40	--	--	--
CL _r , mL/min	72.14 ± 20.76	28.36 ± 5.95	72.04 ± 20.60	25.91 ± 6.90
Urinary Recovery	mg	2.353 ± 0.501	1.195 ± 0.355	2.061 ± 0.853
	% dose	11.97 ± 2.50	6.54 ± 2.33	4.20 ± 1.74
Absolute Bioavailability	--	--	32.6(25.3, 42.1) ^c	--

^a Data normalized to 20.0 mg I.V. and 50.0 mg p.o. dose based on assay potency.
^b Harmonic mean and pseudo standard deviation.
^c Geometric mean with 90% confidence interval.



CONCLUSION: The study supports the sponsor's labeling claim of an absolute bioavailability of about 33%.

BIOEQUIVALENCE / BIOAVAILABILITY STUDY

STUDY NUMBER: 075

VOLUME: 1.48

PAGES: 5424 - 5893

INVESTIGATOR AND LOCATION:

STUDY PERIOD: OCTOBER 1992 - NOVEMBER 1992.

OBJECTIVES: (i) to assess the bioequivalence of 50 mg DuPont-Merck losartan tablet (DMPC) compared to the 50 mg Merck losartan tablet (MRL), (ii) to assess the relative bioavailability of the 50 mg DuPont-Merck capsule compared to the 50 mg losartan tablet, (iii) to compare the plasma concentration profile of the metabolite L-158,641 following administration of the 50 mg Merck losartan tablet, 50 mg DuPont-Merck losartan capsule and 50 mg DuPont-Merck losartan tablet.

FORMULATIONS:

50 mg losartan Tablet (MRL), Formulation # 0954FCT005C003 (Used for Phase III studies)
50 mg losartan Tablet (DMPC), Formulation # 0954FCT018C001 (To be marketed in US)
50 mg losartan Capsule (DMPC), Formulation # 0954DFC002C013 (Used for Phase IIb dose-response study).

STUDY DESIGN: Randomized, three-period, crossover study with 30 subjects and a wash period of 7 days. Subjects received single dose of the 50 mg Merck tablet (Treatment A), the DuPont-Merck tablet (Treatment B) and the DuPont-Merck capsule (Treatment C). Subjects fasted from midnight before and until 3 hours postdose on all of the study days. Blood samples (8 ml) were collected 0, .25, .5, .75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 30, and 36 hours after the oral administration of losartan. A sequential approach was employed towards the data analysis and analysis was completed at Stage I (N= 18 subjects).

ASSAYS: HPLC with UV detection.

Linearity: Satisfactory. Standard curves from 5 to 1000 ng/ml.

Accuracy: Satisfactory. 97.5% at 20 ng/ml, 97.1% at 800 ng/ml for DuP 753; and 100.5% at 20 ng/ml, 101.2% at 800ng/ml for E-3174.

Precision: Satisfactory. %CV - 2.7% at 20 ng/ml, 1.9% at 800 ng/ml for DuP 753; and 3.5% at 20 ng/ml, 3.6% at 800 ng/ml for E-3174.

Sensitivity: LOQ - 5 ng/ml.

Specificity: Satisfactory. Chromatograms submitted.

The assays have been validated over the range of plasma concentrations observed in the study.

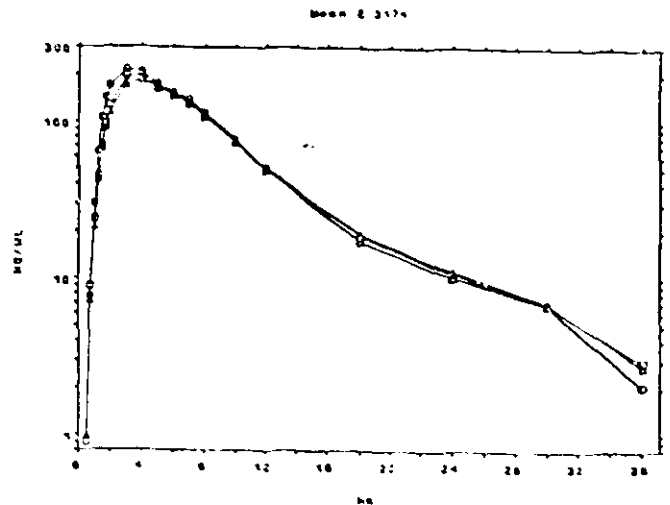
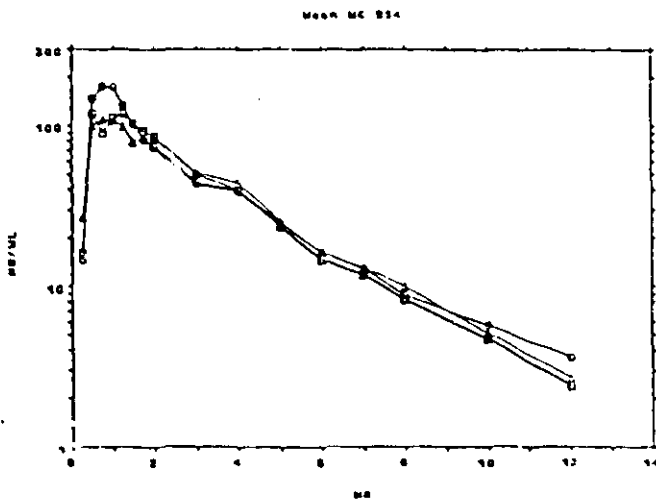
DATA ANALYSIS: AUC_{∞} , C_{max} , $t_{1/2}$, λ and T_{max} , were calculated.

RESULTS:

	MK-954 ^a		
	Merck Tablet, n = 18	DuPont-Merck Tablet, n = 17	DuPont-Merck Capsule, n = 18
C_{max} , ng/ml	204.0 ± 99.4	183.40 ± 79.8	245.0 ± 110.3
T_{max} , hr	1.24 ± 0.86	1.23 ± 1.02	0.91 ± 0.41
AUC_{∞} , ng hr/ml	417.28 ± 115.23	419.08 ± 125.94	451.31 ± 118.45
λ , hr ⁻¹	0.2990 ± 0.1320	0.2631 ± 0.1143	0.2699 ± 0.1421
$t_{1/2}$, hr ^b	2.32 ± 1.03	2.53 ± 1.12	2.57 ± 1.38

	E-3174 ^a		
	Merck Tablet, n = 17	DuPont-Merck Tablet, n = 16	DuPont-Merck Capsule, n = 17
C_{max} , ng/ml	225.4 ± 116.7	203.1 ± 90.1	236.5 ± 99.1
T_{max} , hr	4.47 ± 1.70	4.69 ± 1.89	3.82 ± 1.55
AUC_{∞} , ng hr/ml	1778.33 ± 434.30	1769.55 ± 414.26	1834.95 ± 343.32
λ , hr ⁻¹	0.0753 ± 0.0179	0.0783 ± 0.0189	0.0828 ± 0.0211
$t_{1/2}$, hr ^b	9.21 ± 2.23	8.8 ± 2.24	8.37 ± 2.16

^a C_{max} and AUC_{∞} normalized to 50.0 mg based on assayed potencies of the formulations.
^bHarmonic mean and pseudo standard deviation.



Mean Plasma Concentrations (ng/ml) of MK-954 and E-3174 Following Oral Administration of 50-mg Merck Tablet (□), DuPont-Merck Tablet (△) and DuPont-Merck Capsule (○)

RESULTS:**Bioequivalence:****DMPC Tablet vs. Merck Tablet**

Compound	Variable	N	Ratio Analyses		Difference Analyses	
			Geometric Mean Ratio	Conf. Int. W/O Zero	Diff. in Arith. Means	Conf. Int. W/O Zero
Losartan	AUC (ng*hr/mL)	17	0.97	(0.89,1.07)	-	-
	C _{max} (ng/mL)	17	0.90	(0.69,1.17)	-23.3	(-76.9,+30.3)
	T _{max} (hours)	17	-	-	+0.06	(-0.46,+0.58)
L-158,641	AUC (ng*hr/mL)	16	0.97	(0.91,1.05)	-	-
	C _{max} (ng/mL)	16	0.90	(0.81,1.02)	-22.9	(-45.5,-0.3)
	T _{max} (hours)	16	-	-	+0.17	(-0.61,+0.95)

Relative Bioavailability:**DMPC Capsule vs. Merck Tablet**

Compound	Variable	N	Ratio Analyses		Difference Analyses	
			Geometric Mean Ratio	Conf. Int. w/o Zero	Diff. in Arith. Means	Conf. Int. w/o Zero
Losartan	AUC (ng*hr/mL)	18	1.09	(0.99,1.19)	-	-
	C _{max} (ng/mL)	18	1.20	(0.92,1.56)	+41.0	(-11.8,+93.8)
	T _{max} (hours)	18	-	-	-0.33	(-0.84,+0.18)
L-158,641	AUC (ng*hr/mL)	17	1.08	(1.00,1.15)	-	-
	C _{max} (ng/mL)	17	1.09	(0.97,1.22)	+11.4	(-10.9,+33.7)
	T _{max} (hours)	17	-	-	-0.66	(-1.43,+0.11)

CONCLUSIONS: (i) DuPont-Merck tablet is bioinequivalent to Merck tablet with respect to losartan but bioequivalent with respect to the active metabolite (E-3174); (ii) DuPont-Merck capsule is bioinequivalent to Merck tablet with respect to losartan but bioequivalent with respect to the active metabolite (E-3174).

BIOEQUIVALENCE / BIOAVAILABILITY STUDY

STUDY NUMBER: 022

VOLUME: 1.48

PAGES: 5894 - 6147

INVESTIGATOR AND LOCATION:

STUDY PERIOD: APRIL 1991 - MAY 1991.

OBJECTIVES: (i) to assess the bioequivalence of 100 mg losartan tablets as compared to the 100 mg losartan capsule, (ii) to assess the absolute bioavailability of oral, (iii) to compare the plasma concentration profile of the metabolite L-158,641 following administration of the 100 mg tablet, as compared to 100 mg losartan capsule, and (iv) to compare the plasma concentration profile of the metabolite L-158,641 following administration of losartan, 100 mg orally and 30 mg intravenously.

FORMULATIONS:

100 mg losartan Capsule, Batch # C-W737, Formulation # 0954DFC01D003 (Used for Phases I & II Studies)

100 mg losartan Tablet, Batch # C-W738, Formulation # 0954FCT004D001 (Used for Phase III Studies)

5 mg/ml losartan Solution, Batch # C-W739, Formulation # 0954HSS001a001

STUDY DESIGN: Randomized (Periods I and II only), open, three-period, crossover study with 8 subjects and a wash period of 7 days. Subjects received 100 mg losartan tablet (Treatment A) and 100 mg losartan capsule (Treatment B) during Periods I and II. During Period III, subjects received 30 mg losartan solution (Treatment C) as a 20-minute IV infusion. Subjects fasted from midnight before and until 3 hours postdose on all of the study days. Blood samples (8 ml) were collected 0, 10, 30, 40, 50 minutes, 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 10, 12, 18, 24, 30, and 36 hours after the oral administration of losartan; and at 0, 2, 4, 8, 12, 16, 20, 22, 26, 30, 50, 60, 80, 100, minutes, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, and 30 after IV administration. Urine samples were collected predose (blank) and at 0-3, 3-6, 6-12, 12-24, 24-36, and 36-48 hours.

ASSAYS: HPLC with UV detection.

PLASMA SAMPLES - LOSARTAN (MK-954) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curves from 5 to 1000 ng/ml.

Accuracy: Satisfactory. 98.0% at 20 ng/ml, 102.5% at 800 ng/ml for MK-954 and 96.5% at 20 ng/ml, 98.6% at 800ng/ml for E-3174.

Precision: Satisfactory. %CV - 5.9% at 20 ng/ml, 5.4% at 800 ng/ml for MK-954; and

Sensitivity: LOQ - 5 ng/ml.
 Specificity: Satisfactory. Chromatograms submitted.

URINE SAMPLES - LOSARTAN (MK-954) AND ACTIVE METABOLTE (E-3174):

Linearity: Satisfactory. Standard curve from 10 to 2000 ng/ml for E-3174 and 20 to 2000 ng/ml for MK-954..

Accuracy: Satisfactory. 103.8% at 40 ng/ml, 101.4% at 1600 ng/ml for MK-954; and 105.0% at 40 ng/ml, 100.3% at 1600 ng/ml for total E-3174.

Precision: Satisfactory. %CV - 6.3% at 40 ng/ml, 1.6% at 1600 ng/ml for MK-954; and 2.8% at 40 ng/ml, 1.4% at 1600 ng/ml for E-3174.

Sensitivity: LOQ - 10 ng/ml for E-3174 and 20 ng/ml for MK-954.

Specificity: Satisfactory. Chromatograms submitted.

DATA ANALYSIS: AUC_{∞} , C_{max} , T_{max} , $t_{1/2}$, vd_{ss} , Cl , Cl_r , F , and % Dose excreted in urine were calculated.

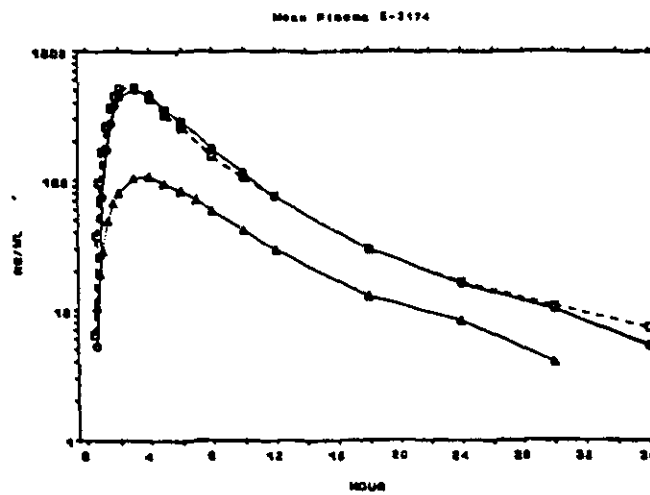
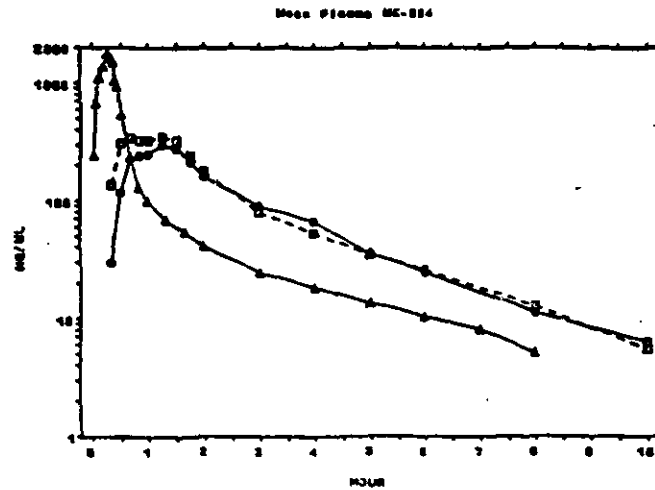
RESULTS:

	MK-954 ^a		
	Tablet	Capsule	I.V.
C_{max} , ng/ml	486.2 ± 231.7	570.1 ± 260.3	-
T_{max} , hr	1.4 ± 0.8	0.9 ± 0.5	-
AUC_{∞} , ng·hr/ml	722.4 ± 375.8	821.0 ± 421.3	925.6 ± 349.7
$t_{1/2}$, hr	1.9 ± 0.5	2.1 ± 0.40	2.3 ± 0.9
Vd_{ss} , L	-	-	40.2 ± 13.0
Cl , ml/min	-	-	618 ± 247
Cl_{renal} , ml/min	90 ± 42	79 ± 35	76 ± 39
% Dose in urine	3.7 ± 1.3	3.6 ± 1.0	11.6 ± 2.5
F_{tab}	0.23 (0.17 - 0.30) ^b		-
F_{cap}	0.25 (0.18 - 0.34) ^b		
F_{rel} (tab/cap)	0.93 (0.69 - 1.24) ^b		
C_{max} ratio (tab/cap)	0.86 (0.55 - 1.32) ^b		

	E-3174 ^a		
	Tablet	Capsule	I.V.
C_{max} , ng/ml	584 ± 120	547 ± 105	-
T_{max} , hr	3.1 ± 1.0	2.6 ± 0.6	-
AUC_{∞} , ng·hr/ml	3561 ± 686	3458 ± 542	1066 ± 198
$t_{1/2}$, hr	8.3 ± 1.2	9.1 ± 1.2	7.7 ± 1.8
Cl_{renal} , ml/min	23 ± 6	25 ± 6	24 ± 5
% Dose in urine	5.0 ± 1.7	5.4 ± 1.6	5.3 ± 1.5
C_{max} ratio (tab/cap)	1.07 (0.93 - 1.23) ^b		
AUC ratio (tab/cap)	1.02 (0.96 - 1.09) ^b		

^a C_{max} and AUC values for MK-954 and E-3174 were normalized to nominal doses of 100.0 mg (oral) and 30.0 mg (i.v.) based on actual doses given.

^b90% confidence interval limits.



Mean Plasma Concentrations of MK-954 and E-3174 Following 100 mg of MK-954 Tablet (o, n = 8), 100 mg of MK-954 Capsule (□, n = 8) and 30 mg of MK-954 I.V. Infusion (Δ, n = 7).

CONCLUSIONS: (i) the absolute bioavailability of the 100 mg tablet used for Phase III studies is 23%; (ii) the absolute bioavailability of the 100 mg capsule used for Phases I & II studies is 25%; (iii) the 100 mg capsule used for Phases I & II studies is bioequivalent to 100 mg tablet used for Phase III studies with respect to losartan but bioequivalent with respect to the active metabolite (E-3174).

FOOD EFFECT STUDY

STUDY NUMBER: 015

VOLUME: 1.49

PAGES: 6148 - 6476

INVESTIGATOR AND LOCATION:

STUDY PERIOD: DEC. 1990 - FEB. 1991.

OBJECTIVES: (i) to investigate the effect of a standard meal on the plasma concentration profiles of losartan following administration of a single oral dose of losartan 100 mg; (ii) to determine whether any food effect on absorption has pharmacodynamic consequences as measured by an effect on losartan-induced increases in plasma renin activity and angiotensin II activity; (iii) to provide preliminary data on the absorption of losartan following administration of the tablet formulation.

FORMULATIONS:

100 mg losartan (MK-954) Tablet, Batch # C-W438, Formulation # 0954FCT004D001.

STUDY DESIGN: Randomized, open, two-period crossover study with 8 subjects and a wash period of 5-7 days. Subjects received a single 100 mg oral dose of losartan on two occasions (once under fasting conditions and once under fed conditions). Subjects fasted overnight prior to dosing, the fed were given a standard meal immediately prior to dosing and then fasted for at least four hours while the fasted group remained fasting for at least four hours post dose. Blood samples (8 ml) were collected 0, 10, 30, 40, 50 minutes, 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 10, 12, 18, 24, 30, and 36 hours post dose.

The standard meal consisted of :

- 1 fried egg
- 2 pieces of toast
- 20 g jelly or marmalade
- 2 strips of bacon
- 150 ml of whole milk
- 100 ml orange juice

Caloric content = 469 Kcal (18.8 g of protein, 53.8 g of carbohydrate, 19.5 g of fat).

Blood samples for measurement of plasma renin activity and angiotensin II concentration were obtained at -1, 2, 4, 6, 8, 12 and 24 hours post dose.

ASSAYS: HPLC with UV detection

Linearity: Satisfactory. Standard curves from 5 to 1000 ng/ml.

Accuracy: Satisfactory. 98.0% at 20 ng/ml, 97.4% at 800 ng/ml for MK-954; and 97.9% at 20 ng/ml, 99.6% at 800ng/ml for E-3174.

Precision: Satisfactory. %CV - 6.2% at 20 ng/ml, 4.2% at 800 ng/ml for MK-954; and 7.5% at 20 ng/ml, 5.3% at 800 ng/ml for E-3174.

Sensitivity: LOQ - 5 ng/ml.

Specificity: Satisfactory. Chromatograms submitted.

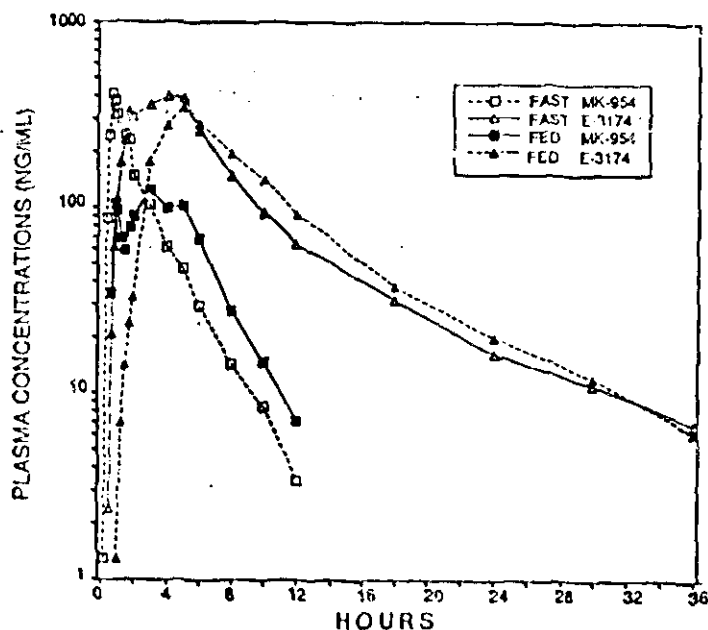
The assays have been validated over the range of plasma concentrations observed in the study.

DATA ANALYSIS: AUC_{∞} , C_{max} , T_{max} and $t_{1/2}$ were calculated.

RESULTS:

	MK-954		E-3174	
	Fasted	Fed	Fasted	Fed
C_{max} , ng/ml	514 ± 199	267 ± 166	502 ± 124	415 ± 189
T_{max} , hr	1.3 ± 0.8	2.9 ± 1.7	3.1 ± 1.3	4.8 ± 1.2
AUC_{∞} , ng·hr/ml	826 ± 181	681 ± 163	3097 ± 633	2766 ± 877
$t_{1/2}$, hr	2.2 ± 0.6	2.1 ± 0.6	8.3 ± 0.8	8.0 ± 1.7
$\frac{AUC_{\infty} (Fed)}{AUC_{\infty} (Fasted)}$		0.82*		0.87*
$\frac{C_{max} (Fed)}{C_{max} (Fasted)}$		0.48*		0.76*

*Geometric mean.



CONCLUSIONS: (i) Administration of losartan with food results in decrease in C_{max} and AUC_{∞} (52% and 18% respectively) and a delay of 1.6 hour in T_{max} of losartan; and a decrease in C_{max} and AUC_{∞} (24% and 13% respectively) and a delay of 1.7 hour in T_{max} of the active metabolite (E-3171).

PHARMACOKINETICS STUDY IN THE ELDERLY

STUDY NUMBER: 063

VOLUME: 1.49

PAGES: 6477 - 6772

INVESTIGATOR AND LOCATION:

OBJECTIVES: (i) To determine the pharmacokinetics of 50 mg losartan tablets and 10 mg IV losartan in elderly hypertensive patients, (ii) to compare the bioavailability and systemic clearance of losartan in elderly hypertensive patient with young normal volunteers, (iii) to compare the plasma concentration profiles of losartan in the elderly to those in young, normal volunteers, (iv) to assess the tolerability of single dose treatments of losartan in elderly hypertensive patients.

FORMULATIONS:

Losartan 50 mg Tablet, Formulation No. 0954 FCT005C001

Losartan (5 mg/ml fill) IV solution, Formulation No. 0954 HSS001A001

STUDY DESIGN: Randomized, open, two-period, cross-over study in 10 (5 males, 5 females) elderly (> 65 years) hypertensive patients and a washout period of 14 days. On each study day, patients received either the 50 mg tablet or the 10 mg losartan IV solution administered over a 20-minute interval after an overnight fast. Blood samples were drawn following oral losartan at 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 30, and 36 hours and following IV losartan administration at 0, 5, 10, 15, 20, 23, 26, 30, 45, 60, 90 minutes and 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 30 and 36 hours. Urine was collected at 0-3, 3-6, 6-12, 12-24, 24-36, and 36-48-hours post dose.

ASSAYS: HPLC with UV detection.

PLASMA SAMPLES - LOSARTAN (MK-954) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curves from 5 to 1000 ng/ml.

Accuracy: Satisfactory. 93.5% at 20 ng/ml, 98.6% at 800 ng/ml for MK-954 and 97.5% at 20 ng/ml, 100.8% at 800ng/ml for E-3174.

Precision: Satisfactory. %CV - 8.8% at 20 ng/ml, 1.8% at 800 ng/ml for MK-954; and 4.8% at 20 ng/ml, 3.5% at 800 ng/ml for E-3174.

Sensitivity: LOQ - 5 ng/ml.

Specificity: Satisfactory. Chromatograms submitted.

URINE SAMPLES - LOSARTAN (MK-954) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curves from 10 to 2000 ng/ml.

Accuracy: Satisfactory. 92.8% at 40 ng/ml, 96.4% at 1600 ng/ml for MK-954; and 101.5%

at 40 ng/ml, 101.2% at 1600 ng/ml for total E-3174.
Precision: Satisfactory. %CV - 2.8% at 40 ng/ml, 2.1% at 1600 ng/ml for MK-954; and
6.0% at 40 ng/ml, 3.4% at 1600 ng/ml for E-3174.
Sensitivity: LOQ - 10 ng/ml .
Specificity: Satisfactory. Chromatograms submitted.

The assays have been validated over the range of plasma and urine concentrations observed in the study.

DATA ANALYSIS: AUC_{∞} , C_{max} , $t_{1/2}$, CL, CL_r , V_{dss} , T_{max} , F, and % Dose excreted in urine were calculated.

RESULTS:

MK-954				
	50-mg Tablet		10 mg I.V.	
	Male (n = 5)	Female (n = 5)	Male (n = 5)	Female (n = 5)
C_{max} , ng/ml	249.1 ± 123.0	533.1 ± 217.2	-	-
T_{max} , hr	1.15 ± 0.68	1.10 ± 0.55	-	-
AUC, ng-hr/ml	478.15 ± 150.17	1008.38 ± 271.48	284.97 ± 33.10	410.72 ± 57.68
$t_{1/2}$, hr ^a	2.06 ± 0.39	2.92 ± 1.41	1.64 ± 0.62	2.30 ± 0.47
V_{dss} , L	-	-	29.33 ± 12.20	29.63 ± 9.78
CL, ml/min	-	-	597.16 ± 69.95	415.99 ± 54.85
CL_r , ml/min	46.57 ± 17.08	32.82 ± 11.31	46.13 ± 19.00 ^b	38.25 ± 9.16
% Dose in Urine	2.73 ± 0.35	4.10 ± 1.47	8.66 ± 1.76 ^b	9.84 ± 2.39 ^b
Bioavailability, % ^c	33.4 (25.9-43.0)	49.4 (37.9-64.5)	-	-

^aHarmonic mean and pseudo standard deviation.

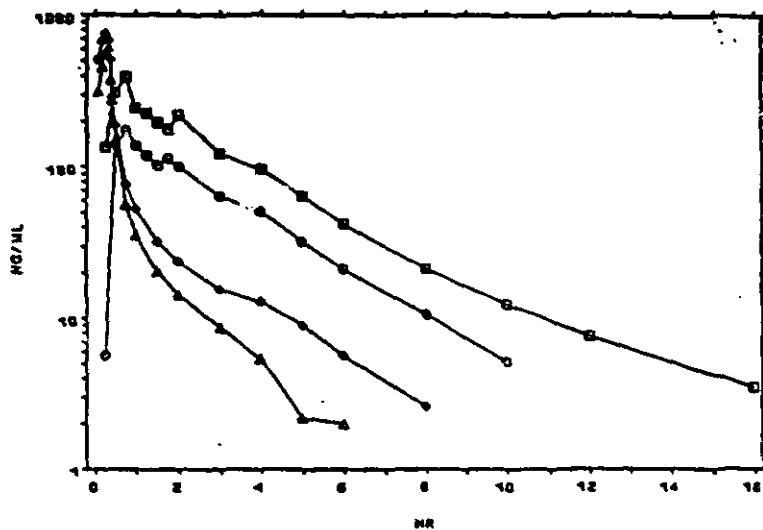
^bn = 4.

^cGeometric mean and 90% confidence interval limits.

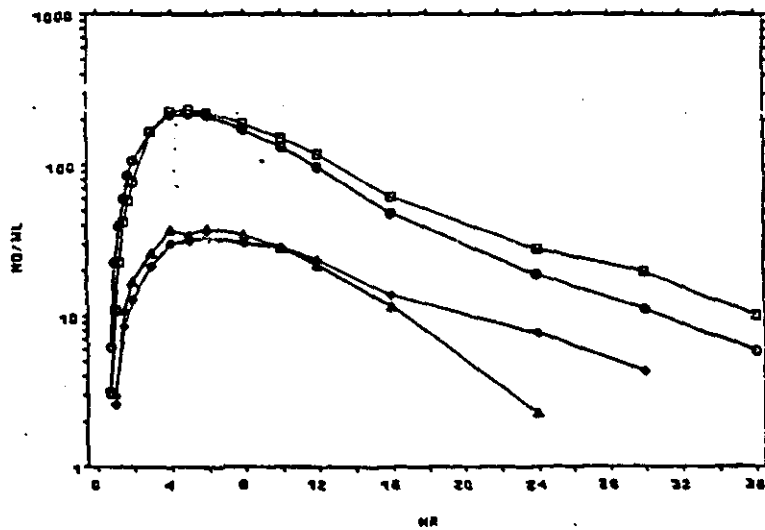
E-3174				
	50-mg Tablet		10 mg I.V.	
	Male (n = 5)	Female (n = 5)	Male (n = 5)	Female (n = 5)
C_{max} , ng/ml	247.2 ± 55.2	246.0 ± 75.4	41.3 ± 12.4	33.9 ± 14.3
T_{max} , hr ^a	4.8 ± 1.3	4.6 ± 1.1	5.4 ± 1.7	7.2 ± 1.8
AUC, ng-hr/ml	2476.81 ± 559.69	2886.59 ± 962.61	502.14 ± 194.33	576.25 ± 253.11
$t_{1/2}$, hr ^a	6.53 ± 1.55	8.01 ± 2.29	5.67 ± 1.93	7.58 ± 4.95
CL_r , ml/min	19.22 ± 7.24	15.50 ± 5.85	21.30 ± 8.28	14.60 ± 6.05
% Dose in Urine	5.83 ± 1.26	5.46 ± 1.80	5.63 ± 0.81	4.84 ± 1.78

^aHarmonic mean and pseudo standard deviation.

Mean MK-954, Study 053



Mean E-3174, Study 053



Mean Plasma Concentrations of MK-954 and E-3174 in Elderly Hypertensives Following I.V. MK-954 (□-Female, ▲-Male) and P.O. MK-954 (□-Female, ○-Male)

MK-954 and E-3174 Data Following Oral MK-954 in Studies #063, #004, #007, #015 and #022 (Data Normalized to 50 mg^a)

Study	MK-954					E-3174				
	C _{max} ng/ml	T _{max} hr	AUC ng-hr/ml	t _{1/2} ^b hr	Cl _{CR} ml/min	C _{max} ng/ml	T _{max} hr	AUC ng-hr/ml	t _{1/2} ^b hr	Cl _{CR} ml/min
Elderly Pooled Study #063, n = 10	391 ± 224	1.1 ± 0.6	743 ± 348	2.4 ± 0.8	40 ± 15	247 ± 62	4.7 ± 1.2	2682 ± 773	7.2 ± 1.9	17 ± 7
Elderly Female Study #063, n = 5	533 ± 217	1.1 ± 0.6	1008 ± 271	2.9 ± 1.4	33 ± 11	246 ± 75	4.6 ± 1.1	2887 ± 963	8.0 ± 2.3	16 ± 6
Elderly Male Study #063, n = 5	249 ± 123	1.2 ± 0.7	478 ± 150	2.1 ± 0.4	47 ± 17	247 ± 55	4.8 ± 1.3	2477 ± 560	6.5 ± 1.6	19 ± 7
Male Patients Study #004, n = 13 ^c	NC	NC	572 ± 200	NC	ND	NC	NC	2613 ± 735	NC	ND
Female Patients Study #004, n = 5 ^c	NC	NC	823 ± 317	NC	ND	NC	NC	2953 ± 714	NC	ND
Young Subjects Study #007, n = 10 ^d	NC	NC	413 ± 181	2.0 ± 0.7	74 ± 18	NC	NC	1843 ± 559	9.0 ± 1.7	25 ± 5
Young Subjects Study #015, n = 8 ^d	259 ± 100	1.3 ± 0.8	416 ± 91	2.2 ± 0.6	ND	253 ± 63	3.1 ± 1.3	1561 ± 319	8.3 ± 0.8	ND
Young Subjects Study #022, n = 8 ^d	243 ± 116	1.4 ± 0.8	361 ± 188	1.9 ± 0.5	90 ± 42	292 ± 60	3.1 ± 1.0	1780 ± 343	8.3 ± 1.2	23 ± 6

^aIndividual data from Studies #004, #007, #015 and #022 can be found in Tables 1-4 in Appendix 5.

^bHarmonic mean and pseudo standard deviation.

^cData from Study #004 (hypertensives)—male mean age 52 yr (range 32-65), female mean age 52 yr (range 43-58), capsule formulations.

^dHealthy young male volunteers—capsule formulation (Study #007), tablet formulations (Studies #015 and #022).

NC - Not compared.

ND - Not determined.

MK-954 and E-3174 Data Following I.V. MK-954 in Studies #063 and #022*

Study	MK-954				E-3174	
	CL _r , ml/min	V _{dss} , L	CL _r , ml/min	t _{1/2} ^b , hr	CL _r , ml/min	t _{1/2} ^b , hr
Elderly Pooled Study #063, n = 10	507 ± 112	30 ± 10	42 ± 14	1.9 ± 0.7	18 ± 8	6.5 ± 2.9
Elderly Female Study #063, n = 5	416 ± 55	30 ± 10	38 ± 9	2.3 ± 0.5	15 ± 6	7.6 ± 5.0
Elderly Male Study #063, n = 5	597 ± 70	29 ± 12	46 ± 19	1.6 ± 0.6	21 ± 8	5.7 ± 1.9
Young Male Study #022, n = 8	618 ± 247	40 ± 13	76 ± 39	2.3 ± 0.9	24 ± 5	7.7 ± 1.8

*Individual data from Study #022 can be found in Table 4 in Appendix 5.

^bHarmonic mean and pseudo standard deviation.

The key pharmacokinetic results (LSmeans) for losartan (normalized 50 mg dose) and L-158,641 for the elderly patients and healthy, male volunteers:

	AUC _{0-∞} (ng/ml-hr)		F (%)		CL _r (ml/min)		CL _r (ml/min)	
	Mean	LSmean	Mean	LSmean	Mean	LSmean	Mean	LSmean
<u>Losartan</u>								
<u>Elderly Study 063</u>								
Both	743	743	43	43	507	507	39.7	39.7*
Female	1008	-	51	-	416	-	32.8	-
Male	478	-	34	-	597	-	46.6	-
<u>Healthy Males</u>								
Study 007	413	678	-	-	-	-	74.2	67.4
Study 015	416	681	-	-	-	-	-	-
Study 022	361	626	25	33	618	527	90	83.2
<u>L-158,641</u>								
<u>Elderly Study 063</u>								
Both	2682	2682*	-	-	-	-	17.4	17.4
Female	2887	-	-	-	-	-	15.5	-
Male	2477	-	-	-	-	-	19.2	-
<u>Healthy Males</u>								
Study 007	1843	2048	-	-	-	-	24	23.2
Study 015	1561	1766	-	-	-	-	-	-
Study 022	1780	1985	-	-	-	-	22.5	20.7

*Significantly different from pooled data in young p<0.01.

Age range for healthy, male volunteers 18-31 yr (Study #007), 19-29 yr (Study #015), and 21-35 yr (Study #022).

CONCLUSION: The data obtained from the study shows that there are gender differences in the clearance of losartan in elderly patients, with systemic clearance greater in the elderly males and bioavailability greater in the elderly females. Comparison of the data from this study to those from Study #022 shows that the renal clearance of losartan is decreased in elderly male patients when compared to young, healthy males. These differences should be included in the labeling.

LIVER IMPAIRMENT STUDY

STUDY NUMBER: 067

VOLUME: 1.49

PAGES: 6773 - 7101

INVESTIGATOR AND LOCATION: THEODORE HERMAN, M.D.
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USA.

OBJECTIVES: (i) To determine the pharmacokinetics of 50 mg losartan tablets and 10 mg IV losartan in patients with hepatic insufficiency, (ii) to compare the bioavailability and systemic clearance of losartan in patients with hepatic insufficiency to that in normal volunteers, (iii) to determine the percentage of the metabolite (L-158,641 or E-3174) produced after an intravenous dose of losartan, (iv) to compare the plasma concentration profiles of losartan and L-158,641 following administration of 50 mg losartan tablet and 10 mg IV losartan in patients with hepatic insufficiency with the profiles seen in normal volunteers, (v) to assess the tolerability of single dosetreatments of losartan in patients with hepatic insufficiency.

FORMULATIONS:

Losartan (MK-954) 50 mg Tablet, Formulation No. 0954 FCT005C003

Losartan (MK-954) IV Solution (5 mg/ml), Formulation No. 0954 HSS001A002

L-158,641 (E-3174) IV Solution (5 mg/ml), Formulation No. 9519HSS001A001

STUDY DESIGN: Randomized, open, three-period, cross-over study in 9 patients with hepatic insufficiency and a washout period of 7 days. On each study day, patients received the 50 mg tablet or the 10 mg losartan IV solution or 10 mg E-3174 solution administered over a 20-minute interval after an overnight fast. Blood samples were drawn following oral losartan at 0, 20, 40 minutes, and 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 16, 24, 30, and 36 hours; and following IV losartan administration at 0, 7, 14, 20, 30, and 40 minutes and 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 16, 24 and 30 hours; and following IV E-3174 at 0, 7, 14, 20 and 30 minutes and 1, 1.5, 2, 4, 6, 9, 12, 24, 30 and 36 hours. Urine was collected at 0-3, 3-6, 6-12, 12-24, 24-36, and 36-48-hours post dose.

ASSAYS: HPLC with UV detection.

PLASMA SAMPLES - LOSARTAN (MK-954) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curves from 5 to 1000 ng/ml.

Accuracy: Satisfactory. 103.0% at 20 ng/ml, 104.3% at 800 ng/ml for MK-954 and 96.0% at 20 ng/ml, 107.2% at 800ng/ml for E-3174.

Precision: Satisfactory. %CV - 6.4% at 20 ng/ml, 2.0% at 800 ng/ml for MK-954; and

10.8% at 20 ng/ml, 4.1% at 800 ng/ml for E-3174.
 Sensitivity: LOQ - 5 ng/ml.
 Specificity: Satisfactory. Chromatograms submitted.

URINE SAMPLES - LOSARTAN (MK-954) AND ACTIVE METABOLITE (E-3174):
 Linearity: Satisfactory. Standard curves from 10 to 2000 ng/ml for E-3174; 20 to 2000 ng/ml for MK-954.

Accuracy: Satisfactory. 103.0% at 40 ng/ml, 107.2% at 1600 ng/ml for MK-954; and 110.8% at 40 ng/ml, 107.0% at 1600 ng/ml for total E-3174.

Precision: Satisfactory. %CV - 4.2% at 40 ng/ml, 1.8% at 1600 ng/ml for MK-954; and 9.1% at 40 ng/ml, 2.2% at 1600 ng/ml for E-3174.

Sensitivity: LOQ - 10 ng/ml for E-3174; 20 ng/ml for MK-954.

Specificity: Satisfactory. Chromatograms submitted.

The assays have been validated over the range of plasma and urine concentrations observed in the study.

DATA ANALYSIS: AUC_{∞} , C_{max} , $t_{1/2}$, CL , CL_r , Vd_{ss} , T_{max} , F , and % Dose excreted in urine were calculated.

RESULTS:

	Intravenous E-3174	Intravenous MK-954		Oral MK-954	
	E-3174	MK-954	E-3174	MK-954	E-3174
$C_{20\text{ min}}$, ng/ml ^a	2405.8 ± 550.4	1056.1 ± 249.5	-	-	-
C_{max} , ng/ml ^a	-	-	50.3 ± 26.5	1171.8 ± 667.1	296.2 ± 108.9
T_{max} , hr	-	-	4.9 ± 1.8	0.98 ± 0.47	4.56 ± 0.88
AUC , ng-hr/ml ^a	5626.59 ± 1764.97	653.72 ± 230.44	623.27 ± 288.73	2162.83 ± 1095.38	3131.19 ± 1219.56
λ , hr ⁻¹	0.1368 ± 0.0581	0.3889 ± 0.1542	0.1187 ± 0.0376	0.2885 ± 0.0778	0.1065 ± 0.0246
$t_{1/2}$, hr ^b	5.07 ± 2.40	1.78 ± 0.74	5.84 ± 1.91	2.40 ± 0.67	6.51 ± 1.54
Vd_{ss} , L	8.57 ± 2.53	19.65 ± 9.77	-	-	-
CL , ml/min	33.18 ± 13.17	285.04 ± 97.46	-	-	-
CL_r , ml/min	19.08 ± 7.80	44.27 ± 17.01	23.43 ± 12.23	55.41 ± 20.39	21.38 ± 8.17
% Dose recovered in urine	59.05 ± 13.89	19.69 ± 9.98	8.14 ± 2.97	16.21 ± 11.00	7.84 ± 1.93
Oral bioavailability, % ^c	-	-	-	64.8 ± 21.8	-

^aData normalized to 10.0-mg I.V. E-3174 free acid dose and 10.0-mg I.V. and 50.0-mg oral dose of MK-954.

^bHarmonic mean and pseudo standard deviation.

^cGeometric mean was 61.3%, with 90% confidence interval limits of 49.1% to 76.6%.

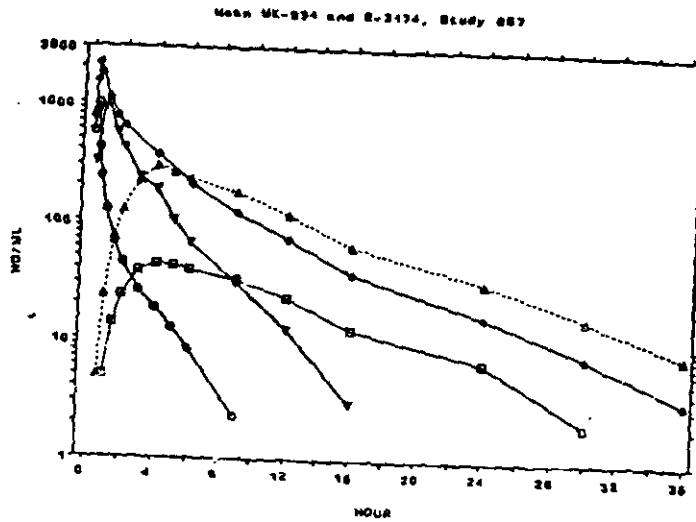


Figure 1. Mean Plasma Concentrations of MK-954 and E-3174 in Fasting Patients Following the Administration of A Single Intravenous Infusion Dose of 10-mg MK-954 (○ = MK-954, □ = E-3174), A Single 50-mg Tablet Oral Dose of MK-954 (△ = MK-954, ◆ = E-3174), and A Single Intravenous Infusion Dose of 10-mg E-3174 (◇ = E-3174)

MK-954 and E-3174 Data Following a Single Oral Dose of 50-mg MK-954 Tablet in Studies #067, #074 and #075 (Data Normalized to 50.0 mg From Assayed Potency)*

Study	MK-954						E-3174				
	C _{max} , ng/ml	T _{max} , hr	AUC, ng hr/ml	t _{1/2} ^b , hr	CL _r , ml/min	F _r , %	C _{max} , ng/ml	T _{max} , hr	AUC, ng hr/ml	t _{1/2} ^b , hr	CL _r , ml/min
Hepatic Study #067, n = 9	1172 ± 667	1.0 ± 0.5	2163 ± 1095	2.4 ± 0.7	55 ± 20	61 (49, 77)	296 ± 109	4.6 ± 0.9	3131 ± 1220	6.5 ± 1.5	21 ± 8
Healthy Subjects Study #074, n = 12	296 ± 217	1.0 ± 0.5	476 ± 200	2.1 ± 0.5	72 ± 21	33 (26, 42)	249 ± 74	4.1 ± 1.6	1915 ± 538	6.4 ± 2.3	26 ± 7
Healthy Subjects Study #075, n = 17	209 ± 100	1.2 ± 0.9	403 ± 100	2.2 ± 0.9	N.D.	N.D.	225 ± 117	4.5 ± 1.7	1778 ± 434	9.2 ± 2.2	N.D.

*Individual data from Studies #074 and #075 can be found in Tables 1 and 2 in Appendix 5.

^aHarmonic mean and pseudo standard deviation.

^bGeometric mean and 90% confidence interval limits.

N.D. - Not determined.

MK-954 and E-3174 Data Following I.V. MK-954 in Studies #067, #060 and #074*

Study	Dose, mg	MK-954				E-3174			
		CL, ml/min	Vd _{ss} , L	CL _r , ml/min	t _{1/2} ^b , hr	CL _r , ml/min	t _{1/2} ^b , hr	f _m , %	f _m ^c , %
Hepatic Study #067, n = 9	9.2 ± 0.7	285 ± 97	20 ± 10	44 ± 17	1.8 ± 0.7	23 ± 12	5.8 ± 1.9	13 ± 4	16 ± 5
Healthy Subjects Study #060, n = 6	26.4 ± 1.0	559 ± 188	47 ± 21	64 ± 26	3.2 ± 0.8	25 ± 7	5.3 ± 2.1	14 ± 4	16 ± 4
Healthy Subjects Study #074, n = 12	19.7 ± 1.8	636 ± 107	28 ± 14	72 ± 21	1.8 ± 0.6	28 ± 6	4.6 ± 1.3	N.D.	N.D.

*Individual data from Studies #060 and #074 can be found in Tables 1 and 3 in Appendix 5.
^bHarmonic mean and pseudo standard deviation.
 N.D. - Not determined.

Table 21. E-3174 Data Following I.V. E-3174 in Studies #067 and #060*

Study	Dose ^a , mg	E-3174			
		CL, ml/min	Vd _{ss} , L	CL _r , ml/min	t _{1/2} ^b , hr
Hepatic Study #067, n = 9	8.9 ± 0.6	33 ± 13	8.6 ± 2.5	19 ± 8	5.1 ± 2.4
Healthy Subjects Study #060, n = 6	16.6 ± 0.3	47 ± 6	10.3 ± 1.1	26 ± 6	6.3 ± 1.4

*Individual data from Study #060 can be found in Table 4 in Appendix 5.

CONCLUSION: Comparison of the data from this study to those from healthy male subjects (Study #074, #075, #060) shows that (i) the systemic clearance of losartan is reduced to about 50%, (ii) the oral bioavailability of losartan is increased (from 33% to 65%), (iii) the C_{max} and AUC for losartan following oral administration are about 5-fold greater, (iv) the AUC for E-3174 following oral losartan is about 1.7-fold greater. These differences should be included in the labeling.

RENAL IMPAIRMENT STUDY

STUDY NUMBER: 012

VOLUME: 1.50

PAGES: 7103 - 7457

INVESTIGATOR AND LOCATION:

OBJECTIVES: (i) To determine the effect of renal insufficiency on the pharmacokinetics of losartan (MK-954) and E-3174 following chronic 100-mg doses of MK-954, (ii) to determine to what extent MK-954 and E-3174 are cleared by hemodialysis, (iii) to investigate in hypertensive patients with four degrees of renal function the chronic-dose effects of MK-954 on blood pressure and pulse, (iv) to evaluate the safety of multiple doses of MK-954 in patients with different levels of renal function.

FORMULATIONS:

Losartan (MK-954) 50 mg Capsule, Formulation No. 0954 DFC 002C002

Losartan (MK-954) 100 mg Capsule, Formulation No. 0954 DFC 002D001

STUDY DESIGN: Open label study in 24 patients (from two centers) with various levels of renal function and divided into four groups based on 24-hour creatine clearance (CLcr) determined during baseline: Group I - normal renal function (CLcr $\geq$ 75 ml/min); Group II - mild to moderate renal insufficiency (CLcr = 30-74 ml/min); Group III - severe renal insufficiency (CLcr = 10-29 ml/min); Group IV - hemodialysis patients (CLcr < 10 ml/min). Following 1 week washout after discontinuation of antihypertensive therapy, patients in Groups I, II and III received losartan 100 mg for 7 days. On Day 6, a trough blood specimen was taken and on Day 7, the patient was admitted to the study clinic for 30 to 60 hours. Blood samples were drawn following oral losartan on Day 7 at 0, 20, 30, 45, 60, 75, and 90 minutes, and 2, 3, 4, 6, 8, 10, 15, 18, 24, 30, 36, 48, and 60 hours. Urine was collected at 0-4, 4-8, 8-12, and 12-24, hours post dose on Day 7. Hemodialysis patients received 100 mg losartan for 7 days, with dose being taken 4 hours before dialysis on dialysis days (Days 2, 4, 6, 9 of the study). Peripheral venous blood samples were taken at times mentioned above. Pre- and postdialysis blood samples were taken from the dialysis shunt circuit at Hours 0, 1, 2, 3, and 4 of dialysis on Day 6 to evaluate the clearance of losartan and E-3174 by dialysis.

ASSAYS: HPLC with UV detection.

PLASMA SAMPLES - LOSARTAN (MK-954) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curves from 5 to 1000 ng/ml.

Accuracy: Satisfactory. 93.4% at 20 ng/ml, 97.1% at 800 ng/ml for MK-954 and 100.0% at 20 ng/ml, 99.4% at 800ng/ml for E-3174.

Precision: Satisfactory. %CV - 7.8% at 20 ng/ml, 5.7% at 800 ng/ml for MK-954; and 7.7% at 20 ng/ml, 3.5% at 800 ng/ml for E-3174.

Sensitivity: LOQ - 5 ng/ml.

Specificity: Satisfactory. Chromatograms submitted.

URINE SAMPLES - LOSARTAN (MK-954) AND ACTIVE METABOLTE (E-3174):

Linearity: Satisfactory. Standard curves from 10 to 2000 ng/ml for E-3174; 20 to 2000 ng/ml for MK-954.

Accuracy: Satisfactory. 97.0% at 40 ng/ml, 102.7% at 1600 ng/ml for MK-954; and 101.8% at 40 ng/ml, 99.8% at 1600 ng/ml for total E-3174.

Precision: Satisfactory. %CV - 8.1% at 40 ng/ml, 1.5% at 1600 ng/ml for MK-954; and 1.9% at 40 ng/ml, 1.6% at 1600 ng/ml for E-3174.

Sensitivity: LOQ - 10 ng/ml for E-3174; 20 ng/ml for MK-954.

Specificity: Satisfactory. Chromatograms submitted.

The assays have been validated over the range of plasma and urine concentrations observed in the study.

DATA ANALYSIS: AUC_{24} , C_{max} , $t_{1/2}$, CL_r , T_{max} , λ and % Dose excreted in urine were calculated.

RESULTS:

MK-954								
Parameter	n	Group I, CL_r ≥ 75 ml/min	n	Group II, CL_r 30-74 ml/min	n	Group III, CL_r 10-29 ml/min	n	Group IV, CL_r <10 ml/min
C_{max} , ng/ml	6	854.2 $\pm$ 315.2	6	1164.6 $\pm$ 746.0	6	801.0 $\pm$ 445.4	6	1615.1 $\pm$ 417.4
T_{max} , hr	6	0.79 $\pm$ 0.37	6	0.66 $\pm$ 0.23	6	0.88 $\pm$ 0.41	6	0.68 $\pm$ 0.32
AUC_{24} , ng hr/ml	6	1106.9 $\pm$ 265.1	6	1212.2 $\pm$ 755.1	6	1760.6 $\pm$ 1389.8	6	2065.6 $\pm$ 551.0
$t_{1/2}$, hr	6	2.13 $\pm$ 0.68	6	2.17 $\pm$ 0.97	5	3.22 $\pm$ 2.19	5	2.64 $\pm$ 1.02
λ , hr ⁻¹	6	0.326 $\pm$ 0.103	6	0.319 $\pm$ 0.142	5	0.215 $\pm$ 0.136	5	0.262 $\pm$ 0.106
CL_r , ml/min	6	50.2 $\pm$ 18.4	6	16.5 $\pm$ 6.5	6	2.3 $\pm$ 0.9		N.A.
Urinary Recovery, % dose	5	3.25 $\pm$ 1.23	5	1.33 $\pm$ 1.03	6	0.27 $\pm$ 0.32		N.A.

E-3174								
Parameter	n	Group I, CL_r ≥ 75 ml/min	n	Group II, CL_r 30-74 ml/min	n	Group III, CL_r 10-29 ml/min	n	Group IV, CL_r <10 ml/min
C_{max} , ng/ml	6	681.3 $\pm$ 210.5	6	623.0 $\pm$ 214.1	6	402.6 $\pm$ 344.2	6	715.3 $\pm$ 578.0
T_{max} , hr	6	2.42 $\pm$ 0.92	6	2.06 $\pm$ 0.49	6	4.1 $\pm$ 1.60	6	2.50 $\pm$ 1.00
AUC_{24} , ng hr/ml	6	4362.2 $\pm$ 1143.2	6	3694.3 $\pm$ 953.1	6	3912.4 $\pm$ 2768.1	6	5011.6 $\pm$ 4037.5
$t_{1/2}$, hr	6	9.55 $\pm$ 3.47	5	11.04 $\pm$ 5.44	6	13.45 $\pm$ 5.78	4	11.25 $\pm$ 9.06
λ , hr ⁻¹	6	0.0726 $\pm$ 0.0256	5	0.0628 $\pm$ 0.0297	6	0.0516 $\pm$ 0.0220	4	0.0616 $\pm$ 0.0390
CL_r , ml/min	6	18.1 $\pm$ 4.1	6	6.9 $\pm$ 2.6	6	1.3 $\pm$ 0.8		N.A.
Urinary Recovery, % dose	5	4.44 $\pm$ 1.34	5	1.85 $\pm$ 0.92	6	0.24 $\pm$ 0.08		N.A.

N.A. - Not applicable.

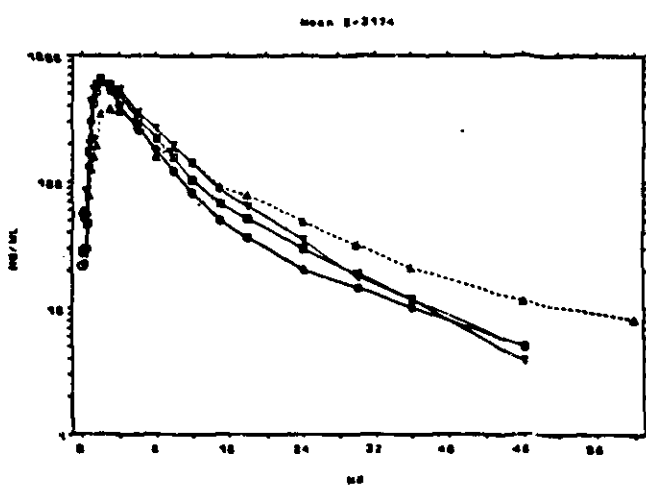
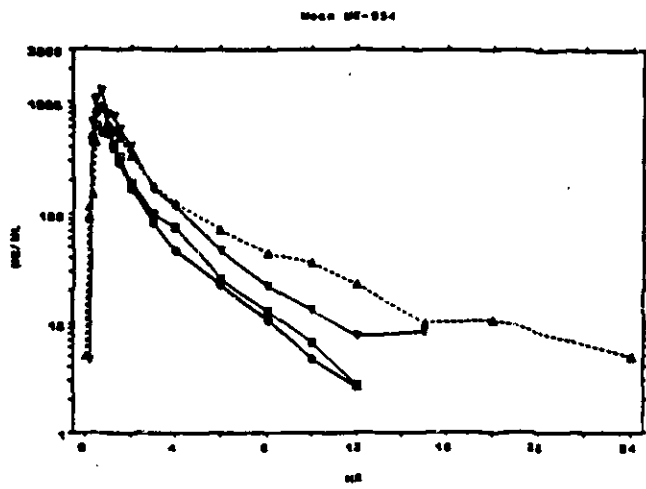


Figure 1. Mean Plasma Concentrations of E-954 and E-3174 in Patients With Renal Insufficiency: (o) Group I, (c) Group II, (Δ) Group III and (▽) Group IV.

CONCLUSIONS: (i) The renal clearance of losartan decreases with renal impairment (but renal clearance constitutes only about 12% of total body clearance of losartan); (ii) the renal clearance of E-3174 decreases with renal impairment (renal clearance constitutes about 55% of total body clearance of E-3174) but the AUC does not increase with decreasing renal clearance; (iii) AUC of losartan is higher in hemodialysis patients; (iv) losartan and E-3174 do not appear to be cleared by hemodialysis. These observations should be included in the labeling.

LOSARTAN - PHENOBARBITAL INTERACTION STUDY

STUDY NUMBER: 072

VOLUME: 1.50

PAGES: 7524 - 7905

INVESTIGATOR AND LOCATION:

OBJECTIVES: To determine whether the pharmacokinetics of a single dose of losartan are altered to a clinically significant degree after administration of phenobarbital for 2 weeks.

FORMULATIONS:

Losartan 100 mg Tablet, Formulation No. 0954 FCT004D003

Phenobarbital 100 mg Tablet, Formulation No. CO954 FCT008D002

Phenobarbital Placebo, Formulation No. PO217 OCT001P004

STUDY DESIGN: Single-blind, placebo-controlled, randomized, two-period study in 15 subjects. Each subject received a single dose of losartan (100 mg tablet) orally on Day 1 of Period 1. After a washout period of at least 48 hours, Period 2 commenced, consisting of a 16-day course of either phenobarbital 100 mg or placebo, taken once daily at 10 p.m. ($\pm$ 1 hr). On the morning of Day 15, subjects received another single dose of losartan 100 mg after an overnight fast and fasted until 1 hour post dose. Blood samples were drawn following oral losartan at 0, 15, 30, 45, minutes, and 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, and 36 hours. Urine was collected predose and at 0-3, 3-6, 6-12, and 12-24, 24-36, and 36-48 hours post losartan dose.

ASSAYS: HPLC with UV detection.

PLASMA SAMPLES - LOSARTAN (MK-954) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curves from 5 to 1000 ng/ml.

Accuracy: Satisfactory. 98.5% at 20 ng/ml, 99.5% at 800 ng/ml for MK-954 and 100.0% at 20 ng/ml, 101.9% at 800 ng/ml for E-3174.

Precision: Satisfactory. %CV - 8.0% at 20 ng/ml, 4.3% at 800 ng/ml for MK-954; and 6.7% at 20 ng/ml, 5.7% at 800 ng/ml for E-3174.

Sensitivity: LOQ - 5 ng/ml.

Specificity: Satisfactory. Chromatograms submitted.

URINE SAMPLES - LOSARTAN (MK-954) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curves from 10 to 2000 ng/ml for E-3174; 20 to 2000 ng/ml for MK-954.

Accuracy: Satisfactory. 96.8% at 40 ng/ml, 95.0% at 1600 ng/ml for MK-954; and 98.8% at 40 ng/ml, 98.1% at 1600 ng/ml for total E-3174.

Precision: Satisfactory. %CV - 6.8% at 40 ng/ml, 3.0% at 1600 ng/ml for MK-954; and

4.4% at 40 ng/ml, 2.9% at 1600 ng/ml for E-3174.
 Sensitivity: LOQ - 10 ng/ml for E-3174; 20 ng/ml for MK-954.
 Specificity: Satisfactory. Chromatograms submitted.

The assays have been validated over the range of plasma and urine concentrations observed in the study.

DATA ANALYSIS: AUC_{0-∞}, C_{max}, t_{1/2}, CL_r, T_{max}, λ and % Dose excreted in urine were calculated.

RESULTS:

Losartan L-158,641 Pharmacokinetic Parameters (arithmetic mean ± S.D.)
 in the Phenobarbital and Placebo Treatment Groups

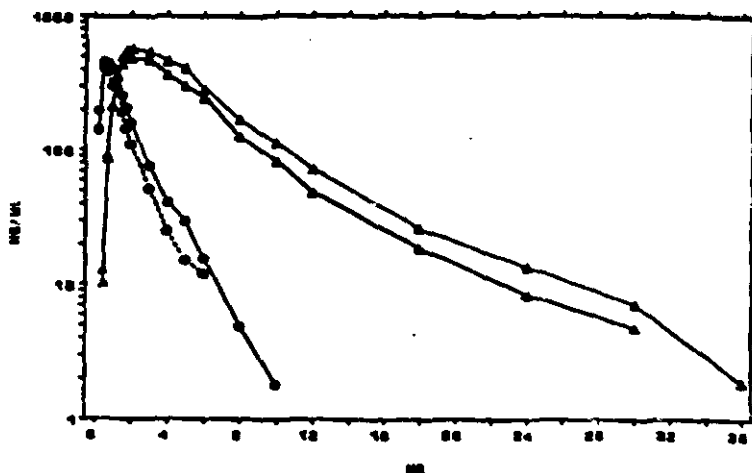
	Period I - 100 mg of MK-954 Given Prior to Phenobarbital or Placebo Administration		Period II - 100 mg of MK-954 Taken on Day 15 of Phenobarbital or Placebo Administration		
	MK-954	L-158,641	MK-954	L-158,641	
Phenobarbital Treatment Group (n=10), 100 mg Once a Day for 16 Days					
C _{max} , ng/mL	588.4 ± 300.1	646.3 ± 136.8	586.9 ± 268.8	583.8 ± 132.9	
T _{max} , hr	0.88 ± 0.29	2.23 ± 0.70	0.88 ± 0.46	2.38 ± 1.14	
AUC, ng-hr/mL	854.31 ± 193.97	3784.92 ± 468.61	673.84 ± 124.98	3022.17 ± 361.38	
λ, hr ⁻¹	0.4041 ± 0.1298	0.1012 ± 0.0391	0.4049 ± 0.1100	0.1102 ± 0.0482	
t _{1/2} , hr ^a	1.72 ± 0.55	6.85 ± 2.76	1.71 ± 0.45	6.29 ± 2.88	
CL _r , mL/min	69.55 ± 4.96	22.70 ± 2.08	68.50 ± 6.29	22.19 ± 3.11	
Urinary Recovery	mg	3.725 ± 0.931	5.105 ± 0.504	2.825 ± 0.634	3.964 ± 0.429
	% Dose	3.75 ± 0.94	5.42 ± 0.54	2.84 ± 0.64	4.21 ± 0.45
Placebo Treatment Group (n=5), Placebo Once a Day for 16 Days ^b					
C _{max} , ng/mL	381.5 ± 140.7	470.9 ± 119.3	355.8 ± 83.8	444.4 ± 172.2	
T _{max} , hr	1.31 ± 0.13	3.50 ± 0.58	1.25 ± 0.41	3.50 ± 1.29	
AUC, ng-hr/mL	684.16 ± 206.49	3048.38 ± 909.43	697.93 ± 189.38	3179.42 ± 1098.9	
λ, hr ⁻¹	0.4098 ± 0.0622	0.0958 ± 0.0438	0.3172 ± 0.083	0.0656 ± 0.0248	
t _{1/2} , hr ^a	1.69 ± 0.25	7.23 ± 3.13	2.18 ± 0.59	10.56 ± 4.02	
CL _r , mL/min	78.87 ± 8.26	26.37 ± 2.19	77.13 ± 5.64	24.77 ± 1.09	
Urinary Recovery	mg	3.440 ± 1.125	4.816 ± 1.654	3.291 ± 0.929	4.655 ± 1.798
	% Dose	3.46 ± 1.13	5.11 ± 1.76	3.31 ± 0.93	4.94 ± 1.91

^a Harmonic mean and pseudo standard deviation.

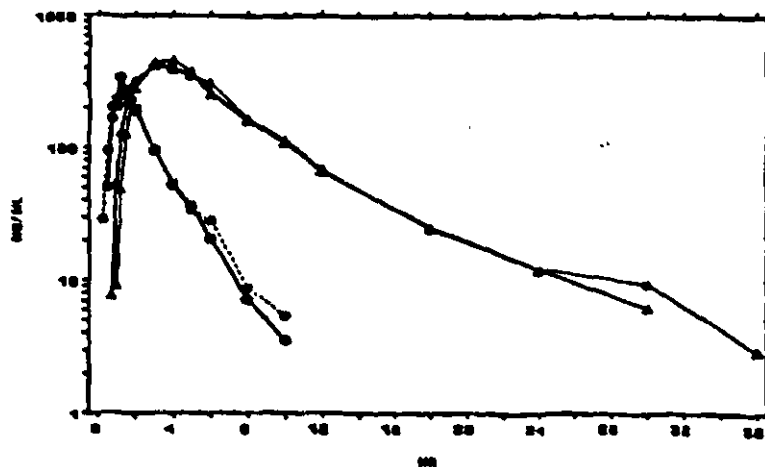
^b C_{max}, T_{max}, AUC, λ, t_{1/2}, CL_r and urinary recovery n=4, data for subject #5 excluded.

Mean Plasma Concentration vs. Time Profiles For Losartan and L-158,641 in the Groups which Received Phenobarbital (TOP) and Placebo (BOTTOM)

Phenobarbital Group(N=10)



Placebo Group(N=4)



O = MK-954 Pre-Rx; ● = MK-954 During Rx; Δ = L-158,641 Pre-Rx;
▲ = L-158,641 During Rx

CONCLUSIONS: (1) Consistent with induction of cytochrome P450 by phenobarbital: (i) the AUC for losartan and E-3174 are reduced by about 20% during phenobarbital administration, (ii) the amount of 6-β-hydroxycortisol excreted in urine is increased during phenobarbital treatment. (2) A subject was identified who did not make appreciable amounts of E-3174 from losartan. These observations should be included in the labeling.

LOSARTAN - CIMETIDINE INTERACTION STUDY

STUDY NUMBER: 024

VOLUME: 1.51

PAGES: 7906 - 8237

INVESTIGATOR AND LOCATION:

OBJECTIVES: (i) To investigate the effect of a clinically relevant dose of cimetidine on the plasma concentration profiles of losartan, (ii) to determine whether any observed effect of cimetidine on the pharmacokinetics of losartan has pharmacodynamics consequences as measured by an effect on losartan-induced increases in plasma renin concentration.

FORMULATIONS:

Losartan 100 mg capsule, Formulation No. E-4359

Cimetidine tablet, 400 mg , Lot No. 10 (Smith Kline French)

STUDY DESIGN: Randomized, open, two-period, cross-over study in 8 subjects with a wash period of at least 7 days. Each subject received a single dose of losartan (100 mg capsule) orally, with and without cimetidine pretreatment (Treatments A and B respectively). Treatment A consists of 100 mg losartan administered orally on Day 1, following an overnight fast. Treatment B consists of cimetidine (400 mg tablet) administered orally every 6 hours on Days 1-7 and 2 hours after the morning cimetidine dose on Day 6 losartan (100 mg) administered orally following an overnight fast. After dosing no food was allowed for four hours. Blood samples were drawn following oral losartan at 0, 10, 20, 30, 40, and 50 minutes, and at 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 30, and 36 hours. Plasma renin activity was determined at 0, 2, 4, 6, 8, 12, and 24 hours post losartan dose.

ASSAYS: HPLC with UV detection.

LOSARTAN (MK-954) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curves from 5 to 1000 ng/ml.

Accuracy: Satisfactory. 96.5% at 20 ng/ml, 98.7% at 800 ng/ml for MK-954; and 93.0% at 20 ng/ml, 93.8% at 800ng/ml for E-3174.

Precision: Satisfactory. %CV - 3.1% at 20 ng/ml, 1.3% at 800 ng/ml for MK-954; and 8.1% at 20 ng/ml, 9.3% at 800 ng/ml for E-3174.

Sensitivity: LOQ - 5 ng/ml.

Specificity: Satisfactory. Chromatograms submitted.

The assays have been validated over the range of plasma concentrations observed in the study.

DATA ANALYSIS: AUC , Cmax, $t_{1/2}$, T_{max} , and λ were calculated.

RESULTS:

	Losartan		L-158,641	
	-Cimetidine	+Cimetidine	-Cimetidine	+Cimetidine
C_{max} , ng/mL†	614 ± 366	836 ± 921	504 ± 253	499 ± 218
T_{max} , hr	0.7 ± 0.2	1.2 ± 1.2	2.6 ± 0.8	2.8 ± 1.1
AUC_X , ng·hr/mL†	849 ± 383	1047 ± 647	3359 ± 1329	3430 ± 1553
$t_{1/2}$, hr@	1.7 ± 0.6	1.7 ± 0.5	8.7 ± 3.6	8.1 ± 2.1
λ , hr ⁻¹	0.40 ± 0.13	0.42 ± 0.12	0.080 ± 0.031	0.085 ± 0.021
$\frac{AUC_{\infty} (+Cimetidine)}{AUC_{\infty} (-Cimetidine)}$	1.18 (1.10, 1.27)‡		1.00 (0.92, 1.08)‡	
$\frac{C_{max} (+Cimetidine)}{C_{max} (-Cimetidine)}$	1.07 Δ (0.89, 1.38)		1.02 (0.88, 1.15)‡	

@ Harmonic mean and pseudo standard deviation.

† Geometric mean

‡ Geometric mean ratio (90% Confidence Interval).

Δ Hodges-Lehmann Estimate (W/WO) with Moses Confidence Interval 88.5% and 94.2%, respectively.

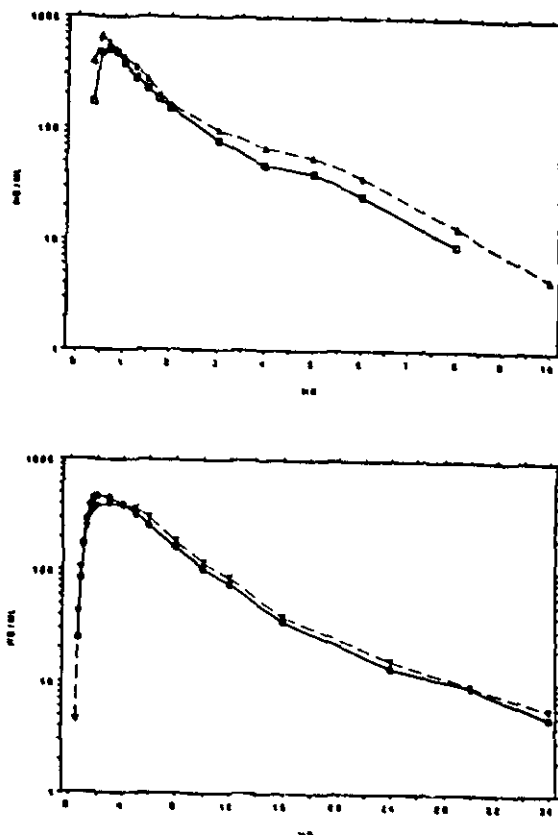


Figure 1. Mean Plasma Concentrations of MK-954 (□) and E-1174 (○) in Eight Subjects Following 100 mg Oral MK-954 With (dash line) and Without (solid line) Cimetidine Pretreatment.

PLASMA RENIN ACTIVITY

PREDOSE

Treatment A Time	AN 01	AN 02	AN 03	AN 04	AN 05	AN 06	AN 07	AN 08	AVG
0 hr	0.69	1.95	0.64	1.18	0.96	1.00	0.92	3.53	1.36
2 hr	0.67	2.82	0.87	0.89	1.01	0.47	0.90	3.72	1.29
4 hr	0.54	1.79	0.56	0.98	0.99	0.65	0.72	3.80	1.25
6 hr	1.07	1.68	0.72	2.16	1.28	0.78	1.03	5.21	1.74
8 hr	0.57	0.89	0.72	1.14	0.66	0.26	0.94	1.59	0.85
12 hr	0.35	0.87	0.54	0.70	0.61	0.56	0.65	1.09	0.67

POSTDOSE

Treatment A Time	AN 01	AN 02	AN 03	AN 04	AN 05	AN 06	AN 07	AN 08	AVG
0 hr	0.73	1.66	1.35	1.08	1.02	1.39	1.28	3.00	1.43
2 hr	0.92	17.96	5.73	5.05	4.02	3.52	8.24	14.96	7.55
4 hr	1.04	24.41	1.64	4.53	5.23	2.44	6.64	30.81	9.55
6 hr	13.81	25.38	6.86	13.33	7.00	4.53	8.78	32.23	13.99
8 hr	6.34	6.77	4.05	8.44	2.46	3.21	2.98	16.54	6.35
12 hr	1.40	6.30	2.97	2.82	2.89	1.90	2.10	6.78	3.40
24 hr	2.52	2.41	3.47	3.51	1.81	4.71	3.18	14.10	4.46

MK-954 Cimetidine Interaction
Dr. Hoeglund/Lund Sweden

PREDOSE

Treatment B Time	AN 01	AN 02	AN 03	AN 04	AN 05	AN 06	AN 07	AN 08	AVG
0 hr	0.71	1.03	0.65	1.17	1.27	1.55	0.82	4.04	1.41
2 hr	1.15	1.24	0.60	0.63	1.05	1.03	0.65	5.55	1.49
4 hr	0.54	0.76	0.71	1.29	0.96	0.96	0.61	3.93	1.22
6 hr	0.88	1.20	0.93	1.78	1.29	1.03	0.69	5.28	1.64
8 hr	0.57	0.24	1.24	1.00	0.48	0.79	0.47	1.82	0.83
12 hr	0.44	0.17	0.39	0.87	0.49	0.69	0.35	1.08	0.56

POSTDOSE

Treatment B Time	AN 01	AN 02	AN 03	AN 04	AN 05	AN 06	AN 07	AN 08	AVG
0 hr	0.83	0.92	1.10	1.57	1.27	1.44	1.16	2.63	1.37
2 hr	6.55	2.02	2.50	5.97	4.18	3.66	9.27	24.74	7.36
4 hr	9.13	2.82	2.34	5.07	7.31	2.85	6.63	31.44	8.45
6 hr	9.42	18.13	2.18	14.19	11.51	2.52	10.31	39.16	11.43
8 hr	3.51	6.95	9.81	6.08	4.92	1.47	4.81	13.30	6.36
12 hr	1.38	1.89	9.05	2.68	4.32	1.11	1.71	5.16	3.41
24 hr	1.89	2.80	4.62	3.23	3.75	2.74	3.92	13.12	4.51

CONCLUSIONS: Co-administration of cimetidine with oral losartan results in an increase of about 23% in the AUC and 36% increase in Cmax of losartan but no alteration in the pharmacokinetics of E-3174 and plasma renin activity. These observations should be included in the labeling.

LOSARTAN - WARFARIN INTERACTION STUDY

STUDY NUMBER: 070

VOLUME: 1.51

PAGES: 8238 - 8681

INVESTIGATOR AND LOCATION:

STUDY PERIOD: JULY 1992 - SEPTEMBER 1992.

OBJECTIVES: (i) to whether the pharmacokinetics of a single dose of warfarin are altered to a clinically significant degree by coadministration with losartan, and (ii) to determine whether the pharmacodynamics of a single dose of warfarin are altered to clinically significant degree by coadministration with losartan.

FORMULATIONS:

100 mg losartan Tablet, Batch No. C-Y064, Formulation No. 0954FCT004D003

Losartan Matching Placebo Tablet, Batch No. C-Y064, Formulation No. PO954FCT005D001

Coumadin (sodium warfarin) 10 mg Tablets, Batch No. C-Y064, Formulation No. DB036B

STUDY DESIGN: Randomized, double-blind, placebo-controlled, two-period, crossover study with 10 subjects and a washout period of two weeks. Subjects received either losartan 100 mg orally (Treatment A) or matched placebo (Treatment B) for 12 days (study days 1-12) according to a random allocation schedule, with a single 30 mg oral dose of warfarin on day 7. Subjects fasted from midnight before and until 1 hour post losartan or placebo dose on study days 1-12 and until 3 hours post warfarin dose on study day 7. Plasma for warfarin levels were drawn at 0, 1, 2, 4, 8, 12, 24, 32, 48, 56, 72, 80, 96, 120, and 144 hours after the oral administration of warfarin and frozen at -20°C until analysis. All subjects had prothrombin time (PT) determinations performed at 0, 1, 2, 4, 8, 12, 24, 32, 48, 56, 72, 80, 96, 120, and 144 hours after the warfarin dose.

ASSAYS: HPLC with UV detection.

Linearity: Satisfactory. Standard curves from 100 to 1250 ng/ml.

Accuracy: Satisfactory. 102.0% at 200 ng/ml, 99.4% at 1000 ng/ml for R-warfarin; and 104.5% at 200 ng/ml, 95.4% at 1000 ng/ml for S-warfarin.

Precision: Satisfactory. %CV - 8.6% at 200 ng/ml, 10.2% at 1000 ng/ml for R-warfarin; and 8.1% at 200 ng/ml, 7.9% at 1000 ng/ml for S-warfarin

Sensitivity: LOQ - 100 ng/ml.

Specificity: Satisfactory. Chromatograms submitted.

The assays have been validated over the range of plasma concentrations observed in the study.

DATA ANALYSIS: AUC_{∞} , C_{max} , $t_{1/2}$, T_{max} , and λ were calculated.

Pharmacokinetics (N=9): The description of warfarin pharmacokinetic parameters (arithmetic mean $\pm$ S.D.) following losartan 100 mg or placebo administration.

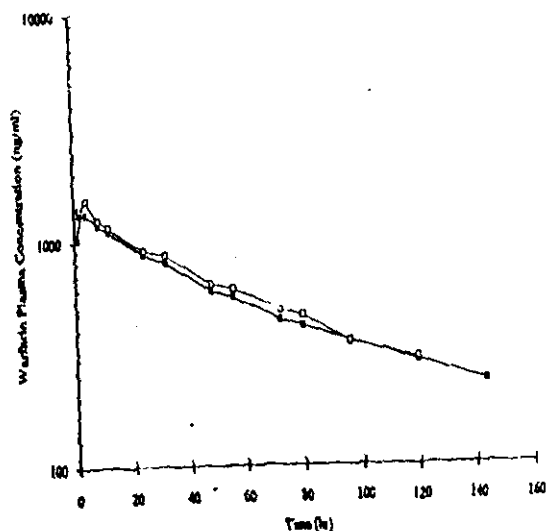
Parameter	R-Warfarin		S-Warfarin	
	Losartan	Placebo	Losartan	Placebo
AUC(ng•hr/mL) ($\pm$ S.D.)	87861.0 (14941.7)	87195.4 (22525.9)	70266.0 (13956.1)	70194.9 (17945.9)
C_{max} (ng/mL) ($\pm$ S.D.)	1656.3 (382.9)	1496.3 (256.1)	1647.0 (308.8)	1615.6 (258.1)
λ (hr ⁻¹) ($\pm$ S.D.)	0.015 (0.002)	0.016 (0.003)	0.020 (0.003)	0.020 (0.003)
$t_{1/2}$ (hr) ¹ ($\pm$ S.D.)	44.97 (2.49)	44.34 (3.11)	34.97 (2.06)	36.00 (2.20)

The analysis of warfarin (R + S) pharmacokinetic parameters (geometric mean ratios and treatment differences) following losartan 100 mg or placebo administration.

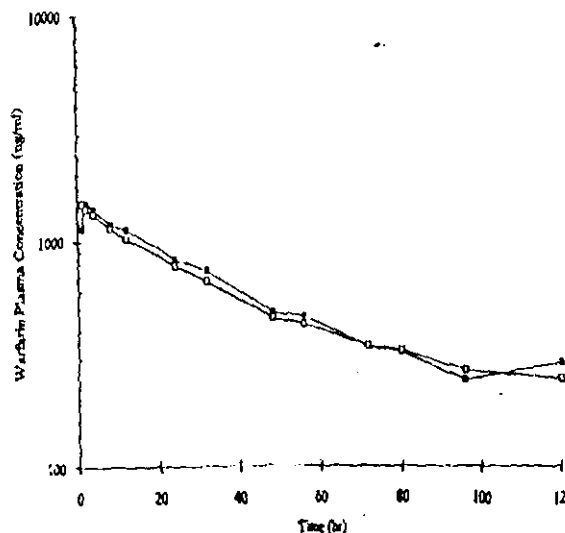
Parameter	Least Square Means		Tr Diff ²	90% CI
	Losartan	Placebo		
R-Warfarin				
AUC(ng•hr/mL) ³	87040.29	84199.81	1.034	(.967, 1.105)
C_{max} (ng/mL) ³	1608.71	1489.29	1.080	(.953, 1.224)
T_{max} (hr)	2.90	2.77	.125	(-1.59, 1.836)
S-Warfarin				
AUC(ng•hr/mL) ³	69461.29	67787.18	1.024	(.945, 1.111)
C_{max} (ng/mL) ³	1616.49	1603.22	1.008	(.928, 1.096)
T_{max} (hr)	1.70	2.08	-.375	(-.999, 0.249)

- ¹ Harmonic mean and pseudo standard deviation.
- ² Treatment effect estimates are geometric mean ratios for log-transformed values, otherwise treatment estimates reflect arithmetic mean differences (losartan - placebo)
- ³ Log transformed for analysis by ratio.

Mean (Arithmetic) Concentration vs. Time Profiles for the R Enantiomer



Mean (Arithmetic) Concentration vs. Time Profiles for the S Enantiomer



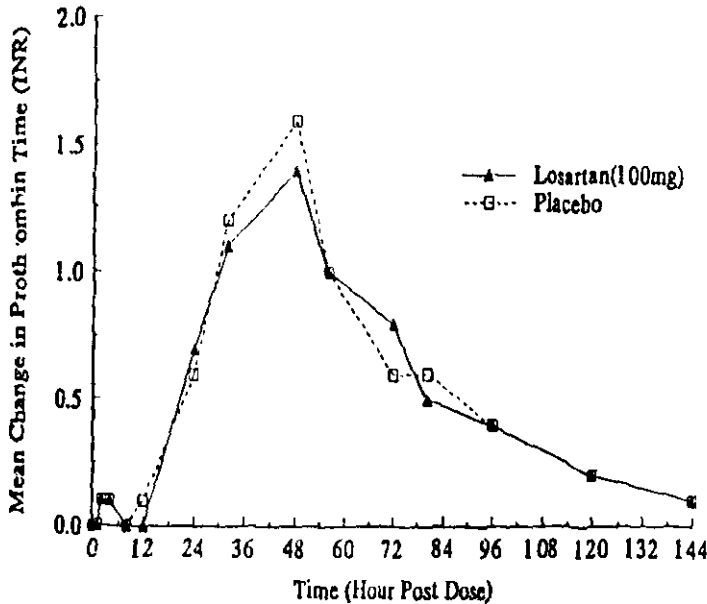
Least Square Mean Areas Under the Curve for Change from Baseline for Prothrombin Time and 90% Confidence Interval on the Difference Between Treatments (Losartan - Placebo)

Prothrombin Time Units	Least Squares Mean AUC (0-144 hr)		Mean Difference	90% CI on Difference
	Losartan	Placebo		
Seconds•hr	433.20	415.42	17.78	(-78.18, 113.74)
INR•hr	76.64	81.10	-4.46	(-17.74, 8.81)

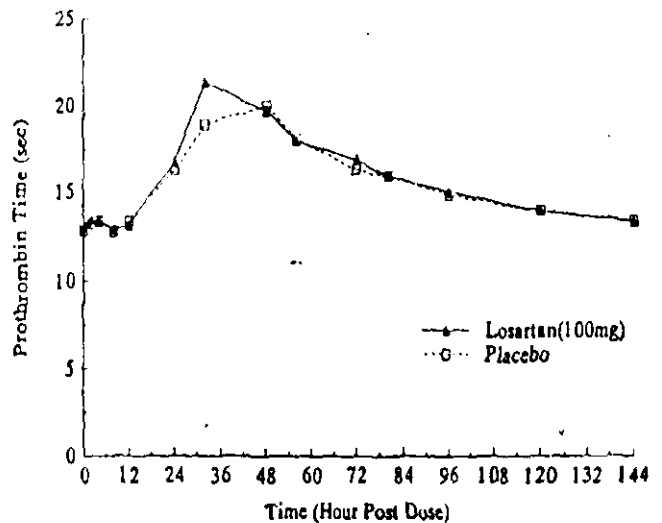
Least Square Mean Maximal Change in Prothrombin Time and 90% Confidence Interval on the Difference Between Treatments (Losartan - Placebo)

Prothrombin Time Units	Least Squares Mean Maximum Change		Mean Difference	90% CI on Difference
	Losartan	Placebo		
Seconds	9.04	7.88	1.163	(-4.176, 6.501)
INR	1.37	1.73	-0.355	(-0.836, 0.126)

Prothrombin Time (INR)
Mean Changes Across Time



Prothrombin Time (Seconds)
Means Across Time



CONCLUSION: The study supports the sponsor's labeling claim that losartan does not affect the pharmacokinetics of (R) or (S) warfarin and the pharmacodynamics response to warfarin under the conditions of the study.

LOSARTAN - DIGOXIN INTERACTION STUDY

STUDY NUMBER: 079

VOLUME: 1.52

PAGES: 8692 - 9217

INVESTIGATOR AND LOCATION:

OBJECTIVES: To determine whether the serum concentrations of immunoreactive digoxin after intravenous and oral digoxin are altered by losartan.

FORMULATIONS:

Losartan 50 mg Tablets, Lot # GBC-Y568, Batch # E-4712
Matching Placebo Tablets, Lot # GBC-Y568, Batch # E-4644
Lanoxin Injection (Wellcome), Lot # 052-928
LANOXIN Tablet (Wellcome) Lot # 865-212

STUDY DESIGN: Double-blind, randomized, two-period study in 13 subjects. Each subject received losartan (50 mg tablet) or placebo daily for 15 days in each period. On Days 4 and 11 of each period, subjects received single 0.5 mg intravenous (Day 4) and oral (Day 11) doses of digoxin. Blood samples were drawn following intravenous digoxin on Day 4 at 0, 10, 20, 30, 45 minutes, and at 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, 72, and 96 hours; and following oral digoxin on Day 11 at 0, .5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, and 96 hours. Urine was collected pre-dose (-1-0) and at 0-6, 6-12, 12-24, 24-36, 36-48, 48-72 and 72-96 hours post digoxin dose on Days 4 and 11. Urine and plasma samples were stored at -20°C until analyzed.

ASSAYS: Radioimmunoassay.

PLASMA SAMPLES

Linearity: Satisfactory. Standard curve from 0.18 to 5 ng/ml.
Accuracy: Satisfactory. 110.0% at 0.5 ng/ml, 93.0% at 4.0 ng/ml.
Precision: Satisfactory. %CV - 5.2% at 0.5 ng/ml, 7.5% at 4.0 ng/ml.
Sensitivity: LOQ - 0.18 ng/ml.
Specificity: Satisfactory. Dihydrodigoxin (a metabolite of digoxin) approximately 4.5% cross-reactivity.

URINE SAMPLES

Linearity: Satisfactory. Standard curve from 0.25 to 8 ng/ml.
Accuracy: Satisfactory. 110.0% at 0.5 ng/ml, 110.0% at 4.0 ng/ml.
Precision: Satisfactory. %CV - 7.8% at 0.5 ng/ml, 5.5% at 4.0 ng/ml.
Sensitivity: LOQ - 0.25 ng/ml.
Specificity: Satisfactory. Dihydrodigoxin (a metabolite of digoxin) approximately 5.4% cross-reactivity.

The assays have been validated over the range of plasma and urine concentrations observed in the study.

DATA ANALYSIS: AUC, C_{max}, T_{max}, and % Dose excreted in urine were calculated.

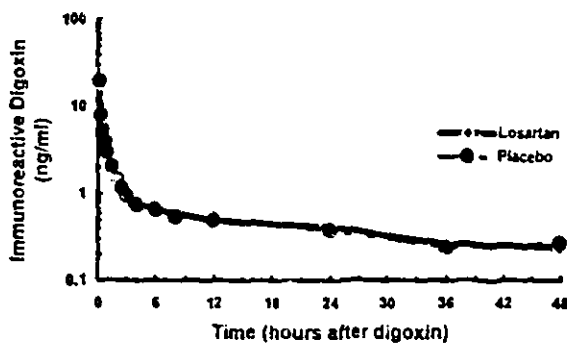
RESULTS:

Pharmacokinetic Parameters for Immunoreactive Digoxin After I.V. and Oral Digoxin During Losartan 50 mg and Placebo

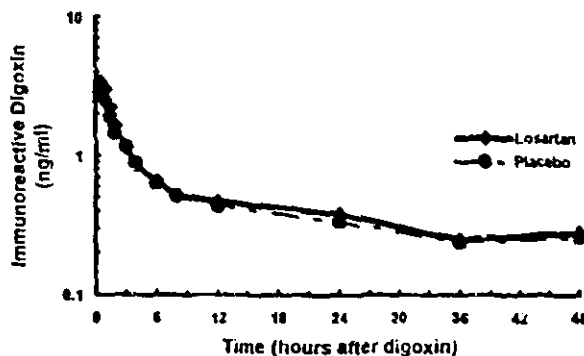
Parameter	With Losartan				Without Losartan			
	Day 4 (I.V.)	N	Day 11 (Oral)	N	Day 4 (I.V.)	N	Day 11 (Oral)	N
C _{max} (ng/mL)	—	—	3.46 (0.70)	11	—	—	3.07 (0.53)	11
AUC ₀₋₄₈ (ng·hr/mL)	28.76 (2.93)	10	23.63 (3.67)	11	28.45 (3.92)	9	22.43 (2.57)	9
AU (% dose)	54.01 (7.20)	7	51.16 (6.30)	8	51.89 (6.48)	7	46.26 (2.44)	8
T _{max} (hr)	—	—	0.64 (0.23)	11	—	—	0.86 (0.74)	11

Mean Plasma Immunoreactive Digoxin Concentrations During Treatment* with Losartan (50 mg/day) and Placebo

Intravenous Digoxin



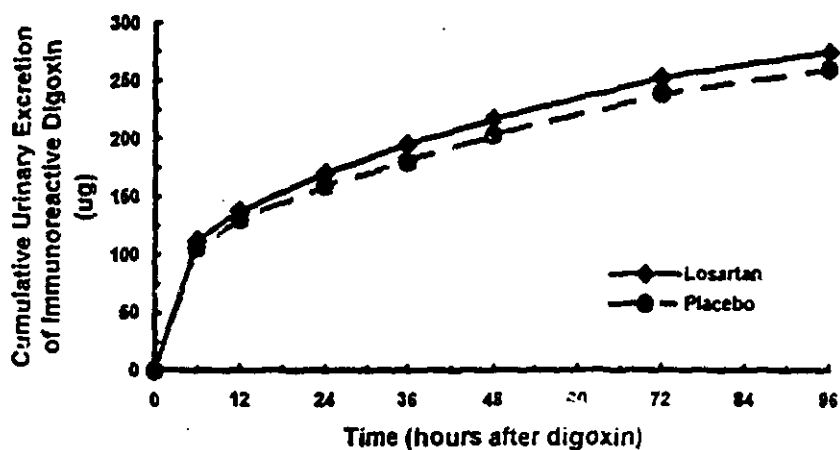
Oral Digoxin



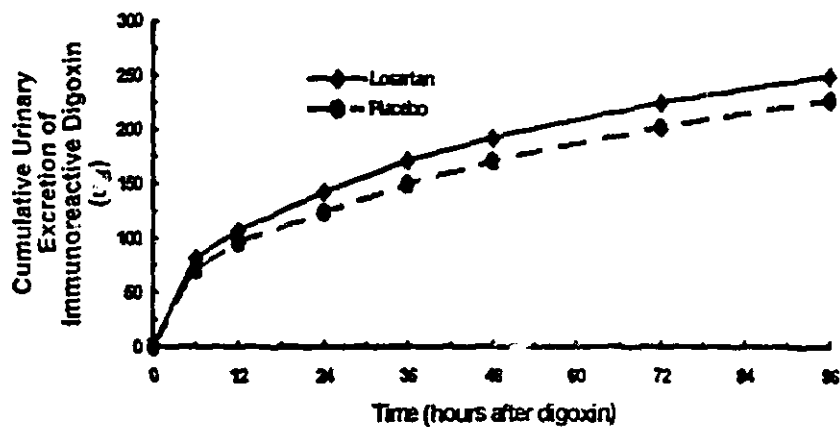
* Intravenous digoxin (0.5 mg/5 min) was administered on Day 4; oral digoxin (0.5 mg) was given on day 11.

Mean Cumulative Urinary Excretion of Immunoreactive Digoxin During Treatment* with Losartan (50 mg/day) and Placebo

Intravenous Digoxin



Oral Digoxin



* Intravenous digoxin (0.5 mg/5 min) was administered on Day 4; oral digoxin (0.5 mg) was given on day 11.

CONCLUSIONS: The study shows that losartan does not alter to a significant degree the pharmacokinetics of immunoreactive digoxin after intravenous or oral digoxin under the conditions of the study.

LOSARTAN - HYDROCHLOROTHIAZIDE (HCTZ) INTERACTION STUDY

STUDY NUMBER: 073 VOLUME: 1.53

PAGES: 9218-9810

INVESTIGATOR AND LOCATION:

OBJECTIVES: (i) To determine whether losartan alters the pharmacokinetics of HCTZ to a clinically significant degree. (ii) To determine whether HCTZ alters the pharmacokinetics of losartan to a clinically significant degree.

FORMULATIONS:

Losartan 50 mg Tablets, Formulation No. 0954FCT005C003, Control No. C-Y244

HCTZ 12.5 mg Tablets, Formulation No. CO954AFCT006C001, Control No. C-Y245

Losartan/HCTZ 50 mg/12.5 mg Tablets, Formulation No. 0954AFCT003B001, Control No. C-Y246

STUDY DESIGN: Open, randomized, three period crossover study in 12 subjects with mild to moderate hypertension and a washout period of seven days. Following a 2 week washout of their hypertension medications, subjects were randomized to receive 3 treatments: (a) one losartan 50 mg tablet daily for 7 days (b) one HCTZ 12.5 mg tablet daily for 7 days and (c) one combination losartan 50 mg/HCTZ 12.5 mg tablet daily for 7 days. Subjects were instructed follow a sodium replete diet 150-200 mEq/24 hours throughout the study. On the night prior to the seventh dose subjects fasted from midnight until 4 hours post the seventh dose. Following the seventh dose, blood samples were collected at 0, 15, 30, and 45 minutes and at 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, and 36 hours for MK-954 and E-3174 plasma concentrations, and at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18 and 24 hours for HCTZ plasma concentrations. Urine samples were collected for assay of MK-954, E-3174 and HCTZ concentrations predose and at 0-2, 2-4, 4-6, 6-8, 8-12, 12-18 and 18-24 hours post dose. Plasma and urine samples were stored at -20°C until analyzed.

ASSAYS: HPLC with UV detection.

PLASMA SAMPLES-LOSARTAN (MK-954) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curves from 5 to 1000 ng/ml

Accuracy: Satisfactory. 95.5% at 20 ng/ml, 95.9% at 800 ng/ml for MK-954; and 98.5% at 20 ng/ml, 96.3% at 800 ng/ml.

Precision: Satisfactory. %CV-6.4% at 20 ng/ml, 4.8% at 800 ng/ml for MK-954; and 5.8% at 20.0 ng/ml, 4.5% at 800 ng/ml.

Sensitivity: LOQ - 5 ng/ml for MK-954 and E-3174.

Specificity: Satisfactory. Chromatograms submitted.

URINE SAMPLES-LOSARTAN (MK-954) AND ACTIVE METABOLITE (E-3174):

Linearity: Satisfactory. Standard curves from 20 to 2000 ng/ml for MK-954; and 10 to 2000 ng/ml for E-3174.

Accuracy: Satisfactory. 90.5% at 40 ng/ml, 93.1% for 1600 ng/ml for MK-954; and 93.0% at 40 ng/ml, 95 % at 1600 ng/ml.

Precision: Satisfactory. %CV-7.0% at 40 ng/ml, 2.8% at 1600 ng/ml for E-3174. MK-954; and 3.7% at 40 ng/ml, 3.5% at 1600 ng/ml for E-3174.

Sensitivity: LOQ - 20 ng/ml for MK-954; 10 ng/ml for E-3174.

Specificity: Satisfactory, Chromatograms submitted.

PLASMA SAMPLES-HYDROCHLOROTHIAZIDE (HCTZ):

Linearity: Satisfactory. Standard curves from 2 to 100 ng/ml.

Accuracy: Satisfactory. 101.3% at 3.75 ng/ml, 101.7% at 75 ng/ml.

Precision: Satisfactory. %CV-3.4% at 3.75 ng/ml, 5.5% at 75 ng/ml.

Sensitivity: LOQ - 2.0 ng/ml.

Specificity: Satisfactory, Chromatograms submitted.

URINE SAMPLES-HYDROCHLOROTHIAZIDE (HCTZ):

Linearity: Standard curves from 0.1 to 20 µg/ml.

Accuracy: Satisfactory. 101.3% at 0.75 µg/ml, 95.6% at 15 µg/ml.

Precision: Satisfactory. %CV-3.3% at 0.75 µg/ml, 5.3% at 15 µg/ml.

Sensitivity: LOQ - 0.10 µg/ml.

Specificity: Satisfactory, Chromatograms submitted.

DATA ANALYSIS: AUC_{∞} , C_{max} , $t_{1/2}$, CL_r , λ and %Dose excreted in urine were calculated.

RESULTS:

	50-mg MK-954 Tablets Once a Day for 7 days		12.5-mg HCTZ Tablets Once a Day for 7 Days	Combination Tablets of 50 mg MK-954 and 12.5 mg HCTZ Once a Day for 7 Days			
	MK-954	B-3174	HCTZ	MK-954	B-3174	HCTZ	
C_{max} , ng/ml ^a	223.7 ± 81.9	211.5 ± 72.6	87.5 ± 28.3	240.2 ± 85.3	215.8 ± 68.3	79.0 ± 28.8	
T_{max} , hr	1.0 ± 0.5	3.9 ± 1.4	1.9 ± 0.6	1.2 ± 1.3	3.7 ± 1.1	2.4 ± 0.8	
$AUC_{0-\infty}$, ng·hr/ml ^a	441.5 ± 173.1	1684.6 ± 451.6	634.0 ± 186.8	449.6 ± 163.8	1724.8 ± 460.9	525.8 ± 134.5	
λ , hr ⁻¹	0.3378 ± 0.1152	0.0943 ± 0.0310	0.0671 ± 0.0113	0.3310 ± 0.0730	0.0943 ± 0.0331	0.0711 ± 0.0158	
$t_{1/2}$, hr ^b	2.1 ± 0.7	7.4 ± 2.4	10.3 ± 1.8	2.1 ± 0.5	7.3 ± 2.6	9.7 ± 2.1	
CL_r , ml/min	55.8 ± 25.4	20.1 ± 2.7	227.0 ± 54.8	51.5 ± 11.5	18.1 ± 3.4	243.0 ± 56.4	
Urinary Recovery ^c , %	mg ^d	1.448 ± 0.467	2.037 ± 0.652	8.245 ± 1.528	1.407 ± 0.461	1.851 ± 0.502	7.513 ± 1.790
	% Dose	2.9 ± 0.9	4.3 ± 1.4	66.0 ± 12.2	2.8 ± 0.9	3.9 ± 1.1	60.1 ± 14.3
AUC Geometric mean ratio (Combo/Single) and confidence interval limits ^e	-	-	-	1.02 (0.952, 1.09)	1.02 (0.964, 1.09)	0.832 (0.771, 0.900)	
C_{max} Geometric mean ratio (Combo/Single) and confidence interval limits ^e	-	-	-	1.07 (0.985, 1.17)	1.03 (0.943, 1.12)	0.889 (0.789, 1.00)	
Urinary recovery geometric mean ratio (Combo/Single) and confidence interval limits ^e	-	-	-	-	-	0.898 (0.790, 1.02)	

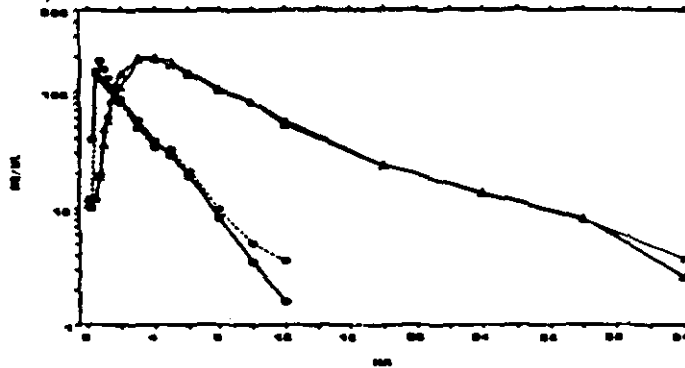
^a C_{max} , AUC and urinary recovery normalized to 50.0 mg for MK-954 and B-3174, and to 12.50 mg for HCTZ, based on assayed potencies of the formulations.

^bHarmonic mean and pseudo standard deviation.

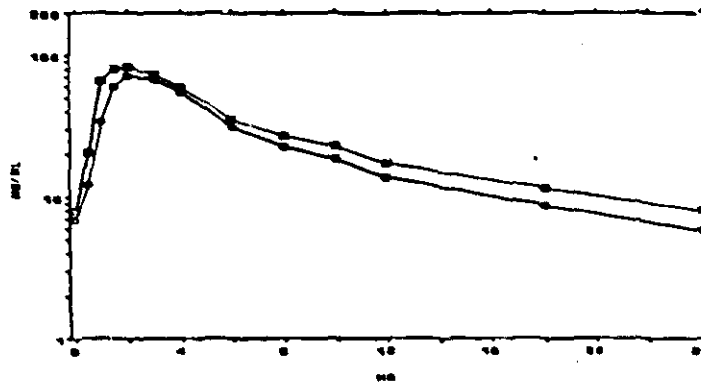
^c90% Confidence interval limits.

Mean Plasma Concentration vs. Time Profiles in Hypertensive Patients for Losartan, L-158,641, and Hydrochlorothiazide (HCTZ) Following Once-a-Day Administration of Losartan (50 mg), HCTZ (12.5 mg) and a Combination Tablet of Losartan/ HCTZ (50 mg/12.5 mg) for 7 Days

Losartan/ L-158,641



Hydrochlorothiazide



Key. Losartan/ L-158,641-single tablet = O/ Δ; Losartan/ L-158,641-combination tablet = ●/▲
Hydrochlorothiazide-single tablet = □; Hydrochlorothiazide-combination tablet = ○

CONCLUSIONS: There is no significant pharmacokinetic between losartan and HCTZ when both drugs are co-administered under the conditions of the study.

PHARMACOKINETIC / PHARMACODYNAMIC RELATIONSHIP

INTRODUCTION: In relating effects of losartan in humans to plasma concentrations of losartan and/or E-3174 (or L-158,641) (the active metabolite), a number of factors must be considered in the analyses: (i) both losartan and E-3174 are active and potent angiotensin II antagonists, (ii) the intrinsic potency of E-3174 is greater (by 5 to 10-fold) than losartan, (iii) only free drug is available for distribution to, and interaction with the receptor, (iv) losartan is a competitive antagonist while E-3174 is a non-competitive antagonist, (v) the elimination of E-3174 is slower ($t_{1/2} = 6-9$ hrs, $CL = 50$ ml/min; concentration can be measured at trough at steady state) than the elimination of losartan ($t_{1/2} = 2$ hrs, $CL = 600$ ml/min, only detectable in plasma through 12 hours after dosing, depending on the dose).

Concentration-effect analyses done by the sponsor have focused only on E-3174, or have utilized a semiadditive approach (for example, $[E-3174] + [losartan]/2$) to account for the presence of both antagonists.

STUDY #006: This study was designed to investigate the capacity of higher single doses (40, 80, 120 mg) of losartan to antagonize pressor responses to bolus injections of angiotensin II which increase systolic blood pressure approximately 20-30 mmHg. The systolic blood pressure responses (% inhibition) to exogenous angiotensin II and concentration of E-3174 were fit to a Hill-Sigmoid-Emax model (Figure 1). Mean model parameters (range) for E-3174 were: $E_{max} - 91\%$ (66-100); $EC_{50} - 32$ ng/ml (1-99 ng/ml); Hill coefficient - 0.9 (0.13-3.0). The time-integrated (i. e. AUC) response to losartan was fit to an E_{max} model (Figure 2) and the model shows that the 80- and 120-mg doses of losartan resulted in similar average levels of inhibition of the pressor response over 9-hour period. Model parameters ($\div 9$ hours) were: $E_{max} - 774\% \cdot hr$ (86); $EC_{50} - 577$ ng*hr/ml (64 ng/ml).

STUDY #035: In this study forearm blood flow responses to brachial artery infusions of angiotensin I, II and bradykinin were determined, with blood collected for measurement of plasma renin concentration (PRC), losartan and E-3174 concentrations at the time of agonist infusions. Treatments included placebo, 20 mg and 100 mg losartan and 10 mg enalapril. Table 1 shows the mean (or median) effects, and losartan and E-3174 concentration obtained from this study. The average pre- and post-angiotensin I (pre-, post-AI) blood flow responses are expressed as a ratio relative to the non-infused arm. ED_{50} is the median angiotensin I infusion rate which was estimated (by interpolation or extrapolation) to result in a blood flow ratio of 0.5. PRC ratio is the PRC measurement just prior to angiotensin I infusion divided by the predose PRC measurement. Figures 3-5 are scatter plots that show that both concentration-effect and dose-effect relationships are apparent and that the results are consistent with the E_{max} model derived above with near-maximal inhibition achieved at concentrations above 250 ng/ml.

STUDY # 013 AND STUDY #017: In these studies the tolerability of 20-minute IV infusions of losartan (40 mg, Study #013) and E-3174 (80 mg, Study #017) was assessed. Figure 6 shows that high losartan and E-3174 concentrations achieved at the end of the infusion were not associated with the greatest changes in blood pressure during the observation period thus indicating that some distribution of losartan/E-3174 is necessary for the expression of this presumed pharmacodynamic effect in healthy subjects.

STUDY #011: Patients with mild to moderate essential hypertension were treated for 8 weeks with losartan doses of 0 (placebo), 10, 25, 50, 100, and 150 mg/day, or 20 mg enalapril. In 181 patients, plasma was collected for measurement of losartan and E-3174 concentrations at trough (predose) and peak (about 6 hours postdose) blood pressure response. The data obtained from this study (Table 2) shows that mean drug concentration (losartan and E-3174) increased with increasing dose of losartan and an apparent dose-response relationship for the antihypertensive effect at peak and trough. The scatter plots of peak and trough E-3174 concentrations versus change at peak and trough in supine diastolic blood pressure (Figure 7) show that individual peak or trough drug concentrations do not correlate with antihypertensive effect in this population.

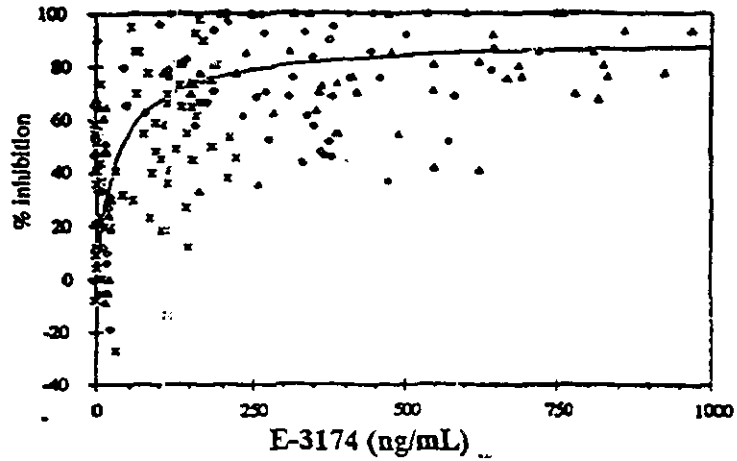
STUDY #043: In this study, plasma drug concentrations, blood pressure effects and Renin Angiotensin Aldosterone System (RAAS) mediators (i.e. PRA, and plasma concentrations of angiotensin II and aldosterone) were measured during the 8-12 hours after dosing following the first and last (6 weeks) dose of once-daily placebo and 25 and 100 mg losartan. The effects of losartan on blood pressure and RAAS mediators are summarized in Figures 8-11 (for each individual AUC for effect, an individual AUC for drug concentration ([losartan]_{1/2} + [E-3174]) over the appropriate interval was calculated) from it can be concluded that at 6 weeks, as the concentration AUC of [losartan]_{1/2} + [E-3174] increased, the observed effect also increased.

STUDY #069: In this study 12 hypertensive patients received a 20 mg dose of E-3174 as an intravenous infusion at a rate of 5 mg/hour and 8 received placebo. Blood pressure was measured for 12 hours following initiation of the infusion. Figure 12 shows that supine diastolic blood pressure declined as the drug concentrations increased and that there was a further decrement in blood pressure after termination of the infusion (even with adjustment for diurnal changes in the placebo group). Plotting supine diastolic blood pressure change vs. E-3174 concentration (Figure 13) resulted in an open hysteresis plot with a somewhat linear portion up to achievement of maximal concentrations, followed by additional decreases in blood pressure as concentration declined.

CONCLUSION: The results of the studies summarized above support the sponsor's labeling claims on the relationship between plasma drug concentration (losartan and E-3174) and pharmacodynamic effect.

Figure 1

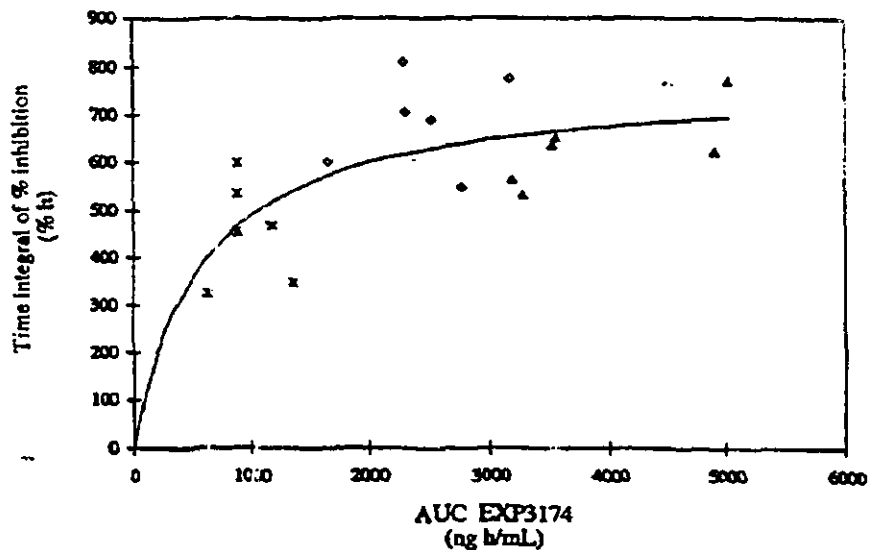
Inhibition of Systolic Pressor Responses to Angiotensin II as a Function of E-3174 (L-158,641) Concentration -- Brunner Protocol #006 [References C-5; C-43]



Solid line is Hill equation fit to the data
* = 40 mg; ◊ = 80 mg; Δ = 120 mg losartan

Figure 2

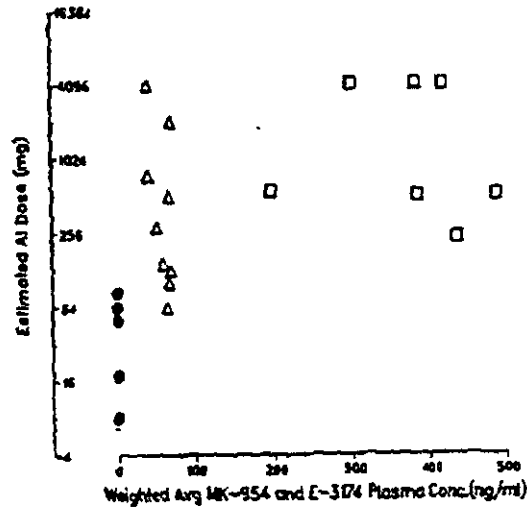
Inhibition of Systolic Pressor Responses to Angiotensin II Injections: AUC for Inhibition vs. AUC for E-3174 (L-158,641) -- Brunner Protocol #006 [References C-5; C-43]



Solid line is Hill equation fit to the data
* = 40 mg; ◊ = 80 mg; Δ = 120 mg losartan

Figure 5

Angiotensin I ED₅₀ vs. Plasma Concentration of Losartan + L-158,641 (Weighted Average) Ritter Protocol #035 [Reference C-13]

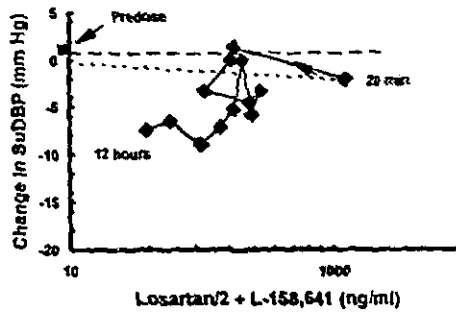


• = placebo; Δ = 20 mg losartan; □ = 100 mg losartan

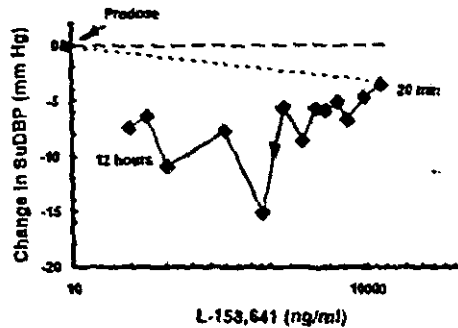
Figure 6

Mean Changes in Supine Diastolic Blood Pressure vs. Plasma Drug Concentration Following 20-minute Intravenous Infusions of Losartan (40 mg) and L-158,641 (80 mg) Protocols # 013 (Losartan) [Reference C-8] and #017 (L-158,641) [Reference C-11]*

Losartan- 40 mg/20 minutes



L-158,641- 80 mg/20 minutes



* Solid lines connect actual data points; dashed lines connect data pre-infusion (i.e., no changes in BP, no drug in blood) with the first measurement after start of infusion. Graphs are redrawn from: Top - [Reference C-8: Appendix 1, Tables 4 and 6; Appendix 3] and Bottom - [Reference C-11: Appendix 1, Table 5; Appendix 3].

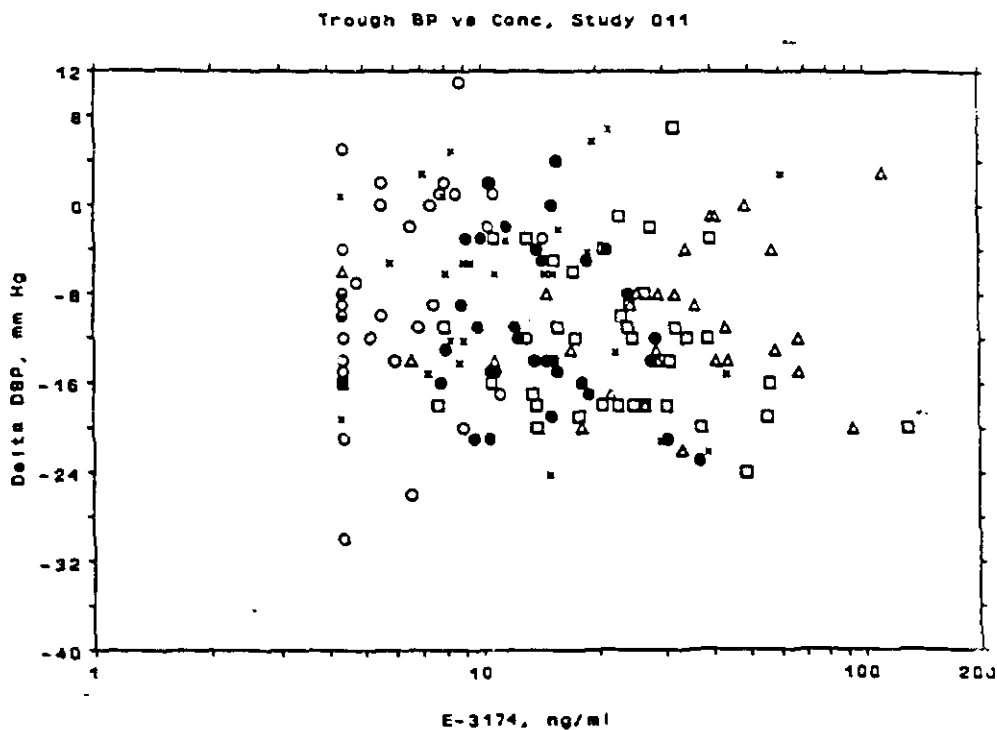
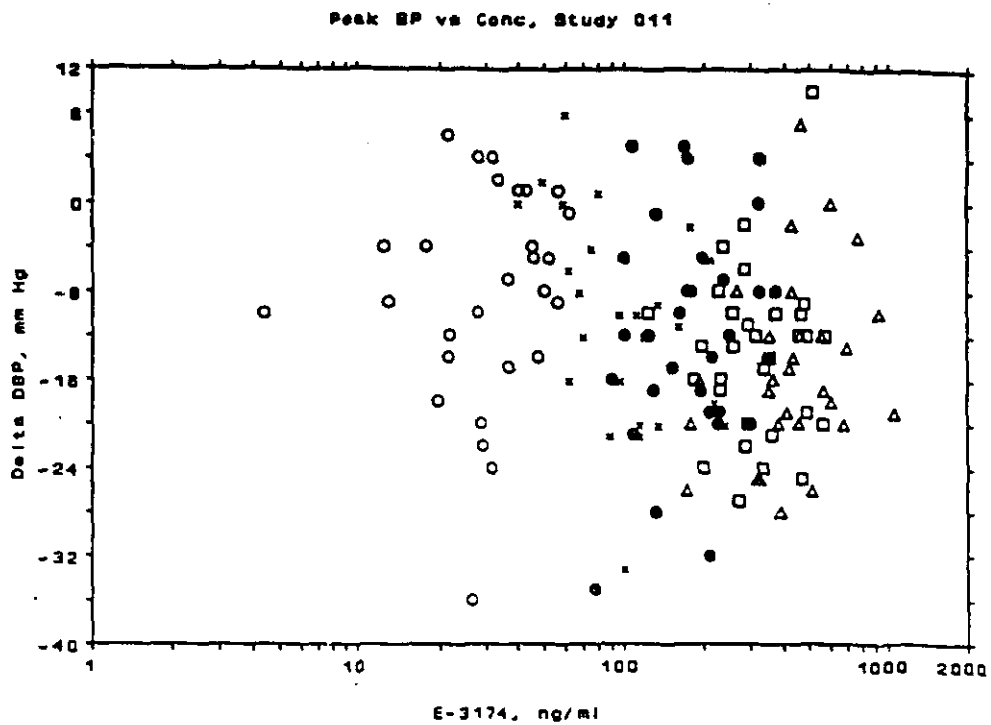


Figure 7 Peak (5-8-hr) and Trough Change in Diastolic Blood Pressure Versus Plasma E-3174 Concentration Relationship in Patients Treated With 10 mg (O), 25 mg (x), 50 mg (●), 100 mg (□) and 150 mg (Δ) of Oral MK-954 Once a Day for Eight Weeks. Concentrations Below the Detection Limit Are Plotted As 4.4 ng/ml.

Figure 8

Change (difference) in Supine Diastolic Blood Pressure vs. Weighted Average Drug Concentration AUC after 6 Weeks Treatment with Placebo (X), 25 mg Losartan (▲) and 100 mg Losartan (●) - (RAAS Study- Protocol #043) [Reference C-28]

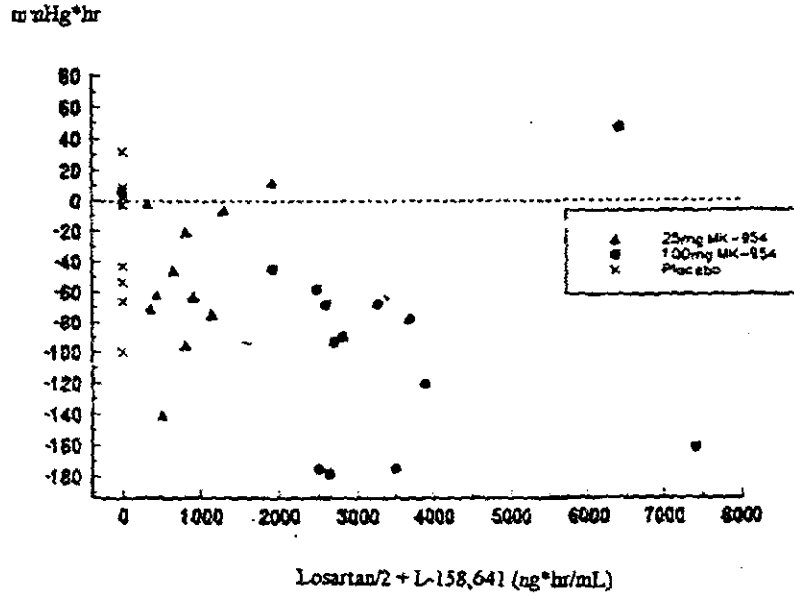


Figure 9

Change (ratio) in Supine Plasma Angiotensin II Concentration (Direct RIA) vs. Weighted Average Drug Concentration AUC after 6 Weeks Treatment with Placebo (X), 25 mg Losartan (▲) and 100 mg Losartan (●) - (RAAS Study- Protocol # 043) [Reference C-28]

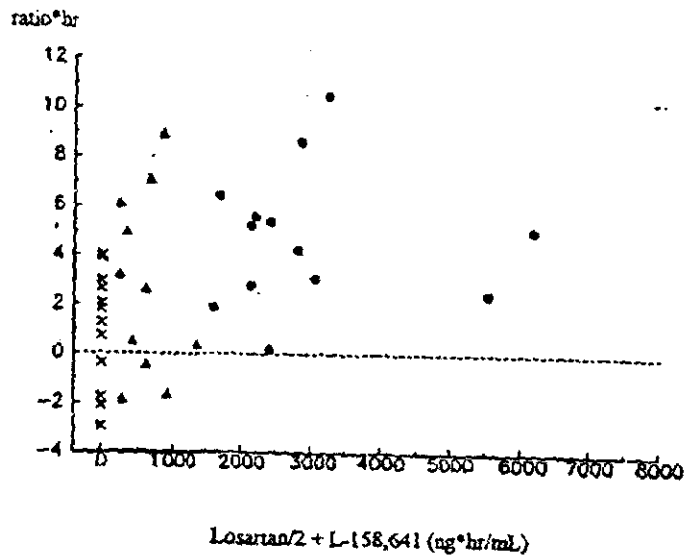


Figure 10

Change (ratio) in Supine Plasma Renin Activity vs. Weighted Average Drug Concentration (AUC) after 6 Weeks Treatment with Placebo (X), 25 mg Losartan (Δ) and 100 mg Losartan ($\bullet$) - (RAAS Study- Protocol # 043) [Reference C-28]

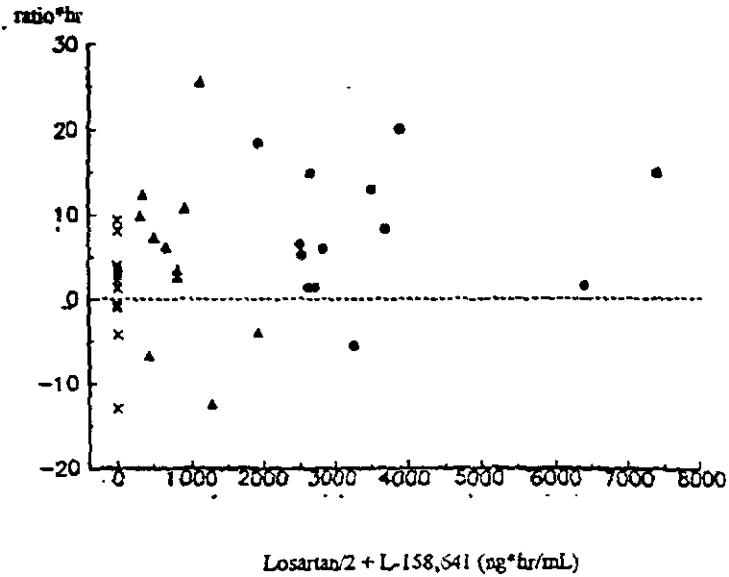


Figure 11

Change (difference) in Supine Plasma Aldosterone Concentration vs. Weighted Average Drug Concentration (AUC) after 6 Weeks Treatment with Placebo (X), 25 mg Losartan (Δ) and 100 mg Losartan ($\bullet$) - (RAAS Study- Protocol # 043) [Reference C-28]

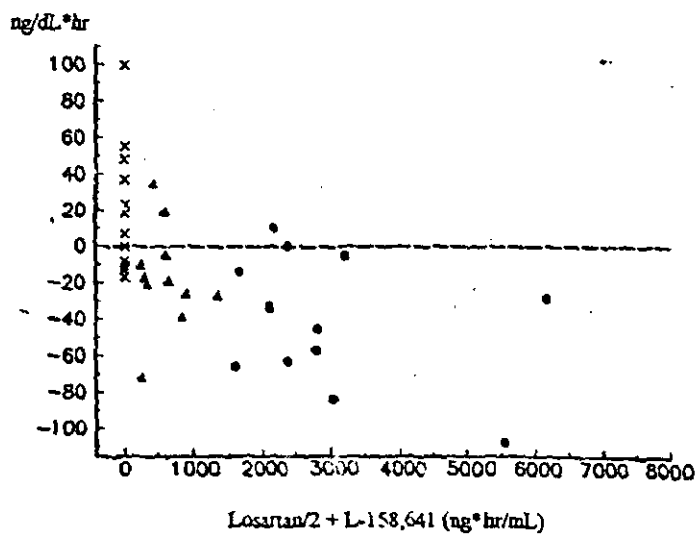
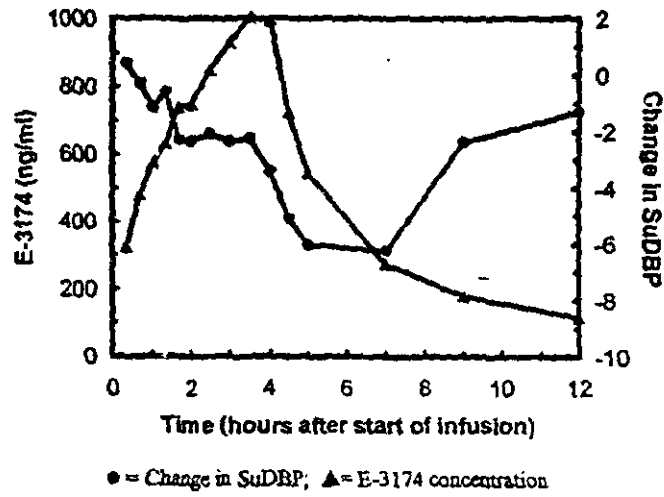


Figure 12

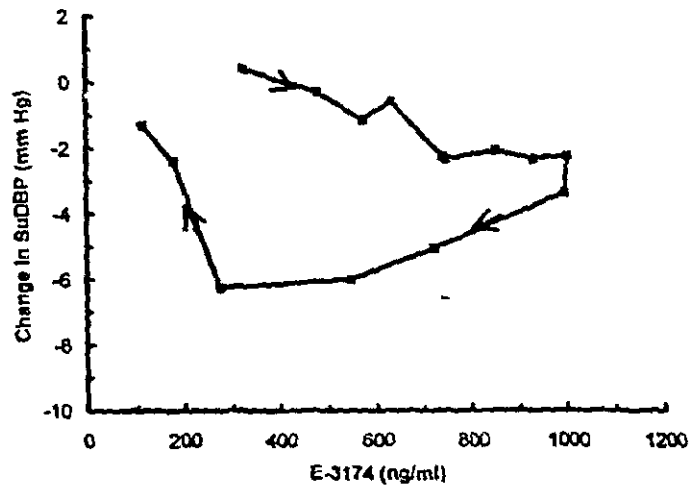
Mean Plasma L-158,641 (E-3174) Concentrations and Changes in Supine Diastolic Blood Pressure (placebo-adjusted) During and After Infusion of L-158,641 at 5 mg/hour for 4 Hours— (Protocol # 069) [Reference C-27]*



*Drawn from [Reference C-2]: p. C-19317, Table 8; Appendix 5]

Figure 13

Mean Plasma L-158,641 Concentrations vs. Changes in Supine Diastolic Blood Pressure (placebo-adjusted) during and after infusion of L-158,641 at 5 mg/hour — (Protocol # 069) [Reference C-27]*



* Redrawn from data in Figure C-63 [Reference C-27: p. C-19317, Table 8, Appendix 5]

Table 1

Summary of Plasma Concentration and Angiotensin Antagonism Data from Forearm Blood Flow Study – Ritter #035 [Reference C-13]*

	Drug Concentration				Responses to Angiotensin I (AI)			Plasma Renin
	Losartan (ng/mL)		L-158,641 (ng/mL)		Blood Flow Ratio		ED ₅₀ (pmol/min)	
	Pre-AI	Post-AI	Pre-AI	Post-AI	AI: 16 pmol/min	AI: 64 pmol/min		PRC Ratio
	PBO					0.5	0.37	
20 mg	16.2	10.4	49.9	57.2	0.78	0.63	292	3.09
100 mg	41.5	21.5	413.8	312.7	0.92	0.81	553	7.33

* All values are means except ED₅₀ which is median.

Table 2

Mean Plasma Drug Concentrations and Mean Changes in Supine Diastolic Blood Pressure (SuDBP) in Hypertensive Patients given Losartan for 8 Weeks – Multicenter Study #011 [Reference C-56]

Dose (mg)	N*	Drug Concentrations (ng/mL)				Change in SuDBP (mmHg)	
		Trough		Peak		Trough	Peak
		Losartan	L-158,641	Losartan	L-158,641		
placebo	75	–	–	–	–	-5.8	-4.7
10	79	<5	5.3	6.1	33.5	-7.9	-7.3
25	80	<5	14.9	17	111.0	-7	-9.9
50	77	<5	14.6	29.9	196.7	-10.2	-11.9
100	86	<5	27.2	39.9	337.9	-10.0	-10.5
150	81	<5	38	48.2	475.7	-10.0	-13.1
Enal 20	82	–	–	–	–	-11.2	-16.2

*N is the number of patients with blood pressure data; the number with concentration data ranged from 32 to 40 patients/dose.

HUMAN LIVER MICROSOMAL METABOLISM

VOLUME: 1.50

PAGES: 7849 - 7861

INVESTIGATOR AND LOCATION: R. CHEN *ET AL*
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OBJECTIVE: To investigate the mechanism of the biotransformation of losartan (L-158,086) to its pharmacologically more potent metabolite (l-158,641 or E-3174) and to identify the enzyme(s) responsible for this conversion.

PROCEDURES:

Losartan was incubated with human liver microsomes and microsomes containing recombinant human P-450 isoforms at 2-4 mg/ml protein in 0.1M phosphate buffer, pH 7.4, containing 150 mM KCl and 1 mM EDTA. The incubation was carried out in the presence of NADPH and oxygen as well as in the absence of either cofactor.

Both losartan and its putative aldehyde intermediate (L-158,610) were incubated with human liver microsomes under an atmosphere of $^{18}\text{O}_2$.

L-158,610 was incubated with microsomes isolated from cells containing recombinant isoforms of human cytochrome P-450 (CYP1A1, 1A2, 2B6, 2C8, 2C9, 2D6, 2E1, and 3A4).

Human liver microsomal incubations with losartan were performed in the presence of specific inhibitors of cytochrome P-450. Microsomes were either pretreated for 30 minutes with mechanism based inhibitors (gestodene, 17 α -ethynylestradiol, troleandomycin, 1-aminobenzotriazole, and SKF525A) or preincubated for 5 minutes with competitive inhibitors (ketoconazole -CYP2C inhibitor, and sulfaphenazole - CYP3A4 inhibitor). The experiment with sulfaphenazole (1, 5, and 50 μM) was repeated using L-158,610 and L-158,086. Aliquots of the incubation medium were analyzed using HPLC and mass spectrometry.

RESULTS:

**Metabolism of L-158,086 to L-158,641
by Human Liver Microsomes-
Effect of Cytochrome P-450 Inhibitors and Cofactors**

<u>Incubation^a containing</u>	<u>nmol L-158,641 formed</u>	<u>% of control</u>
- NADPH	0.02	3
+ NADPH regen. system	0.75	100
+ Gestodene (100 μ M) ^b	0.35	47
+ Ketoconazole (200 μ M)	0.21	28
+ 17 α -ethynlestradiol (100 μ M) ^b	0.30 ^c	40
+ TAO (100 μ M) ^b	0.60 ^c	80
+ TAO (1mM) ^b	0.40	53
+ Sulfaphenazole (1 μ M)	0.43 ^c	57 (89) ^d
+ Sulfaphenazole (5 μ M)	0.19 ^c	25 (79) ^d
+ Sulfaphenazole (50 μ M)	0.10 ^c	14 (48) ^d
+ SKF 525A (100 μ M) ^b	0.40 ^c	53
+ 1-Aminobenzotriazole (500 μ M) ^b	0.30 ^c	40

^a Incubations consisted of 2 mg/ml microsomal protein (0.38 nmol P-450/mg protein) in 0.1 M phosphate buffer, pH 7.4, containing 150 mM KCl and 1 mM EDTA. Microsomes were typically preincubated with substrate for 5 minutes in a reciprocating water bath at 37 degrees C. Metabolism was initiated by addition of an NADPH regenerating system consisting of 1.3 mM NADP, 3.3 mM glucose-6-phosphate and MgCl₂, and 0.5-1 u/ml glucose-6-phosphate dehydrogenase. Incubation time varied from 20-40 minutes.

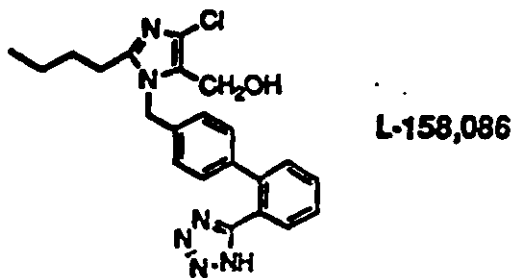
^b Mechanism based inhibitors of cytochrome P-450 were incubated with microsomes and NADPH regenerating system for 30 minutes at 37 degrees C prior to addition of substrate.

^c Data normalized to control value.

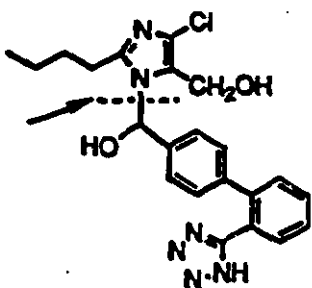
d-Values for incubation of L-158,610 in bracket.

Notebook/Page: 15216/94-99, 142-148 16515/164-169

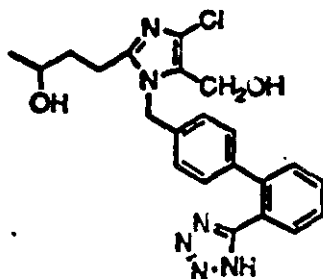
SUMMARY OF METABOLITES FORMED IN LIVER SLICE INCUBATIONS



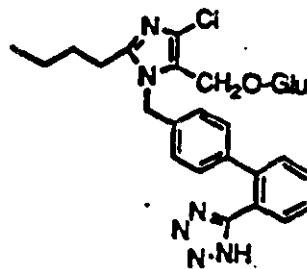
Liver Slices



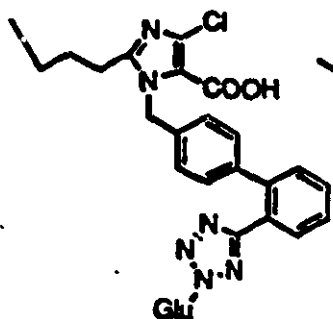
M1
Metabolite is unstable
and fragments (at arrow)
giving L-688,160 and
L-706,591



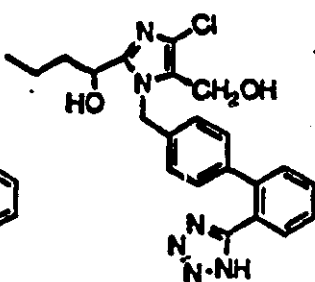
M2
L-158,795



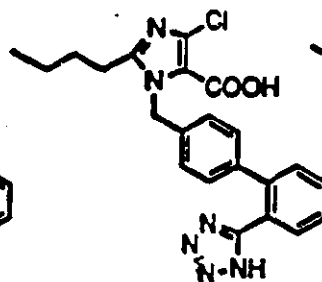
M3
L-158,782



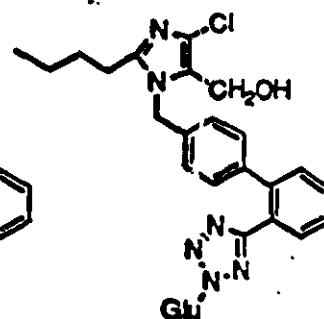
M4
L-158,781



M5
L-158,796



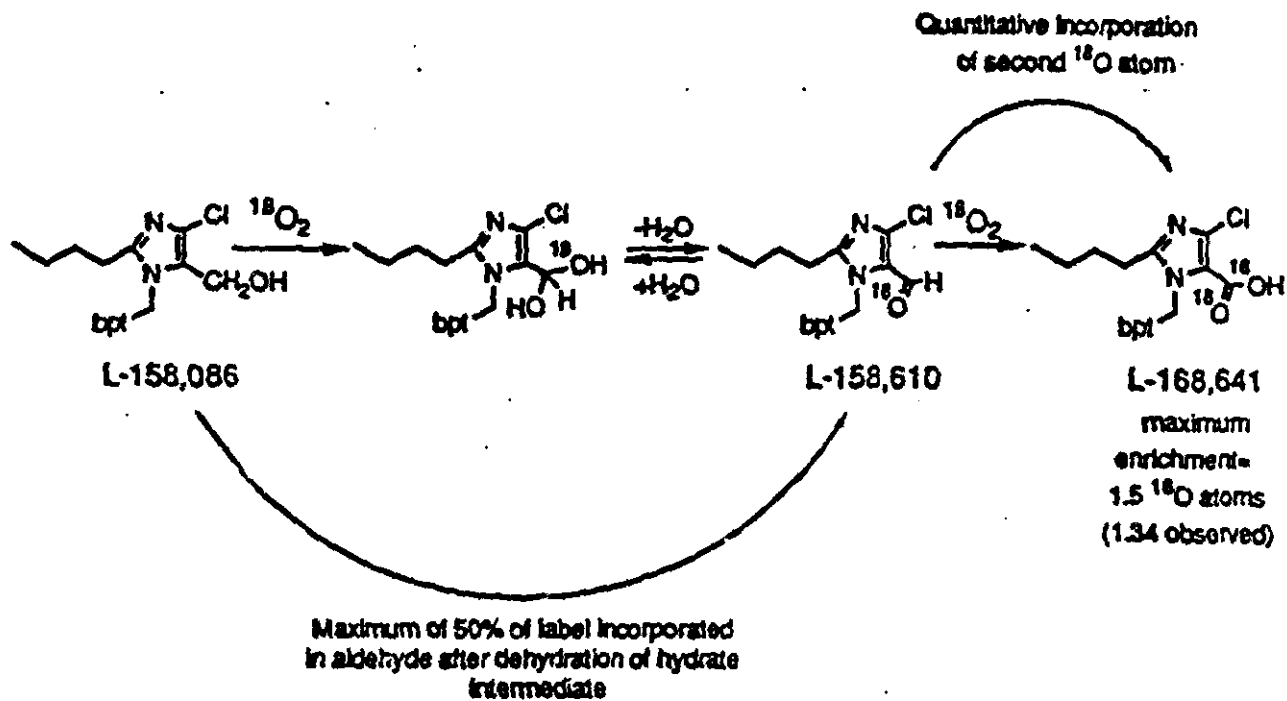
M6
L-158,641



M7
L-158,783

Glu= 2β-glucuronic acid

**Proposed Mechanism for the Biotransformation
of L-158,086 and L-158,610 to L-158,641**



bpt = biphenyl tetrazole

CONCLUSIONS: Conversion of losartan to L-158,641 is catalyzed by cytochrome P-450 and both CYP3A and 2C isozymes are involved in this biotransformation. Both CYP2C9 and 3A4 can metabolize L-158,610 to L-158,641.

IN VITRO PROTEIN BINDING

REPORT NUMBER: DMP 93-008
AMANDA NUMBER: 1009301002

VOLUME:1.53

PAGES: 9993 - 10014

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PROCEDURES:

Methanolic stock solutions of ^{14}C -losartan or ^3H -E3174 were added to glass test tubes and dried under nitrogen. Plasma from human volunteers (N=4) was added to give final concentrations of 0.050, 0.500, 1.000, 2.00, and 5.00 or 0.100, 1.00, and 10.000 $\mu\text{g}/\text{ml}$ of losartan or E-3174 respectively. The samples (in triplicate) were mixed, and incubated for 30 minutes at 37°C and the fraction unbound was determined by ultrafiltration using liquid scintillation counting (LSC).

To determine if the binding varied with pH, aliquots of pooled plasma (N=3 different subjects) were adjusted with 0.14 N HCl or 0.1 N NaOH to values of 6.95, 7.52, 7.95, 8.10, and 8.58 (pH range of the human plasma prior to and after incubation) at 37°C and incubated (in triplicate) with ^{14}C -losartan or ^3H -E3174 ($1\ \mu\text{g}/\text{ml}$) as described above.

To investigate binding to albumin and α_1 -acid glycoprotein (AAG), stock solutions of purified human albumin or AAG were prepared in isotonic pH 7.4 buffer to yield physiological concentrations of 4.5 g/dL and 1 mg/ml. Incubation and analysis were identical to those described previously.

The displacement of losartan and E-3174 from human plasma proteins by other drugs was investigated using ^{14}C -losartan or ^3H -E3174 ($1\ \mu\text{g}/\text{ml}$) and diazepam (0.35, 3.50 $\mu\text{g}/\text{ml}$); aspirin (300, 3000 $\mu\text{g}/\text{ml}$); naproxen (50, 500 $\mu\text{g}/\text{ml}$); warfarin (2, 20 $\mu\text{g}/\text{ml}$); and ibuprofen (20, 200 $\mu\text{g}/\text{ml}$).

The effects of losartan and E-3174 or naproxen on human plasma binding of warfarin was investigated using ^{14}C -warfarin (2 $\mu\text{g}/\text{ml}$) and losartan and E-3174 (0.250, 2.500 $\mu\text{g}/\text{ml}$) or naproxen (500 $\mu\text{g}/\text{ml}$).

The potential effects of unknown metabolites on the binding of losartan and E-3174 were investigated using plasma from volunteers (N=4) dosed orally with either 250 or 300 mg of losartan and ^{14}C -losartan ($1\ \mu\text{g}/\text{ml}$) or ^3H -E3174 ($1\ \mu\text{g}/\text{ml}$). The plasma samples were collected from 0-2 or 4-6 hour postdose, reflecting times to peak levels of losartan and E-3174 respectively. The concentrations of losartan and E-3174 present in the samples prior to the addition of the radiolabelled tracers were determined by HPLC.

RESULTS:

SPECIES-DEPENDENT PLASMA PROTEIN BINDING OF LOSARTAN AND E3174

Concentration µg/mL	Percent Free (f _u)				
	Losartan			E3174	
	Man	Dog	Rat	Man	Rat
0.100	ND	ND	ND	0.2 ± 0.0	0.1 ± 0.0
0.500	1.4 ± 0.2	3.1 ± 0.3 ^a	0.7 ± 0.2 ^{a,b}	ND	ND
1.000	1.3 ± 0.1	2.7 ± 0.5 ^a	0.8 ± 0.0 ^{a,b}	0.2 ± 0.0 ^c	0.2 ± 0.0 ^c
2.000	ND	2.9 ± 0.5	1.0 ± 0.0 ^b	ND	ND
5.000	1.2 ± 0.1	ND	ND	ND	ND
10.000	ND	ND	ND	0.2 ± 0.0	0.1 ± 0.0

Mean ± S.D., N=3-4 analyzed in triplicate.

ND, Not Determined.

^a p<0.05 vs human.

^b p<0.05 vs dog.

^c p<0.05 vs losartan.

EFFECTS OF VARYING pH ON THE HUMAN PLASMA PROTEIN BINDING OF 1 µg/mL OF LOSARTAN AND E3174

pH	Percent Free (f _u)	
	Losartan	E3174
6.95	2.2 ± 0.2	1.1 ± 0.1
7.52	1.7 ± 0.3	1.0 ± 0.1
7.95	1.5 ± 0.2	0.8 ± 0.0 ^a
8.10	1.3 ± 0.2	0.7 ± 0.1
8.58	1.5 ± 0.3	0.8 ± 0.1
Unadjusted	1.3 ± 0.2	0.7 ± 0.1

Mean ± S.D., triplicate analyses.

^a duplicate analyses.

BINDING OF 1 µg/mL OF LOSARTAN AND E 3174 TO PURIFIED RAT OR HUMAN ALBUMIN AND ALPHA₁-ACID GLYCOPROTEIN (AAG)

Protein	Percent Free (f _u)			
	Losartan		E3174	
	Human	Rat	Human	Rat
Albumin	4.0 ± 0.4	1.4 ± 0.0 ^a	1.5 ± 0.4	0.8 ± 0.0
AAG	60.2 ± 0.8	14.9 ± 1.4	76.4 ± 4.5	76.0 ± 4.5

Mean ± S.D., triplicate analyses.

^a duplicate.

HUMAN PLASMA PROTEIN BINDING OF 1 µg/mL OF LOSARTAN AND E3174 IN THE PRESENCE OF OTHER COMMONLY ADMINISTERED DRUGS.

Drug	Conc. µg/mL	Percent Free (f _u)			
		Losartan		E3174	
		Subject 1	Subject 2	Subject 1	Subject 2
None	-	1.2 ± 0.1	1.3 ± 0.1	0.8 ± 0.0	0.7 ± 0.0
ASA	300	2.7 ± 0.1 ^a	2.8 ± 0.2 ^a	1.4 ± 0.1 ^a	1.4 ± 0.2 ^a
	3000	9.0 ± 1.0 ^a	9.0 ± 0.6 ^a	5.4 ± 0.2 ^a	5.5 ± 1.1 ^a
Naproxen	50	1.4 ± 0.0	1.3 ± 0.1	0.8 ± 0.0	0.8 ± 0.1
	500	2.9 ± 0.5 ^a	3.7 ± 0.2 ^a	2.9 ± 0.0 ^a	2.6 ± 0.5 ^a
Ibuprofen	20	1.2 ± 0.0	1.2 ± 0.1	0.8 ± 0.0	0.8 ± 0.0
	200	1.8 ± 0.3 ^a	1.9 ± 0.1 ^a	1.1 ± 0.0 ^a	1.0 ± 0.1 ^a
Diazepam	0.35	1.3 ± 0.1	1.1 ± 0.1	0.8 ± 0.0	0.8 ± 0.0
	3.50	1.1 ± 0.2	1.5 ± 0.0	0.8 ± 0.0	0.6 ± 0.0
Warfarin	2	1.3 ± 0.1	1.2 ± 0.2	0.7 ± 0.0	0.8 ± 0.1
	20	1.0 ± 0.1	1.5 ± 0.1	0.8 ± 0.0	0.6 ± 0.1

Mean ± S.D. of triplicate analyses.

^a Greater than control (none), p < 0.05.

HUMAN PLASMA PROTEIN BINDING OF WARFARIN (2.0 µg/mL) IN THE PRESENCE OF LOSARTAN AND E3174.

Drug	Conc µg/mL	Percent Free (f _u)
None		1.3 ± 0.1
Losartan	0.250	1.2 ± 0.1
	2.500	1.3 ± 0.1
E3174	0.250	1.4 ± 0.1
	2.500	1.4 ± 0.2
Losartan + E3174	0.250	1.4 ± 0.1
Naproxen	500	2.4 ± 0.2 ^a

Mean ± S.D., triplicate analyses

^ap < 0.05 vs control (none)

PLASMA BINDING IN VOLUNTEERS DOSED WITH LOSARTAN

Sample	Losartan		E-3174	
	Conc $\mu\text{g/ml}$	f_u %	Conc $\mu\text{g/ml}$	f_u %
Volunteers (0-2 hr)	0.93 ± 0.028	1.5 ± 0.3	1.342 ± 0.06	0.5 ± 0.0
Volunteers (4-6 hr)	0.432 ± 0.065	1.5 ± 0.3	0.535 ± 0.0	0.5 ± 0.0
Naive human plasma	-	1.4 ± 0.1	-	0.4 ± 0.0

CONCLUSIONS: The data obtained from the studies support the sponsor's labeling claims for the plasma protein binding of both losartan and E-3174.

COMMENTS: The lower end of the therapeutic concentrations for losartan (< 500 ng/ml) and E-3174 (< 100 ng/ml) were not used in the binding studies.

DRUG PRODUCT DISSOLUTION TESTING

Summary of Losartan Potassium Tablets Results for Initial Dissolution⁽¹⁾

<u>Dose Strength</u>	<u>Lot No.</u>	<u>Test No.</u>	<u>No. of Tablets</u>	<u>Dissolution 30 minutes (% label)</u>	<u>Mean Dissolution 30 minutes</u>	<u>Dissolution 45 minutes (% label)</u>	<u>Mean Dissolution 45 minutes</u>
25 mg	002B001	1	6		100		101
	002B002	1	6		102		104
	003B001	1	6		101		101
		2	12		102		103

⁽¹⁾Dissolution results reported to ones place for Merck data and to tenths place for DuPont Merck data.

**Summary of Losartan Potassium Tablets
Results for Initial Dissolution**

<u>Dose Strength</u>	<u>Lot No.</u>	<u>Test No.</u>	<u>No. of Tablets</u>	<u>Dissolution 30 minutes (% label)</u>	<u>Mean Dissolution 30 minutes</u>	<u>Dissolution 45 minutes (% label)</u>	<u>Mean Dissolution 45 minutes</u>
25 mg	003B001	3	12		97		97
	007B001	1	5,6		100		101
	4220-88	1	6		97.8		99.0
	E-4639	1	6		100		100

Summary of Losartan Potassium Tablets
Results for Initial Dissolution

<u>Dose Strength</u>	<u>Lot No.</u>	<u>Test No.</u>	<u>No. of Tablets</u>	<u>Dissolution 30 minutes (% label)</u>	<u>Mean Dissolution 30 minutes</u>	<u>Dissolution 45 minutes (% label)</u>	<u>Mean Dissolution 45 minutes</u>
25 mg	E-4957	1	6		104		104
	E-7725	1	6		100		99
	E-7726	1	6		101		101

**Summary of Losartan Potassium Tablets
Results for Initial Dissolution**

<u>Dose Strength</u>	<u>Lot No.</u>	<u>Test No.</u>	<u>No. of Tablets</u>	<u>Dissolution 30 minutes (% label)</u>	<u>Mean Dissolution 30 minutes</u>	<u>Dissolution 45 minutes (% label)</u>	<u>Mean Dissolution 45 minutes</u>
50 mg	005C001	1	6		99		100
	005C002	1	6		98		102
	005C003	1	6		100		103
		2	12		100		102

**Summary of Losartan Potassium Tablets
Results for Initial Dissolution**

<u>Dose Strength</u>	<u>Lot No.</u>	<u>Test No.</u>	<u>No. of Tablets</u>	<u>Dissolution 30 minutes (% label)</u>	<u>Mean Dissolution 30 minutes</u>	<u>Dissolution 45 minutes (% label)</u>	<u>Mean Dissolution 45 minutes</u>
50 mg	005C004	1	6		96		99
	005C005	1	6		99		101
	016C001	1	6		97		100
	017C001	1	6		99		101
		2	6		99		101

**Summary of Losartan Potassium Tablets
Results for Initial Dissolution**

<u>Dose Strength</u>	<u>Lot No.</u>	<u>Test No.</u>	<u>No. of Tablets</u>	<u>Dissolution 30 minutes (% label)</u>	<u>Mean Dissolution 30 minutes</u>	<u>Dissolution 45 minutes (% label)</u>	<u>Mean Dissolution 45 minutes</u>
50 mg	017C001	3	6		95		99
		4	12		95		99
	4220-92	1	6		90.6		98.3
	018C001	1	6		90.5		97.3

**Summary of Losartan Potassium Tablets
Results for Initial Dissolution**

<u>Dose Strength</u>	<u>Lot No.</u>	<u>Test No.</u>	<u>No. of Tablets</u>	<u>Dissolution 30 minutes (% label)</u>	<u>Mean Dissolution 30 minutes</u>	<u>Dissolution 45 minutes (% label)</u>	<u>Mean Dissolution 45 minutes</u>
50 mg	018C001	2	6		95.3		99.2
		3	12		93.3		96.2
				)		)	
	E-4640	1	6		98		101
	E-4712	1	6		100		102

**Summary of Losartan Potassium Tablets
Results for Initial Dissolution**

<u>Dose Strength</u>	<u>Lot No.</u>	<u>Test No.</u>	<u>No. of Tablets</u>	<u>Dissolution 30 minutes (% label)</u>	<u>Mean Dissolution 30 minutes</u>	<u>Dissolution 45 minutes (% label)</u>	<u>Mean Dissolution 45 minutes</u>
50 mg	E-4757	1	6		94		97
	E-4774	1	6		98		99
	E-4808	1	6		96		99
	E-4811	1	6		100		102

**Summary of Losartan Potassium Tablets
Results for Initial Dissolution**

<u>Dose Strength</u>	<u>Lot No.</u>	<u>Test No.</u>	<u>No. of Tablets</u>	<u>Dissolution 30 minutes (% label)</u>	<u>Mean Dissolution 30 minutes</u>	<u>Dissolution 45 minutes (% label)</u>	<u>Mean Dissolution 45 minutes</u>
100 mg	004D001	1	6		92		99
		2	6		97		101
	004D003	1	6		90		98
	004D004	1	6		95		98
	004D005	1	6		95		100

**Summary of Losartan Potassium Tablets
Results for Initial Dissolution**

<u>Dose Strength</u>	<u>Lot No.</u>	<u>Test No.</u>	<u>No. of Tablets</u>	<u>Dissolution 30 minutes (% label)</u>	<u>Mean Dissolution 30 minutes</u>	<u>Dissolution 45 minutes (% label)</u>	<u>Mean Dissolution 45 minutes</u>
100 mg	006D001	1	6		94		100
		2	12		91		100

**Summary of Losartan Potassium Tablets
Results for Initial Dissolution**

<u>Dose Strength</u>	<u>Lot No.</u>	<u>Test No.</u>	<u>No. of Tablets</u>	<u>Dissolution 30 minutes (% label)</u>	<u>Mean Dissolution 30 minutes</u>	<u>Dissolution 45 minutes (% label)</u>	<u>Mean Dissolution 45 minutes</u>
100 mg	006D001	3	24		86		95

4220-90 1 6 84.0 92.3

**Summary of Losartan Potassium Tablets
Results for Initial Dissolution**

<u>Dose Strength</u>	<u>Lot No.</u>	<u>Test No.</u>	<u>No. of Tablets</u>	<u>Dissolution 30 minutes (% label)</u>	<u>Mean Dissolution 30 minutes</u>	<u>Dissolution 45 minutes (% label)</u>	<u>Mean Dissolution 45 minutes</u>
100 mg	E-4713	1	6		92		98
	E-4775	1	6		90		96
100 mg	E-4888	1	6		94		97

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b) Liquid Emission Controls (Cont.)

Solvent Recovery Plant. Recovery efficiencies can be in the range of 95 to 99% of the primary organic component for subsequent reuse. Aqueous and organic purges, containing the balance of materials, may be treated in-house by discharge to the wastewater treatment plant or by incineration off-site.

Organic materials not recovered will be disposed of in an on-site solvent incinerator permitted under the Air Pollution Act of 1987 (Permit #ENV/A.P/2/91) and the EEC Toxic and Dangerous Waste Regulations, 1982 (Permit #ENV/D/3) or shipped to a permitted hazardous waste treatment facility.

On-site incineration of waste solvent is completed on a batch basis consistent with license ENV/A.P/2/91. The waste solvent is sampled prior to each burn and tested against license conditions. Approval to burn is obtained from the licensing authority prior to each burn. The incinerator consists of a dual natural gas/waste solvent burner, furnace and vertical stack operated typically between 900 to 1000°C. There is no emission control equipment installed on the incinerator. Off-gas emissions are monitored consistent with license requirements.

Aqueous waste streams are discharged to the chemical sewer and treated in an on-site biological wastewater treatment plant. The treatment plant consists of the following processes: equalization,

I. Summary

F. Environmental Assessment

b) Liquid Emission Controls (Cont.)

flow control, neutralization, primary clarification, extended aeration, secondary clarification and tertiary lagoon treatment. The residence time in the on-site wastewater treatment plant at normal hydraulic flows is ca. 8 days.

Waste sludge is dewatered using a belt press or vacuum filter and disposed of in an approved solid waste management facility. The waste treatment plant operation is permitted by the county council of Tipperary County, Ireland.

c) Solids Emission Controls

Waste sludge, general trash and paper at the site will be disposed of off-site in an approved solid waste management facility (a local authority operated landfill). Other solid waste contaminated with pharmaceutical residues or determined to be hazardous are disposed via off-site incineration which fully conforms to local regulatory policy. In the event that off-site incineration facilities are used, such services are contracted for on a competitive bid selection process and will change. A major factor in the selection process is the contract facility's compliance with all applicable *environmental regulations*.

3) Garden City, NY

a) Air Emission Controls

The manufacturing process does not utilize solvents that would result in solvent or volatile organic chemical (VOC) emissions.

a) Air Emission Controls (Cont.)

The manufacturing process is designed to control particulate emissions that can become entrained in the exhaust air from the manufacturing process. This is accomplished by means of baghouse dust collectors and specific ventilation exhausts with separate dry filters with an overall removal efficiency of >99% for particulates. Also, the film-coating of the compressed tablets is designed to capture 99% of the excess overspray solids exhausted in the aqueous film-coating solution.

b) Liquid Emission Controls

Liquid emissions controls reflect good housekeeping practices that minimize the discharge of manufacturing residues to the site wastewater collection system. The plant wastewater is collected and routed to the Nassau County New York wastewater treatment plant. There is no pretreatment at this site. Quarterly monitoring of the discharge is conducted. Discharge from the DuPont Merck facility is only a minor input to the publicly owned treatment works (POTW). Source collection of chemicals (such as QC laboratory solvents) that can have an adverse impact on the POTW is provided as part of the site's operating procedures.

c) Solid Emissions Controls

All product discards, including unused market packages, will be sent to an approved incineration facility, permitted for disposal of pharmaceutical products. This will be accomplished through site

c) Solid Emissions Controls (Cont.)

operating procedures. The expected destruction efficiency of the drug substance, that is present in the product waste as a small portion of the total weight, is expected to exceed 99%.

4) West Point, Pennsylvania

a) Air Emissions Controls

The on-site incineration facility employs necessary operating conditions to ensure compliance with permitted emission levels. As a contingency, off-site incineration will be conducted at a permitted facility (equipped with the necessary and required emission controls).

b) Liquid Emissions Controls

The liquid from the incineration operation will be discharged into the site wastewater collection system and will undergo pretreatment along with other sanitary waste. This wastewater is discharged for further treatment to the UGTA under the limits conditions of the UGTA contract limits.

c) Solid Waste Controls

Controls for the disposal of unused market packages are part of the site solid waste management program. The waste is incinerated at permitted disposal facilities. Ash generated from the on-site incineration process is disposed of at a permitted facility and is monitored to confirm its acceptability with solid waste regulations.

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d) Employee Protection

Material Safety Data Sheets are available on-site for all chemicals required by the Occupational Safety Act of 1971, the Hazards Communication Act of 1985 and Title 29 Code of Federal Regulations Part 1910.1200. Employees associated with the manufacture of drug substance have appropriate MSDSs available for their review. Employee protective clothing, such as gloves, uniforms, and safety glasses are used during the manufacturing process to assure compliance with the Occupational Safety Act of 1971 and the Hazard Communication Act of 1985 and Title 29 Code of Federal Regulations, Subpart I. Refer to Appendix IV for a copy of the MSDS for the drug product.

5) Wilson, North Carolina

a) Air Emissions Controls

The Wilson facility employs specific ventilation systems for manufacturing and packaging. The vented air passes through a cyclone followed by a baghouse filter with a control efficiency greater than 99% before discharge to the atmosphere. The Wilson, NC facility is in an Attainment Area and is not considered a major source of air pollution. The manufacturing process does not utilize solvents that would result in solvent or volatile organic chemicals (VOC) emissions. Particulates released from manufacturing and packaging operations are minimized and controlled by the use of dust collectors. Air emissions from drug product manufacturing and packaging may include trace particulates as described in Appendix II.

b) Liquid Emissions Controls

The plant wastewater is collected and routed directly to the City of Wilson Treatment Facility as regulated by the site's Sewer Discharge Permit Number 8406. No pretreatment takes place at the site. A flow meter and wastewater sampler monitor discharge quantity and quality, and the data is submitted biannually to the City of Wilson.

Liquid emissions as a result of drug product packaging are detailed in Appendix II. Liquid waste from packaging will result from equipment washouts. Equipment is cleaned with water and detergent after a batch campaign. Prior to washing out the equipment, it is customary to remove any loose product residues. This practice minimizes liquid emissions of chemical substances.

c) Solid Emissions Controls

All unused market packages will be sent to West Point, PA for incineration at permitted disposal facilities. Any solid residuals resulting from packaging will be disposed of by off-site incineration at a permitted facility.

Non-hazardous wastes resulting from manufacturing and packaging may consist of paper, aluminum, plastic, drums, and Tyvek® suits and product filter solids. Product filter solids and chemical contaminated wastes are sent to a permitted incineration facility able to accept such waste streams. Other non-hazardous wastes

c) Solid Emissions Controls (Cont.)

which cannot be recycled are disposed of at a state licensed land-fill. In order to minimize the amount of material for disposal, excess raw materials may be returned to the customer or supplier for further use.

d) Employee Protection

Material Safety Data Sheets are available on-site for all chemicals as required by the Occupational Safety Act of 1971, the Hazards Communication act of 1985 and Title 29 Code of Federal Regulations (CFR) Part 1910. Employees associated with the manufacture of drug product have appropriate MSDSs available for their review. Employee protective clothing, such as gloves, uniforms and safety glasses are used during the packaging process to assure compliance with the Occupational Safety Act of 1971 and the Hazard Communication Act of 1985 and Title 29 CFC Subpart I.

c. Applicable Emission Citations and Statements of Compliance Requirements

1) Albany, Georgia

a) Air Citations

Air emissions are subject to and in compliance with the rules of the Georgia Department of Natural Resources, Environmental Protection Division, Chapter 391-3-1, Air Quality Control. Air emissions are discharged subject to the Air Quality Permit Number 2833-047-10356 and 2833-047-11517, as amended.

a) Air Citations (Con't)

Particulate emissions from the manufacture of drug substance are subject to and in compliance with the emission rates set forth by regulation under Table Ia and Ib, Chapter 391-3-1-.02(2)(e), for new and existing equipment. Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements. No new regulated parameters are anticipated as a result of the proposed action.

b) Liquid Citations

Effluent from the on-site wastewater treatment plant is discharged to the Flint River and is subject to and in compliance with the National Pollutant Discharge Elimination System (NPDES) Permit Number GA0001619. The NPDES permit is administered by the Georgia Department of Natural Resources. The existing NPDES permit limits plant effluent to a BOD₅ daily maximum of 2,100 lb/d (June-Oct.), 4375 lb/d (Nov.- May); TSS daily maximum of 4,200 lb/d and pH between 6.0 and 9.0. Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements and no new permit limits are anticipated as a result of the proposed action.

c) Solid Citations

Hazardous solid waste is subject to and conforms with the Georgia Hazardous Waste Management Rules, Chapter 391-3-11, Standards Applicable to Generators of Hazardous Waste. The USEPA

c) Solid Citations (Cont.)

hazardous waste permit identification number for the plant is GA0003324985. The plant has a RCRA permit for the storage of hazardous waste in tanks and containers (permit no. HW008(S)). There are no numerical permit limits associated with the manufacture of losartan potassium at the Albany facility although efforts will be made to minimize the amount of solid waste generated. No new permit conditions are anticipated as a result of the proposed action.

2) Ballydine, Ireland

a) Air Citations

Air emissions are subject to, and in compliance with the Regulations of the Ireland Department of the Environment under the Air Pollution Act, 1987. Permit number ENV/A.P/2/91, issued by the Tipperary County Council, governs the sources of atmospheric emissions from processing activities, waste solvent incinerator, steam boilers and dust emissions from the dry processing equipment.

b) Liquid Citations

Aqueous waste streams are subject to and in compliance with Ireland's Department of the Environment, Local Government (Water Pollution) Regulations of 1977. The wastewater treatment plant operation is permitted by the county council of Tipperary County, Ireland (Permit # ENV/W/36/80, which also governs the effluent discharge to the River Suir).

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c) Solid Citations

Hazardous wastes are disposed of in a manner which fully conforms to local regulatory policy. Hazardous solid wastes are subject to, and in compliance with the Department of the Environment Waste Regulation (1979 and 1984) and the Transfrontier Shipment of Hazardous Waste Regulations, 1985.

3) Garden City, New York

a) Air Citations

Air emissions from site operations are subject to limits established under permits granted by the Nassau County Health Department, which has authorization delegated by the US EPA Clean Air Act.

These permits include:

C-282011-0886-00001 W-CA&CB for the Dust Collection Equipment

C-282011-0886-00007 W-CA, CB & CC for the Main Building.

C-282011-0886-00008 W-CA & CB, for the R&D Building

C-282011-0886-0021 W through C-282011-0886-00023

These permits are subject to Nassau County Health Department inspection on an annual basis, require annual reporting and must be

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a) Air Citations (Cont.)

renewed every two years. The current copies of these permits are maintained by plant engineering personnel. Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements.

b) Liquid Citations

The discharge of plant wastewater to the Town of Hempstead wastewater collection system is approved under Sewer Discharge Permit Number 33. The Cedar Creek Water Pollution Control Plant operated by Nassau County is approved under NPDES permit NY0026859. The county discharge permit requires pH of the site discharge to be maintained between 5.5 and 9.5 at all times. No new permit limits are anticipated as a result of the proposed action.

c) Solid Citations

The collection of waste solvents and related hazardous chemicals not directly involved with the proposed action is approved under a hazardous waste permit, authorized by the US Resource Recovery and Conservation Act. The USEPA hazardous waste identification number for the plant is NYD001315209. Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements.

4) West Point, Pennsylvania

a) Air Citations

The air emission controls for the disposal of this product meet the requirements of the Pennsylvania Air Pollution Control Regulations under Title 25 of the Pennsylvania Code, Part I - Department of Environmental Resources (PA DER), Chapters 121-141. Emissions of volatile organic compounds (VOC) from this site are currently regulated under PA DER No. 46-313-117. VOC emission limit for the site are 50 tons/year, 1000 lbs/day, and 100 lbs/hr. Particulate emissions are limited to 0.04 grains/dscf by regulation.

Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements. No new permit limits are anticipated as a result of the proposed action.

b) Liquid Citations

The effluent from the West Point site is treated by the UGTA, and this effluent is discharged from the UGTA under NPDES Permit Number PA 0023256. This permit is administered by PA DER. The wastewater from the treatment works is subject to and in compliance with the pretreatment standards for existing sources of the Pharmaceutical Manufacturing Category under Title 40 of the Code of Federal Regulations Part 439 (Subcategory A for fermentation products). The wastewater is also regulated by the UGTA and is in compliance with the existing contract and the "Rules and Regulations Governing the Discharge of Sanitary and Industrial Wastewaters into the Public Sewers of the Upper Gynedd

b) Liquid Citations (Cont.)

Township Authority." These regulations are based on the requirements of the Federal Clean Water Act and the Pennsylvania Clean Streams Law. The existing contract with UGTA limits plant effluent flow (calculated from a monthly average) to approximately 1,225,000 gallons/d; BOD = 250 mg/L (daily maximum); TSS = 300 mg/L; and pH between 5.5-9.0. In any event, the facility will be in compliance with their wastewater discharge limits. Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements and no new permit limits are anticipated as a result of the proposed action.

c) Solid Citations

Solid waste management at the West Point plant requires conformance with conditions set forth in Permits 300437, 400459, and 300501 issued by PA DER and Permit PAD002387926 issued by both EPA and PA DER. These requirements assure comprehensive control for management of waste throughout the plant including returned market packages. The requirements of the Pennsylvania Code, Title 25, Part I - Department of Environmental Resources, Chapter 75, are the primary regulations and are subject to the requirements of the Federal Resource Conservation and Recovery Act, the Federal Hazardous and Solid Waste Amendments, and the Pennsylvania Solid Waste Management Act. Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements.

5) Wilson, North Carolina

a) Air Citations

The operation of the Wilson manufacturing packaging and power generating facilities is in compliance with Air Permit Number 4884 R9 issued by the North Carolina Department of Natural Resources and Community Development in accordance with Article 21B, Chapter 143, General Statutes of North Carolina and "Other Laws, Rules and Regulations". Approval of the proposed action will not impact the facility's ability to comply with the permit.

b) Liquid Citations

The discharge of wastewater to the City of Wilson Wastewater Collection System is allowed under the site Sewer Connection and Discharge Permit Number 8406. The site discharge is limited to daily maximum discharges of BOD=582 lbs/d, COD=932 lbs/d, TSS=349 lbs/d, and pH 5-9. These permits are established under the city's "Rules and Regulations for the Discharge of Wastewaters into the Wastewater Treatment System of the City of Wilson, North Carolina". The City of Wilson Department of Public Works Wastewater Treatment Plant operates under National Pollutant Discharge Elimination System (NPDES) Permit Number NC 0023906. No new permit limits are anticipated as a result of the proposed action. Manufacturing and packaging at Wilson will not impact the facility's compliance with the site's sewer Discharge Permit Number 8406.

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c) Solid Citations

The Wilson plant is in compliance with the North Carolina Hazardous Waste Management Rules and manages all hazardous waste in compliance with North Carolina Hazardous Waste Management Permit NCD 980798839. No new permit limits are anticipated as a result of the proposed action. Approval of the proposed action will not impact the facility's ability to comply with the permit.

d. Effect of Application Approval on Compliance with Current Emissions Requirements

Merck & Co., Inc. states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders as well as emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the production of losartan potassium at its facilities in Albany, Georgia, Ballydine, Kilsheelan, Ireland and at its tablet manufacturing and packaging facility in Wilson, NC and for the incineration of unused and returned goods at West Point, PA.

Dupont Merck Pharmaceutical Co., Inc. states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of drug product as well as emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the production of Tablets COZAAR at its facilities in Garden City, New York.

e. Expected Maximum Annual Production

It is expected that the total 5th year production volume will be on the order of kilograms per year and includes losartan potassium used alone (monotherapy) or in combination with other therapeutic agents. Pollution prevention, solvent recovery and recycle will be implemented to the extent practical to minimize the release of chemicals into the environment. In addition, control equipment as indicated in section 6(b) & 6(c) are employed to further reduce chemical emissions. The anticipated production activities represents of total capacity at the Albany facility and of total capacity at the Ballydine facility. Facilities used for manufacture of losartan potassium drug product are subject to, and in compliance with, applicable regulations. Environmental effects as a result of manufacturing, product use and disposal are minimal.

7. Fate of Emitted Substances to the Environment

Environmentally relevant chemical/physical and ecotoxicological properties of losartan potassium have been evaluated by standard and widely accepted laboratory procedures. Except where noted, all studies were conducted by the Merck Research Laboratories, Rahway, New Jersey and West Point, Pennsylvania and the DuPont Merck Pharmaceutical Company, Wilmington, Delaware. Results and studies presented in the technical sections of the NDA document or appendices are only summarized here. Copies of the environmental fate and effect study reports are provided in Appendix V.

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a. Physico-Chemical Properties

1) Aqueous Solubility

Losartan potassium is freely soluble in water (>500 g/L) at ambient temperature (~25°C). The resulting pH is 9.7.

2) Partition Coefficient

The distribution coefficient for losartan between octanol and aqueous phosphate buffer (pH 7; approximately 0.1M PO₄) was determined by the following experimental procedure. A measured volume of an aqueous phosphate buffer solution of losartan (about 0.01M in losartan) was stirred for one hour at room temperature with an equal volume of n-octanol. After the equilibration period, the mixture was centrifuged and the octanol and aqueous phases separated, diluted where necessary and analyzed by HPLC. This was done in triplicate. A more dilute aqueous phosphate buffer solution of losartan (about 0.001M in losartan) was prepared and again a measured volume of the solution was stirred for one hour at room temperature with an equal volume of n-octanol. After the equilibration period, the mixture was centrifuged and the octanol and aqueous phases separated, diluted where necessary and analyzed by HPLC. This was also done in triplicate. The average distribution coefficient, expressed as log P, was found to be 1.19±0.03. The average losartan recovery from the experiments starting with 0.01M losartan aqueous solution was 95% based on the HPLC concentrations and 93% for the 0.001M losartan solutions.

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3) Solution pH

The pH of a solution of losartan potassium (1% w/w) in water is about 8.2.

4) Dissociation Constant (pKa)

The pKa value for the tetrazole hydrogen of losartan potassium is 4.9, determined by the potentiometric titration of losartan potassium in 1:1 methanol:water under acidic conditions. The pKa in aqueous solution containing 1% methanol is 4.1, as determined by ultraviolet spectroscopy using buffers from 1 to 13. The difference in measured pKa values is due to the different levels of methanol present in the solution.

The pKa of losartan was determined by acid titration as follows: The titration was performed with a Metrohm 670 Titroprocessor using a combination glass electrode. The electrode was standardized at pH values of 4.0, 7.0 and 10.0. The hydrochloric acid titrant was standardized against tris (hydroxymethyl) amino methane and was about 0.1M HCl. The sample (about 13 mg) was dissolved in 25 ml of methanol and 25 ml of water was added. The solution was titrated with acid past the equivalent (end) point and pKa calculated as the pH at 1/2 the equivalence point (4.9).

The pKa was also estimated by the change in the UV spectra as a function of pH. The UV spectra for losartan was determined in 1 to 2M HCl and buffers ranging in pH from 1 to 13 containing 1

4) Dissociation Constant (pKa) (Cont.)

volume % methanol using a Perkin-Elmer Lambda 5 spectrophotometer. Losartan (10 mg) was dissolved in 10 ml of methanol (spectrophotometry grade). Aliquots (0.1 ml) of the solution were diluted with the appropriate buffer to a final volume of 10 ml. The UV absorbances of the acid and base forms of losartan were determined at appropriate wavelengths. The UV absorbances at the same wavelengths for losartan at intermediate pH values were determined and the pKa calculated from the following equation:

$$pKa = pH - \log(A - A_a) / (A_b - A)$$

where A_a = UV absorbance of the acid form of losartan,
 A_b = UV absorbance of the base form of losartan,
 A = UV absorbance of losartan at an intermediate pH.

The absorbances (A_a , A_b and A) are all measured at the same wavelength. An average value for the pKa of 4.1 ± 0.1 was determined from a combination of intermediate pH values and wavelengths.

5) Chirality and Specific Rotation

Losartan potassium is achiral and, thus, is not optically active.

6) Thermal Behavior

The thermal behavior of losartan potassium has been investigated (MRL, West Point, PA) with a combination of differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD) techniques in an inert and oxidizing atmosphere.

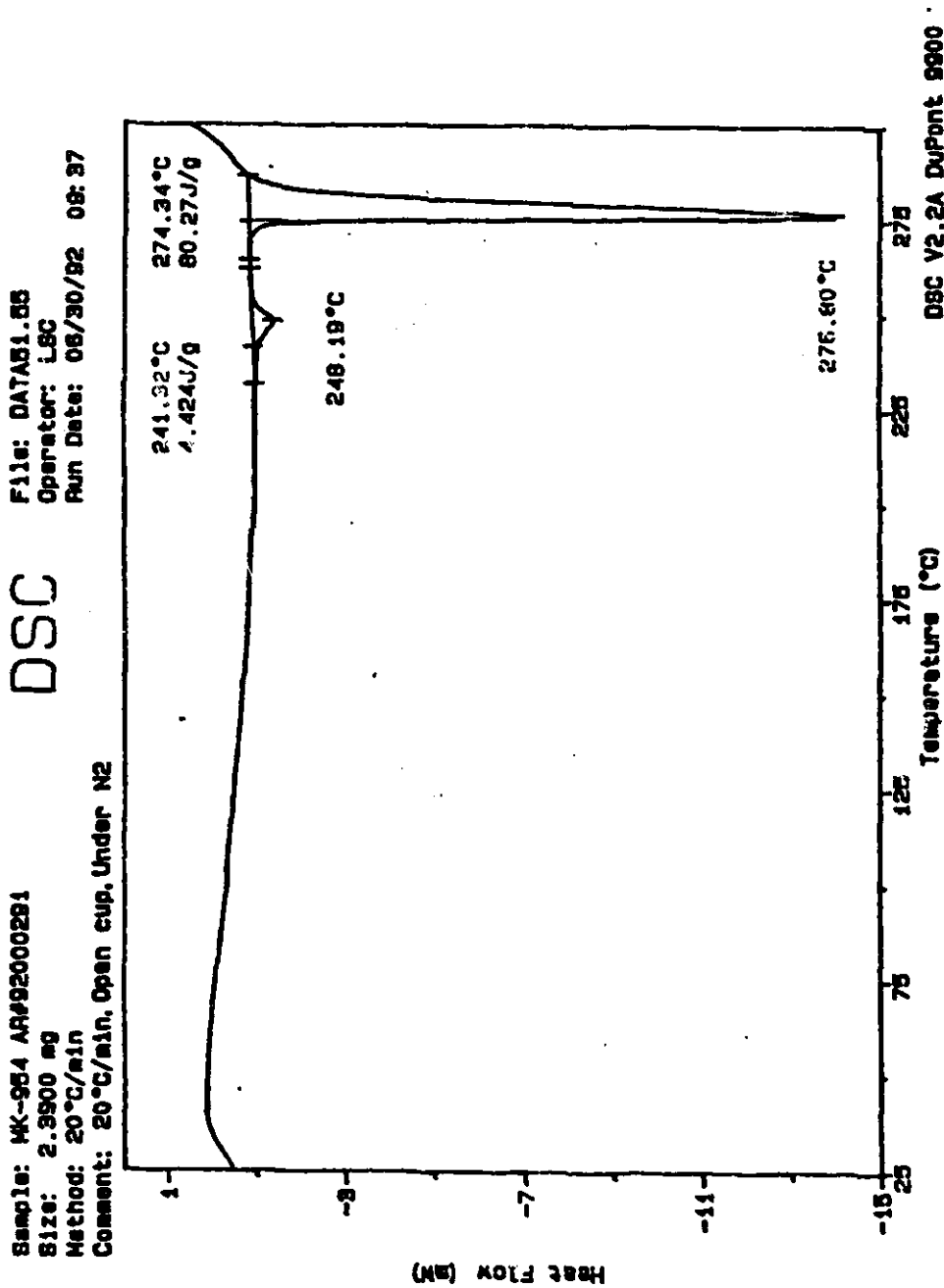
Losartan potassium has been found to exist in two polymorphic forms. The differential scanning calorimetry (DSC) curve for losartan potassium (refer to Figure F1), obtained at 20°C/min in an open cup under nitrogen flow, is characterized by two endotherms. The minor endotherm with an extrapolated onset temperature of ~241°C and a heat of ~4 joule/g corresponds to the enantiotropic polymorphic transition between the two polymorphs. The major endotherm corresponds to the melting of the higher temperature polymorph and occurs at an extrapolated onset temperature of ~274°C (peak temperature ~277°C) with a heat of 80 joule/g. Visual inspection of the sample after the minor endotherm showed no evidence of melting. Inspection by X-ray powder diffraction (XRPD) of a sample heated to above the minor endotherm indicated a change in the crystal structure, and, no chemical change in the heated sample was seen by NMR spectroscopy or HPLC.

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Figure F1

Differential Scanning Calorimetry Curve For Losartan Potassium



6) Thermal Behavior (Cont.)

These results confirm the existence of two polymorphic forms of losartan potassium, which have been designated Form I for the low temperature stable form (up to the transition temperature of about 240°C) and Form II for the polymorph stable above the transition temperature.

An additional study was conducted by MRL, Rahway, NJ in both an inert and oxidizing atmosphere over the entire temperature range at 10°C/min heating rate. Under nitrogen, the low intensity endotherm is observed to occur at ~240°C, followed by a more intense endotherm initiating at 270°C. The absence of a characteristic weight change at 240°C implies a purely physical solid state transition rather than a chemical transformation; thus, confirming the results of the initial study. Furthermore, following termination at 280°C, an exothermic signal occurs, and, at this point, the initiation of a weight loss is observed. This behavior is interpreted as fusion followed by melt decomposition. In an oxidizing atmosphere, the onset of fusion is ~260°C. Exothermic oxidation appears to start at melt termination (endotherm signal peak).

In the inert environment, the melt undergoes a two-stage pyrolysis.

The first stage, probably due to tar formation, is mildly exothermic. The loss of volatiles during tar to char conversion is not accompanied by well defined thermal activity, although there are indications of endothermicity.

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6) Thermal Behavior (Cont.)

In the oxidizing atmosphere, the exothermic oxidation of the two-step release of gaseous pyrolysis products is more clearly defined in both the heat flow and weight loss profiles in the 300-310°C and 450-515°C regions. Furthermore, at ~550°C, exothermic combustion of char proceeds, leaving ~20% mineral ash residue.

There is apparently no weight change until the onset of the melt decomposition in the 260-270°C region, where a small linear loss is observed to occur. In the nitrogen atmosphere at 10°C/min, between 25-270°C, a 1.12% weight loss was obtained. At 1°C/min, between 25-262°C the loss is 1.07%. These losses can be attributed to sublimation and the start of thermal degradation. In the oxygen atmosphere, the monitored weight losses are much less; thus, at 1°C/min between 25-260°C, the loss is 0.51%, while at 1°C/min between 25-240°C, a 0.64% loss was measured. It is conjectured that oxygen chemisorption offsets the purely thermally induced weight losses.

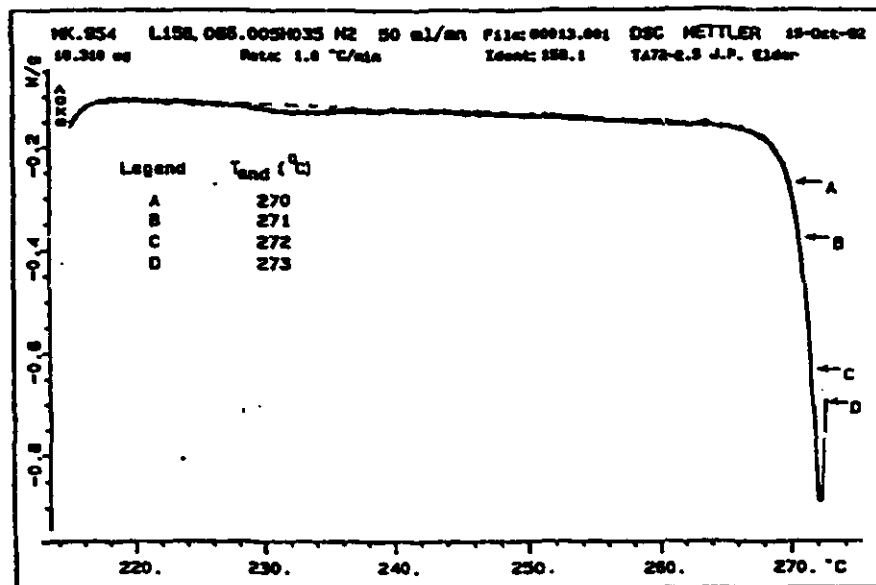
A series of experiments were conducted in which samples of losartan potassium were heated at 10°C/min from 200°C, through the solid state transition region (230-240°C) and beyond the onset of fusion at 269.8°C. The partially melted samples were rapidly cooled to room temperature, examined and weighed. Several heat flow profiles were developed for end-point temperatures at 270, 271, 272, 273 and 274°C. The heat flow profiles are shown superimposed in Figure F2a. The true melting point was deter-

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Figure F2a

Thermal Gravimetric Analysis of Losartan Potassium - Heat Flow Profiles



I. Summary

F. Environmental Stability

Thermal Behavior (Cont.)

determined to be $T_f = 272^\circ\text{C}$. The melting point was determined by analyzing the leading edge of the fusion endotherm using the "short" van't Hoff purity analysis program as shown in Figure F2b. The calculated heat of fusion was 85.8 J/g.

In order to determine if thermal stressing can effect the 244°C polymorphic transition, two losartan potassium samples were subjected to 5-hour stresses in an inert atmosphere at two temperatures. Stressing at 220°C does not cause the change. Stressing at 235°C , just below the onset of the Form I to II transition, does effect the change. These measurements define the upper temperature limit for extended period isothermal TG measurements of possible sublimative loss.

A weight loss-time profile was determined for losartan potassium over a 15-hour period under nitrogen at three temperatures, 200, 225 and 245°C . The data indicates that the Form II polymorph readily decomposes in the solid state. After an induction period of ~1.5 hours, degradation proceeds. The total loss is 13% and the degradative residue is a dark-brown tarry material. At 225°C , there was a 0.8% loss during the 15 hours, and the powdered residue was yellow in color. At 200°C , the weight loss appears linear with time, indicative of sublimation, but the residue appeared very pale yellow. Refer to Figure F3a. At or below 180°C , weight losses were very low during periods of isothermal stress. This is shown in Figure F3b. A best fit of the data was determined and the vapor

Tablets Losartan Potassium
Chemical and Pharmaceutical Manufacturing and
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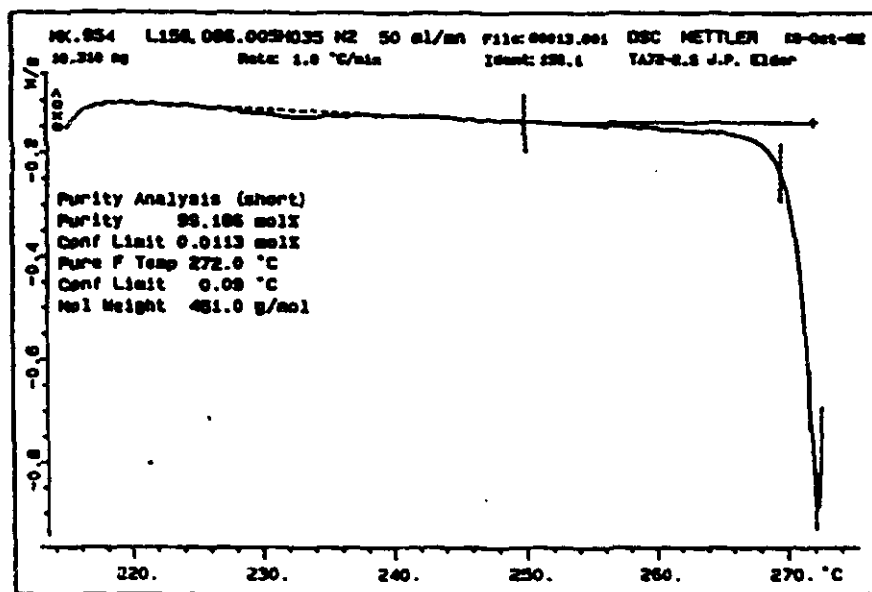
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Figure F2b

Determination of the Melting Point of Losartan Potassium



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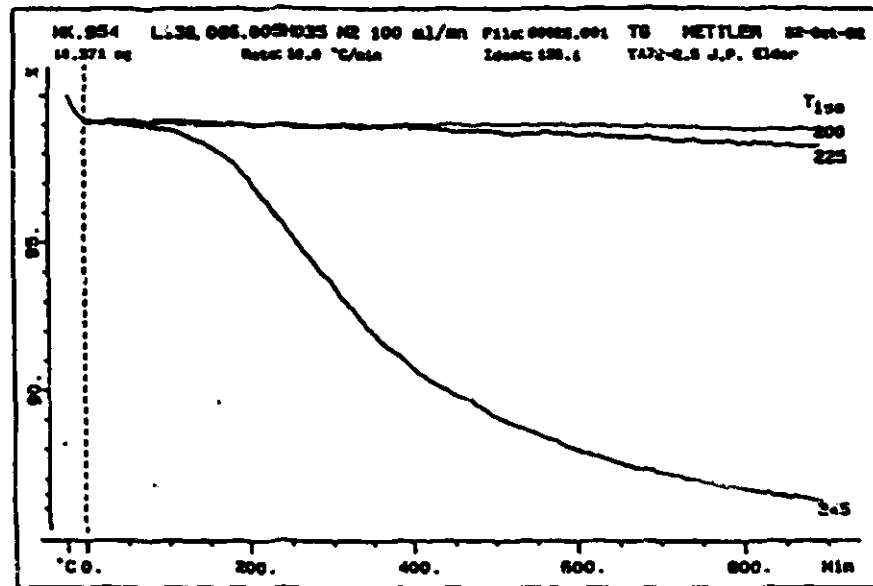
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Figure F3a

Thermal Gravimetric Analysis of Losartan Potassium



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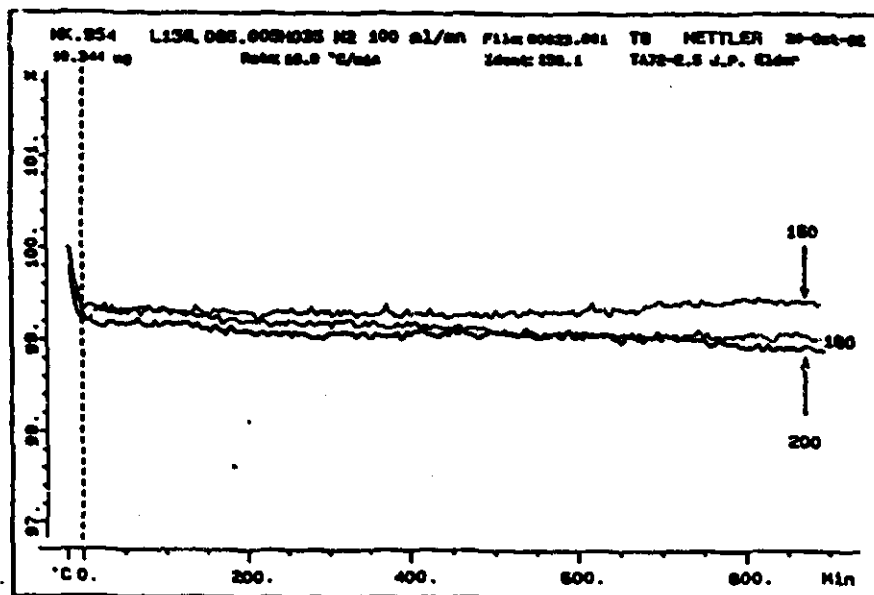
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Figure F3b

Thermal Gravimetric Analysis of Losartan Potassium



I. Summary

F. Environmental Assessment

6) Thermal Behavior (Cont.)

pressure and heat of sublimation were estimated. The heat of sublimation is estimated at $H = 58$ kJ/mol. The vapor pressure, at or below 59°C , is $<10^{-7}$ torr.

To monitor the combustive behavior of losartan potassium, samples were heated in a TG furnace at $50^{\circ}\text{C}/\text{min}$ from room temperature to two chosen upper limits, 550 and 600°C , and then heated at these limits for 30 minutes. The results indicate that a less than two-minute burn in oxygen at 550°C is sufficient to destroy losartan potassium completely to the ash stage.

7) UV-Visible Light Spectrum

The ultraviolet absorbance spectrum of losartan potassium in methanol (Figure F4) was obtained using a Aviv Associates Model 118DS ultraviolet-visible spectrophotometer. The spectrum is characterized by absorbance shoulders at ~ 250 and ~ 228 nm (A 1% 1 cm values of ~ 320 and ~ 574 , dry basis).

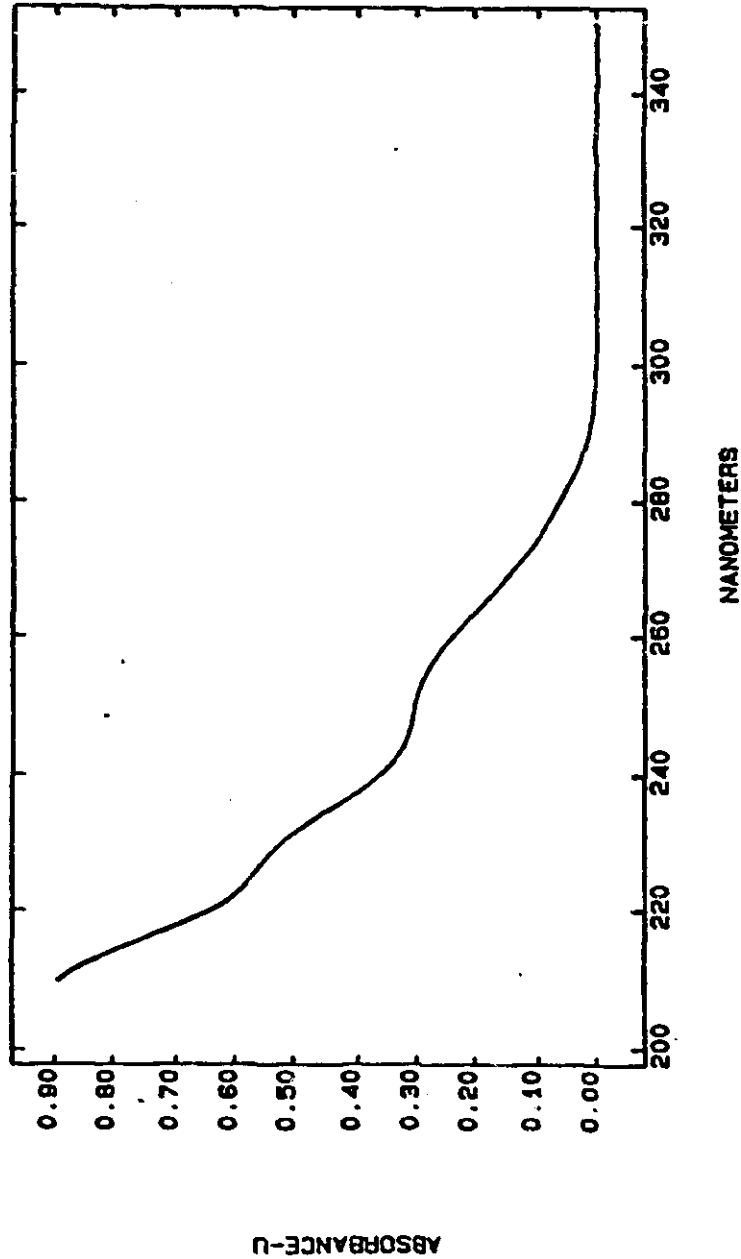
b. Stability

The stability characteristics of losartan potassium drug substance have been extensively evaluated, both for solid state material and in solution.

Figure F4

Ultraviolet Absorbance Spectrum of Losartan Potassium

AVIV PLOT V3.3m cr T. 100.0C. date. 8-11-92 time.15:43:59 c
taken 09-11-92 at 15:46:00, ref 7.050. AVT 0.2 sec
scan from 350.00 nm to 210.00 nm every 0.20 nm w/ 0.20 nm bw 92000291.sm6
y lower 11m -0.0048. y upper 11m 0.8928 Absorbance-U



1) Solid State Stability

a) Ambient Temperature and Relative Humidity Conditions

Solid losartan potassium drug substance has been stored in double polyethylene bags inside cardboard shipping containers under conditions of ambient temperature and relative humidity for up to three years. HPLC was used to monitor the stability of losartan potassium drug substance during the evaluation. No evidence of decomposition was observed during this period.

Additional ambient stability data have been generated by DuPont Merck. These data confirm that losartan potassium stored in double polyethylene bags within a fiber drum is stable for at least two years under ambient conditions.

b) Under Elevated Temperature and Relative Humidity Conditions

Solid losartan potassium has been stored in screw-capped amber glass bottles at 40°C for up to 6 months and at 60°C for up to 12 weeks. The results of these stability studies, conducted by DuPont Merck, showed no changes in physical appearance of the drug substance for the duration of the evaluation and no changes in the HPLC impurity profile or weight percent assay. Losartan potassium is stable for at least 6 months at 40°C and for at least 12 weeks at 60°C.

Three lots of solid losartan potassium were stored at 40°C and 75% relative humidity in double polyethylene bags inside fiber drums. In less than one month the material was no longer free flowing.

b) Under Elevated Temperature and Relative Humidity Conditions (Cont.)

though no degradates were detected by HPLC impurity profile or weight percent analysis. After six months at 40°C/75% RH, the material was still a non-flowing white mass. No changes in HPLC area percent or weight percent were detected and the water content had not increased significantly.

Solid losartan potassium has been stored at 80°C in capped amber glass bottles for four weeks. Analysis of this material by the HPLC assay and impurity analysis showed no change after 4 weeks.

c) Photochemical

Solid losartan potassium was stored in an open dish at 25°C in the presence of light (600 foot candles) for up to 12 weeks. The formation of two degradation products (retention times of ~18 and ~23 minutes) at levels of up to 0.8% total (HPLC) was observed. This study was conducted by DuPont Merck. Losartan potassium solid appears to be slightly photosensitive. Drug substance lots produced later in development, exhibited less photosensitivity than earlier lots as exhibited when solid losartan potassium was stored in transparent glass tubes at ambient temperature and exposed to cool fluorescent light for a total of 1.8 million lux hours (over ~25 days). No photodegradation was observed over the duration of the study. The results were obtained using the HPLC assay and impurity analysis methods.

c. Stability in Aqueous Solution

1) Hydrolysis

In a study conducted by Toxikon Environmental Sciences (Jupiter, FL), the stability of losartan potassium in aqueous solution was evaluated at 50°C and pH 5 (0.01 M sodium acetate buffer), pH 7 (0.067M phosphate buffer) and pH 9 (0.025 M sodium tetraborate buffer) for a test period of five days. Using the criteria ($\geq 10\%$ hydrolysis in five days at 50°C) provided in the US FDA Technical Assistance Document, Section 3.09 (1987), the results from the pH 5, 7 and 9 hydrolysis testing indicate that losartan potassium in water was not susceptible to hydrolysis.

The 5 day study was conducted at a concentration of 100 mg/L in pH 5, 7 and 9 aqueous buffers. The samples were placed on a rotatory shaker located in an incubator maintained at $50 \pm 1^\circ\text{C}$. At day 5, the samples were removed and analyzed by HPLC. The concentration of losartan potassium after five days was compared to the initial concentration. The mean percent initial concentration for the pH 5, 7 and 9 samples was $98.3\% \pm 0.07$, $98.9\% \pm 2.6$ and $97.7\% \pm 0.28$, respectively. The pH of the samples were measured on day 0 and 5 and did not change significantly in any of the test samples.

a) Photochemical

In a study conducted by Toxikon Environmental Sciences (Jupiter, FL), photodegradation of losartan potassium in an aqueous solution exposed to sunlight was studied at three different pHs .

a) Photochemical (Cont.)

Losartan potassium was found to be susceptible to photolysis. The parent compound degrades rapidly under clear sky conditions. Two photodegradates are formed during photolysis; one less polar than the parent compound (formed primarily in neutral and alkaline conditions); one more polar than the parent compound (formed primarily in slightly acidic conditions). The maximum half-life for losartan potassium is less than 18 hours (at pH 9) in direct sunlight.

Losartan potassium solutions were prepared in each of the three buffer solutions, viz, pH 5 (0.01M sodium acetate buffer), pH 7 (0.067M phosphate buffer) and pH 9 (0.025 M sodium borate buffer).

The concentrations of losartan potassium were less than one-half of the water solubility of the test article. Buffer solutions were sterile and saturated with air before use. Controls (dark controls) consisted of losartan potassium solutions of the same concentration and pH as the test solutions. During the test, light was excluded from these solutions. The analysis for losartan potassium was performed by HPLC.

To estimate the photolysis rate of losartan potassium, a 14-hour preliminary study was conducted at a nominal concentration of 100 mg/L (2×10^{-4} M) in pH 5, 7 and 9 aqueous buffers. A chem-

a) Photochemical (Cont.)

ical actinometer, PNAP/PYR (2×10^{-5} M / 1.0 M) was exposed for 6.0 hours to estimate the reaction quantum yield, $\Phi_{F_E^*}$. At each sampling point, the test and actinometer solutions were removed from the photolysis chamber and analyzed by HPLC to determine the percent parent compound concentration. Based on these analyses, the half-life of losartan potassium was <10 hours, and the half-life of the actinometer was <3 hours.

The definitive study was conducted at a nominal losartan potassium concentration of 100 mg/L (2×10^{-4} M) in the same aqueous buffers used in the preliminary study. In an attempt to decrease the rate of photolysis, the concentration of pyridine in the PNAP / PYR actinometer was reduced from 1.0 M to 0.55 M. The concentration of PNAP was maintained at 2×10^{-5} M. Test and actinometer solutions were removed from the photolysis chamber at seven regular time intervals for up to 36 hours. The degradation of the test substance was monitored by HPLC.

The photolysis rate constant (k_p^c) and half-life ($t_{1/2}$) for the pH 5 test samples were determined to be 0.0637 hr^{-1} and 10.9 hours, respectively, for the exposed samples and indeterminate (infinite half-life) for the dark controls. The k_p^c and $t_{1/2}$ for the pH 7 test samples were determined to be 0.0587 hr^{-1} and 11.8 hours, respectively, for the exposed samples and 0.0004 hr^{-1} and 1733 hours for the dark control samples. The k_p^c and $t_{1/2}$ for the pH 9 test samples were determined to be 0.0394 hr^{-1} and 17.6 hours,

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a) Photochemical (Cont.)

respectively, for the exposed samples and indeterminate (infinite half-life) for the dark samples. The correlation coefficient for the rate of disappearance of the test substance and exposure time (hours) was determined to be 0.9776 for the pH 5 samples, 0.9830 for the pH 7 samples, and 0.9771 for the pH 9 samples. The correlation coefficient for the rate of disappearance of the test substance versus cumulative UV radiation was determined to be 0.9770 for the pH 5 samples, 0.9785 for the pH 7 samples, and 0.9840 for the pH 9 samples.

The photolysis rate constant and half-life for the actinometer were determined to be 0.2290 hr^{-1} and 3.03 hours, respectively. The correlation coefficient for the rate of disappearance of the actinometer versus exposure time was determined to be 0.9905. The correlation coefficient for the rate of disappearance of the actinometer versus cumulative UV radiation was determined to be 0.9971.

The HPLC chromatograms of exposed samples revealed two primary photodegradation products. A degradate appeared at a retention time of 13-14 minutes in all pH 5, 7 and 9 exposed samples. As the parent test substance concentration declined over time; the concentration of this degradate increased. In addition to this degradate, another more polar photoproduct formed with increasing exposure time in the pH 9 samples.

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a) Photochemical (Cont.)

Losartan potassium was susceptible to photodegradation in all of the study treatments, based on the criteria set forth in the US FDA Technical Assistance Document, Section 3.10 (1987). The measured concentrations of the dark controls approximated that of each respective sample; no other dark control analysis was deemed necessary. Additionally, the pH did not change significantly in any of the test samples.

d. Biodegradability

Losartan potassium does not appear to be readily biodegradable when exposed to an unacclimated mixed microbial population (activated sludge). Presence of an easily metabolizable cosubstrate such as glucose failed to induce transformation or degradation of losartan potassium. The average recovery of the drug substance at the completion of the 28-day study was 92.1%. Virtually no hydrolysis of losartan potassium was observed during the 28-day test which was performed using phosphate buffer. An average of 98.1% of the drug substance was recovered from the abiotic controls.

A biodegradation study was conducted at Toxikon Environmental Sciences, Jupiter, FL. The study employed losartan potassium in aqueous media with four different bacterial and 1 algal (periphyton) inoculum. Each inoculum was acclimated to the test substance for a maximum of 60 days prior to the initiation of the study.

I. Summary

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d. Biodegradability (Cont.)

After the acclimation period, an aliquot of the inoculum solution was transferred to a biodegradation reaction flask containing mineral salts media and losartan potassium (10 mg carbon/liter) and aerobically incubated for 28 days. After 14 and 28 days, subsamples of each test solution were taken and the concentration of losartan potassium was determined by HPLC. After 28 days, the losartan potassium concentration in each of the 4 bacterial inocula test solutions was greater than 90% of the initial concentration. The losartan potassium concentration in the periphyton inoculum test solution after 28 days was 71% of the initial concentration. The HPLC chromatograms of the periphyton sample showed the presence of two additional peaks, indicating biotransformation of losartan potassium.

e. Aquatic Toxicity

1) Toxicity to *Daphnia magna*

The static acute toxicity of losartan potassium to *Daphnia magna* was evaluated under a standard laboratory operating procedure (SOP) based on US-EPA test protocol (1). Results obtained from a 48-hour *Daphnia magna* static acute aquatic toxicity study with losartan potassium yielded an LC₅₀ of 331 mg/L with a 95% confidence interval of 270 to 404 mg/L. Measured concentrations were 96.4 - 99.6% of the nominal concentrations at the start and 92.6 - 99.6% at the conclusion of the test. The *Daphnia magna* used in the study were obtained from stock cultures maintained by

I. Summary

F. Environmental Assessment

1) Toxicity to *Daphnia magna* (Cont.)

the Environmental Engineering Laboratory, MRL, Rahway, NJ. *Daphnia magna* stock cultures are kept at 20°C in aerated containers using spring water (hardness ~256 mg/L as CaCO₃). The cultures are maintained on a 12-hour light/dark cycle and are fed five times a week with a suspension of trout chow, yeast, and alfalfa, 1.5 mg/L, and *Selenastrum capricornutum* (7 to 10-day-old algal culture), 20 mg/L. Neonates less than 24 hours old were used for the test. All statistical analyses were performed using the Moving Average Angle Method. Water quality parameters (pH, dissolved oxygen, hardness, alkalinity, conductivity) and HPLC analyses of losartan potassium were determined at test initiation and termination.

Sodium lauryl sulfate was used as a reference toxicant to determine the sensitivity of the organisms used in the toxicity test. Acceptable test organisms are those which exhibit a 48-hour LC₅₀ within ± two standard deviations of the average value as determined by the cumulative summation control chart for the reference toxicant. The LC₅₀ obtained was 14.5 mg/L which fell within the acceptable range of 11.3 to 26.6 mg/L.

2) Toxicity to *Pimephales promelas* (Fathead Minnows)

The static acute toxicity of losartan potassium to *Pimephales promelas* was evaluated under a standard laboratory operating procedure (SOP) based on a US-EPA test protocol (1). Results obtained from a 48-hour *Pimephales promelas* static acute aquatic

I. Summary

F. Environmental Assessment

2) Toxicity to *Pimephales promelas* (Fathead Minnows) (Cont.)

toxicity study with losartan potassium, based on nominal concentrations, yielded an LC_{50} of >1000 mg/L. The measured concentration of the compound was 94.3% of the nominal at the start and 92.4% at the conclusion of the test.

The *Pimephales promelas* (Fathead minnows) used in the study were obtained from Aquatic Research Organisms (ARO), Hampton, New Hampshire. The cultures were acclimated in spring water (hardness ~256 mg/L as $CaCO_3$) at 21°C, 12 hour light-dark cycle and fed dry flake food daily for a period of five days. Seventeen-day-old fish were used in the reference toxicant and losartan potassium static acute studies. Water quality parameters (pH, alkalinity, hardness, conductivity, dissolved oxygen) and HPLC analyses of the drug substance were performed at test initiation and termination. All statistical analyses were performed using the Moving Average Angle Method.

Sodium lauryl sulfate was used as the reference toxicant to determine the sensitivity of the Fathead minnows used in the toxicity test. Acceptable test organisms are those which exhibit a 48-hour LC_{50} which is within $\pm$ two standard deviations of the average value as determined by the cumulative summation control chart for the reference toxicant. The LC_{50} obtained was 15.0 mg/L which fell within the acceptable range (9.8 - 23.4 mg/L).

3) Toxicity to *Oncorhynchus mykiss* (Rainbow Trout)

The static acute toxicity of losartan potassium to rainbow trout, *Oncorhynchus mykiss*, was determined in laboratory toxicity tests conducted by Toxikon Environmental Sciences (Jupiter, FL). The 96-hour median lethal and no-observed-effect concentration (LC₅₀ and NOEC) based on mean measured concentrations of losartan potassium were >929 mg/L. Confidence limits to these estimates could not be calculated due to lack of treatments with intermediate levels of mortalities and effects, respectively. Average measured concentrations of losartan potassium ranged from 92-93% of the nominal concentrations.

Rainbow trout, *Oncorhynchus mykiss*, used in tests with losartan potassium were obtained as juveniles from a commercial hatchery (Stoney Creek Trout Farm, Grant, MI). The fish were maintained in the laboratory on treated Jupiter, Florida, town water prior to test initiation. The freshwater possessed a hardness of approximately 100 to 104 mg/L as calcium carbonate (CaCO₃). Holding water temperature ranged from 10.6 to 15.4°C during the 14 days immediately prior to test initiation. Fish used in tests with losartan potassium were approximately seven weeks old at the time of testing. There were no signs of disease among test fish at any time prior to the initiation of tests with losartan potassium. Consequently, these fish were not subjected to any therapeutic treatments.

3) Toxicity to *Oncorhynchus mykiss* (Rainbow Trout) (Cont.)

The juveniles were offered a commercially manufactured pelleted food (#2 Salmon Starter, Zeigler Bros., Inc., Gardners, PA) and live brine shrimp (Aquarium Products, Glen Burnie, MD) nauplii daily. Food was not offered to prospective test fish for 48 hours prior to the initiation of either the screening or definitive test. Mortalities within fish stocks from which fish were taken for use in testing losartan potassium were <<1% immediately prior to the initiation of testing.

Screening and definitive tests with rainbow trout were conducted in static, 23.6 liter glass tanks, containing 12 liters of test solution. Water pH and dissolved oxygen were measured daily in each test vessel during both the screening and definitive tests. Water temperature was measured daily in the dilution water control. Alkalinity, hardness and conductivity were determined for solutions in each test vessel at the end of a test i.e. - when either 100% mortality was observed or at the end of the study. Samples for analysis by HPLC were collected from each replicate immediately prior to the addition of test fish to each exposure vessel and in each vessel either when 100% mortality was observed or at the end of the study. All samples were collected from midway in the water column with a glass pipette. The LC_{50} was estimated by a computer program (Wheat, 1989) using the following statistical methods: moving average angle, probit, logit and non-linear interpolation. The method selected for reporting the test results

3) Toxicity to *Oncorhynchus mykiss* (Rainbow Trout) (Cont.)

was determined by the characteristics of the data, i.e., the presence or absence of 0 and 100% mortality and the number of concentrations in which mortalities between 0 and 100% occurred.

Mortality of rainbow trout, *Oncorhynchus mykiss*, exposed for 96 hours to losartan potassium was zero percent at all test concentrations tested, except 555 mg/L. The mortality at 555 mg/L losartan potassium occurred in only one replicate. Because the mortality for this concentration occurred in only one replicate and because 100 percent survival was observed at the higher concentration of test substance, another factor, other than the toxicity of the test compound, was likely the cause of the fish mortality in this replicate during the study. There was 5 percent mortality in the dilution water control.

4) *Photobacterium phosphoreum* (Microtox)

An EC_{50} of >1000 mg/L was obtained for losartan potassium using the standardized Microtox indicator organism (*Photobacterium phosphoreum*).

A Microtox 500 System was used for the determination of a dose-response curve from which the effective concentration (EC_{50}) of losartan potassium was obtained. The EC_{50} is the concentration at which the luminescence (light output) is 50% of the original luminescence, i.e., when the bacteria are not exposed to a toxicant. The indicator organism used is a bioluminescent marine bacteria

4) *Photobacterium phosphoreum* (Microtox) (Cont.)

(*Photobacterium phosphoreum*) which has been grown, harvested, and then lyophilized (freeze dried under vacuum). The lyophilized bacteria were rehydrated with reconstitution solution and used in the assay as reagent.

The procedure employed a non-toxic control and four serial dilutions of losartan potassium. The mean response of the duplicate reagent blanks was used to normalize the duplicate responses of the four test concentrations. This normalization corrects for the deviation in response from normal drifts of light output with time. The dose-response measured was the decrease in light production (luminescence) of the bacteria caused by increasing toxicity. The EC_{50} is obtained at 30 minutes and 15°C.

Phenol was analyzed as a reference toxicant to evaluate bacterial sensitivity (luminescence). The EC_{50} determined at 30 minutes and 15°C was 19.4 mg/L. This response fell within the acceptable range of 15.7-24.1 mg/L obtained from the cumulative summation control chart for phenol.

5) Chronic Toxicity to Green Alga, *Selenastrum capricornutum*

The chronic toxicity of losartan potassium to the green alga, *Selenastrum capricornutum* was determined in a 10-day laboratory toxicity test conducted by Toxikon Environmental Sciences (Jupiter, FL). The criterion for effect was reduction in cell growth.

5) Chronic Toxicity to Green Alga, *Selenastrum capricornutum* (Cont.)

The no-observed-effect concentration (NOEC) and minimum inhibitory concentration were calculated for the mean of the maximum standing crop and $\mu_{\max}$ (maximum specific growth rate).

Maximum standing crop occurred by day 8. The NOEC and MIC values based on maximum standing crop were 143 and 245 mg/L. The largest specific growth rate occurred between days 0 and 2. The NOEC and MIC values based on $\mu_{\max}$ were 245 and 381 mg/L. Mean measured concentrations of losartan potassium ranged from 106 to 124 percent of the nominal. The definitive exposure was conducted under static conditions in a temperature controlled room set at $24 \pm 2^\circ\text{C}$. All losartan potassium stock solutions were prepared using freshwater algal media as the diluent. Four 50 mL aliquots of each test solution were transferred to sterile 250 mL glass Erlenmeyer flasks. Dilution water controls were maintained concurrently with the six test solutions. All flasks were closed with gas exchange caps.

Each test solution was inoculated with approximately 3000 cells/ml *Selenastrum capricornutum*. The test chambers were impartially positioned in a temperature controlled chamber under continuous fluorescent lighting. Light intensity ranged between 4025 to 5100 lux. Test chambers were impartially re-positioned daily to eliminate spatial effects, and continuously agitated on an orbital shaker at approximately 100 rpm.

5) Chronic Toxicity to Green Alga, *Selenastrum capricornutum* (Cont.)

Algal growth was measured by direct cell counts using a hemacytometer counting chamber with a compound microscope every 48 hours. Temperature was measured in one uninoculated flask of test medium daily during the test. The temperature range of the control chamber was monitored continuously during the test with a minimum/maximum thermometer and the diurnal temperature range recorded daily. Light intensity was measured daily at the level of each test solution, except on day 9. The pH was measured at test initiation and termination in all test treatments and control flasks. Concentrations of losartan potassium were measured by HPLC. Samples were collected at test initiation and termination from all composite solutions of the test treatments and the control.

Based on the results of the test, the no-observed-effect concentration (NOEC) and minimum inhibitory concentration (MIC) were calculated by analysis of variance (ANOVA) with statistical differences between mean cell density by Dunnett's procedure. All statistical differences were determined at a probability level of 0.05.

6) Chronic Toxicity to Bluegreen Alga, *Microcystis aeruginosa*

The chronic toxicity of losartan potassium to the blue green alga, *Microcystis aeruginosa* was determined in a 10-day laboratory toxicity test conducted by Toxikon Environmental Sciences (Jupiter, FL). The criterion for effect was reduction in cell growth.

6) Chronic Toxicity to Bluegreen Alga, *Microcystis aeruginosa* (Cont.)

The no-observed-effect concentration (NOEC) and minimum inhibitory concentration (MIC) were calculated for the mean of the maximum standing crop and the μ_{max} (maximum specific growth rate).

Observations of cell morphology found no changes in losartan potassium-exposed cells as compared to cells in the controls. After 10 days of exposure, reduction in cell growth ranged from 9 percent at 566 mg/L to 26 percent at 949 mg/L. Maximum standing crop occurred by day 8. The NOEC and MIC values based on maximum standing crop were 556 and 949 mg/L, respectively. The maximum specific growth rate (μ_{max}) occurred between days 0 and 2. The NOEC and MIC values based on μ_{max} could not be determined (<75.9 mg/L, the lowest concentration tested). The discrepancy between NOEC and MIC values based on cell numbers and growth rates appears to be related to a slight lag in growth for all losartan potassium treatments during the first two days. Although control growth was very rapid during the first two days, it slowed and increased gradually between days 2 through 8.

During the same period, growth rates for losartan potassium treatments which lagged the control initially, increased to rates exceeding the control during days 2 through 8. Based on the growth rates during days 2 through 8, the NOEC and MIC value was ≥ 949 mg/L.

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6) Chronic Toxicity to Bluegreen Alga, *Microcystis aeruginosa* (Cont.)

The definitive exposure was conducted under static conditions in a temperature controlled room at $24 \pm 2^\circ\text{C}$. All losartan potassium stock solutions were prepared using freshwater algal media as the diluent. Three 50 mL aliquots of each test solution were transferred to sterile 250 mL glass Erlenmeyer flasks. Dilution water controls were maintained concurrently with the six test solutions. All flasks were closed with gas exchange caps.

Each test solution was inoculated with approximately 50,000 cells/ml *Microcystis aeruginosa*. The test chambers were impartially positioned in a temperature controlled chamber under continuous fluorescent lighting. Light intensity ranged between 2142 to 2842 lux. Test chambers were impartially re-positioned daily to eliminate spatial effects, and continuously agitated on an orbital shaker at approximately 100 rpm.

Algal growth was measured by direct cell counts using a hemacytometer counting chamber with a compound microscope every 48 hours. Temperature was measured in one uninoculated flask of test medium daily during the test. The temperature range of the control chamber was monitored continuously during the test with a minimum/maximum thermometer and the diurnal temperature range recorded daily. Light intensity was measured at test initiation, day 7 and at test termination. The pH was measured at test initiation and termination in all test treatments and control flasks. Concentrations of losartan potassium were measured by

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6) Chronic Toxicity to Bluegreen Alga. *Microcystis aeruginosa* (Cont.)

HPLC. Samples were collected at test initiation and termination from all composite solutions of the test treatments and the control. Based on the results of the test, the no-observed-effect concentration (NOEC) and minimum inhibitory concentration (MIC) were calculated by analysis of variance (ANOVA) with statistical differences between mean cell density by Dunnett's procedure. All statistical differences were determined at a probability level of 0.05.

f. Microbial Inhibition

A range-finding or screening test was conducted at Toxikon Environmental Sciences, Jupiter, FL, to define the concentration range within which losartan potassium produces complete inhibition on seven different microorganisms. The criterion for the effect was complete inhibition of growth.

Microbial growth inhibition of losartan potassium in agar plates was conducted with seven pure culture microorganisms, viz, *Scenedesmus quadricauda*, *Aspergillus niger*, *Azotobacter paspali*, *Anabaena flos-aquae*, *Fusarium acuminatum*, *Paramecium caudatum* and *Pseudomonas putida*. [Note: Microbial growth inhibition using *Anabaena flos-aquae* was conducted in Bristol's solution]. All seven organisms tested were able to grow on media containing 1

f. Microbial Inhibition (Cont.)

g/L losartan potassium. Since the drug substance did not inhibit the growth of these organisms, the endpoint (Minimum Inhibitory Concentration - MIC) is greater than the highest concentration tested (1 g/L losartan potassium).

In a study conducted by MRL, Rahway, NJ, the maximum concentration of losartan potassium which is non-inhibitory to an activated sludge culture was determined. The maximum non-inhibitory effect concentration (MNIEC) procedure is based on the "Activated Sludge, Respiration Inhibition Test", which is described in OECD Guidelines for Testing of Chemicals, 1984, Method 209. The purpose of this test is to provide a rapid screening method whereby substances which may adversely affect aerobic microbial treatment plants can be identified and maximum non-inhibitory effect concentration of the test substance determined. This method assesses the effect of different concentrations of the test substance on heterogeneous microorganisms by measuring the respiration (i.e. oxygen uptake) under defined conditions. The MNIEC value is the maximum concentration of the test substance which does not inhibit oxygen uptake by the activated sludge culture. Inhibition is indicated by a decrease in the respiration rate of the microbes present in a test solution as compared to that exhibited in the controls.

f. Microbial Inhibition (Cont.)

The MNIEC value of losartan potassium was determined by plotting the log of the concentration versus the R value. The R value corresponds to the dissolved oxygen uptake rate (DUR) of losartan potassium solution in relation to the DUR of the blank, monitored for a 20 minute period. Using this procedure, nominal concentrations up to 1000 mg/L of losartan potassium did not exert an inhibitory effect.

8. Environmental Effects of Released Substances

a. Bulk Chemical Production

1) Losartan potassium

Environmental concentrations of losartan potassium are estimated to be well below levels of environmental significance. Estimated concentrations of drug substance in the Ballydine facility's on-site wastewater treatment plant will be less than mg/L. As a result of on-site treatment and subsequent dilution, receiving water concentrations of drug substance will be below mcg/L (ppb). (Based on the fifth year total production volume of losartan potassium [kg].)

Aquatic concentrations of losartan potassium will be far below the levels which would cause environmental effects. The low environmental (aquatic) concentrations coupled with the low toxic effects at these concentrations and rapid photodegradation as well as potential biotransformation by periphyton in fresh water bodies indicate that the drug substance will have little impact on the aquatic environment.

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1) Losartan potassium (Cont.)

Losartan potassium is non-toxic to aquatic organisms at the expected environmental concentrations. It is neither toxic nor inhibitory to biological oxidation of other more easily metabolized carbon sources such as glucose and ethanol by an activated sludge system; although, losartan potassium itself is not readily biodegradable by an unacclimated activated sludge culture.

Losartan potassium is very stable in aqueous solution. However, it is biotransformed by periphyton, an algae rich microbial population, commonly found in fresh water bodies. Also, the drug degrades quite rapidly when exposed to natural sunlight. Losartan potassium is practically nontoxic to aquatic indicator organisms (fish, daphnia) and does not inhibit the activity of a marine bacteria and unacclimated mixed microbial population (activated sludge) at the expected environmental concentrations. Losartan potassium does not inhibit the growth of a number of representative microorganisms up to 1 g/L. Losartan potassium is slightly inhibitory to the green alga, *Selenastrum capricornutum* and *Microcystis aeruginosa*. However, there are no observable effects at the expected environmental concentrations. Little or no introduction of losartan potassium to the terrestrial environment will occur. Thermal studies indicate losartan potassium does not volatilize at ambient temperatures and, thus, transport of the drug substance to the air compartment is not deemed to be significant.

I. Summary

F. Environmental Assessment

a) Chemical Operations

Chemical manufacturing operations will be conducted in the United States and Ireland. The environmental impact of the emitted substances from the production of bulk drug and dosage form have been assessed through material balance considerations, physico-chemical and biological characterization of the emitted waste streams. Parameters considered include pH, oxygen demanding materials, nitrogenous materials, organic carbon, solids concentration, hydraulic and organic waste loading, extent of biodegradation, inhibitory effects on the mixed microbial population of the activated sludge system and aquatic toxicity.

Characterization of the waste streams indicate them to be non-inhibitory and readily biodegradable by an unacclimated mixed microbial population of activated sludge origin. Also, the untreated raw wastewater has been found to be only slightly toxic to aquatic indicator organisms, *Daphnia magna* and *Photobacterium phosphoreum*. A data summary is provided in Appendix II - Part 4.

It should be noted that, in the drug substance production process, the trityl intermediate is converted to the free acid, losartan, by removal of the triphenyl-methyl group in a homogeneous aqueous-organic system under acidic conditions. A similar transformation is likely to occur in the environment, albeit very much more slowly. Thus, the ultimate environmental fate of the trityl intermediate is likely to parallel that of losartan itself.

I. Summary

F. Environmental Assessment

a) Chemical Operations (Cont.)

In addition it should be noted that, with the exception of normal processing losses, all of the trityl intermediate produced at the Albany, GA facility is consumed in the manufacture of losartan potassium at the Ballydine, Ireland facility. The intermediate is shipped in sealed plastic bags within fiber drums which are themselves labeled and properly secured. Strict material accountability is maintained throughout and thus little opportunity exists for entry of the trityl intermediate into the environment.

Entry of the trityl intermediate into the environment in amounts likely to have an adverse effect is improbable. Thus, it is unusual to have detailed fate and effects information available. However, in this instance importation of trityl losartan into Ireland required notification under European Directive 67/548/EEC, as amended in 1984 (Sixth Amendment). Under the provisions of the Sixth Amendment, ecotoxicological characterization was carried out by an outside testing laboratory (Huntingdon Research Centre Ltd., Cambridgeshire, England). A summary of the testing results is provided in Appendix 1 - Part 2.

These studies indicate the trityl intermediate, although not readily biodegradable, is not inhibitory to activated sewage sludge microbial populations. In addition, saturated solutions containing ca. 0.07 mg/L (i.e. the highest test concentration that could be prepared due to the compound's low solubility in water and auxiliary solvents) were not toxic to Rainbow trout (NOFC $\geq$ 0.073

I. Summary

F. Environmental Assessment

a) Chemical Operations (Cont.)

mg/L) or *Daphnia magna* (NOEC $\geq$ 0.069 mg/L) and did not inhibit the growth of the green alga, *Scenedesmus subspicatus* (NOEC $\geq$ 0.069 mg/L).

The LD₅₀ of trityl-losartan, administered orally, in mouse and rat is > 5000 mg/kg and >2000 mg/kg, respectively. There were no mortalities and no treatment related clinical observations noted during a 28-day study on male and female Sprague-Dawley rats. Trityl-losartan was administered orally every day for 28-days at dose rates of 15, 150, 1000 mg/kg/day. Based on this study, 1000 mg/kg/day represents a no observed effect level (NOEL) in the rat.

The material is a granular, free-flowing solid with a melting point range of 158-159°C, a relative density of 1.21, a vapor pressure of 1.1×10^{-5} Pa (25°C) and a water solubility < 0.23 mg/L (20°C). It exhibits a relatively high octanol-water partition coefficient; $\log P_{ow} > 3.9$. The compound is not considered to be flammable or explosive and does not possess autoflammable or oxidizing properties.

Based on its physical-chemical properties, (i.e. low aqueous solubility and relatively high octanol-water partitioning), the compound is likely to be preferentially sorbed to the activated sludge biomass and removed from the aqueous compartment. As noted previously, the UV-VIS absorbance spectrum of the trityl intermediate is similar to that of losartan potassium and, like

I. Summary

F. Environmental Assessment

a) Chemical Operations (Cont.)

losartan potassium, the trityl intermediate may be susceptible to photolysis and degrade rapidly under clear sky conditions. Like losartan itself, the trityl intermediate may also undergo biotransformation by algae rich microbial populations commonly found in fresh water bodies.

b) Tablets Losartan Potassium

Losartan potassium will enter the environment primarily by urinary excretion which becomes highly diluted during normal wastewater processing and treatment. When administered orally, about 4% is excreted as losartan and 6% is excreted as the active carboxylic acid metabolite. Following an oral dose of ¹⁴C labelled losartan potassium in man, about 35% of the radioactivity is recovered in urine and 58% in feces demonstrating that losartan potassium is extensively metabolized.

Maximum environmental concentrations in the United States resulting from losartan potassium use are estimated to be mcg/L (ppb). These are based on projected 5th year production estimates and do not include any metabolic or environmental depletion (e.g. photodegradation, microbial transformation). Lifetime exposure to these concentrations (2 L/day, for 365 days/year over a 70 year lifetime) would result in ingestion of approximately of a 100 mg daily dose.

c) Losartan Potassium Toxicology

(1) Acute Toxicity

Significant lethality was observed in mice and rats after oral administration of 1000 mg/kg (3000 mg/m²) and 2000 mg/kg (11,800 mg/m²).

(2) Chronic Toxicity

The toxic potential of losartan potassium was evaluated in a series of repeated dose oral toxicity studies of up to three months in monkeys and up to one year in rats and dogs. There were no findings that would preclude administration at the therapeutic dosage level.

(3) Carcinogenicity

Losartan potassium was not carcinogenic when administered at maximum tolerated dosage levels to rats and mice for 105 and 92 weeks, respectively. These maximum tolerated dosage levels provided respective margins of systemic exposure for losartan and its pharmacologically active metabolite over that achieved in humans treated with 50 mg of losartan of approximately 270- and 150-fold in rats and 45- and 27-fold in mice .

(4) Mutagenicity

Losartan potassium was negative in the microbial mutagenesis and V-79 mammalian cell mutagenesis assays. In addition, there was no evidence of direct genotoxicity in the *in vivo* alkaline elution and *in vitro* chromosomal aberration assays at concentrations that

I. Summary

F. Environmental Assessment

(4) Mutagenicity (Cont.)

were approximately 1700 times greater than the maximum plasma level achieved in man at the recommended therapeutic dosage level. Similarly, there was no induction of chromosomal aberrations in bone marrow cells of male or female mice after the administration of toxic oral doses of up to 1500 mg/kg (4500 mg/m²) (750 times the maximum recommended daily human dose based on a patient weight of 50 kg). In addition the active metabolite showed no evidence of genotoxicity in the microbial mutagenesis, *in vitro* alkaline elution, and *in vitro* chromosomal aberration assays.

(5) Reproduction

Fertility and reproductive performance were not affected in studies with male and female rats given oral doses of losartan potassium up to approximately 150 and 300 mg/kg/day respectively. These dosages provide respective margins of systemic exposure for losartan and its pharmacologically active metabolite of approximately 150/125-fold in male rats and 300/170-fold in female rats over that achieved in man at the maximum recommended daily dose.

(6) Development

Losartan potassium has been shown to produce adverse effects in rat fetuses and neonates. The effects include decreased body weight, mortality and/or renal toxicity. Pharmacokinetic evaluation of fetal plasma samples showed significant levels of losartan and

I. Summary

F. Environmental Assessment

(6) Development (Cont.)

its active metabolite on Gestation Day 20 compared to negligible value on Gestation Day 15. In addition, significant levels of losartan and its active metabolite were shown to be present in rat milk. Based on these findings, the fetal and neonatal effects of losartan in rats are attributed to drug exposure in late gestation and during lactation.

d) Pharmacokinetics

(1) Absorption

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan potassium tablets is approximately 33 %. Mean peak concentrations of losartan and the active metabolite are reached in 1 hour and in 3-4 hours, respectively. There was no clinically significant effect on the plasma concentration profile of losartan when the drug was administered with a standardized meal.

(2) Distribution

Both losartan and the active metabolite are $\geq 99\%$ bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 liters. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

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(2) Distribution (Cont.)

About 14% of intravenously or orally-administered losartan is converted to the active metabolite. Following oral and intravenous administration of ¹⁴C-labeled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and the active metabolite. Minimal conversion of losartan to the active metabolite was seen in about one percent of the individuals studied.

In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N-2 tetrazole glucuronide.

(4) Elimination

Plasma clearance of losartan and the active metabolite is about 600 mL/min and 50 ml/min, respectively. Renal clearance of losartan and the active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with losartan doses up to 200 mg.

Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal

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(4) Elimination (Cont.)

half-life of about 2 hours and 6-9 hours, respectively. During once a day dosing, neither losartan nor the active metabolite accumulates significantly in plasma.

Both urinary and biliary excretion routes are important for the elimination of losartan and its metabolites. Following an oral dose of ¹⁴C-labeled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the feces. Following an intravenous dose of ¹⁴C-labeled losartan in man, about 43% of radioactivity is recovered in urine and 50% in the feces.

(5) Characteristics in Patients

The plasma concentrations of losartan and the active metabolite observed in elderly male hypertensives are not significantly different from those observed in young male volunteers.

Following oral administration in patients with stable alcoholic cirrhosis of the liver, plasma concentrations of losartan and the active metabolite were, respectively, 5-fold and 1.7-fold than those seen in young male volunteers.

Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 ml/min. Compared to patients with normal renal function, the AUC for losartan is about 2-fold greater in hemodialysis patients. Neither renal impairment nor

(5) Characteristics in Patients

hemodialysis affects plasma concentrations of the active metabolite. Neither losartan nor the active metabolite can be removed by hemodialysis.

9. Use of Resources and Energy

The raw materials utilized to manufacture the drug substance and dosage form are common chemicals all of which are in ample commercial supply. Energy commitment for dosage form production in the United States is nominal and not excessive. Only very small increases in the utilization of energy is anticipated since production occurs at existing facilities. No effects upon endangered or threatened species and upon property listed in or eligible for listing in the National Register of Historic Places are anticipated.

10. Mitigation Measures

No potential adverse environmental impacts are foreseen from the production and use of drug substance and product. The manufacture, distribution and use of the product takes place under highly regulated and controlled conditions which act to further mitigate against negative environmental consequences.

A variety of pollution prevention initiatives were evaluated during development of the current process and, where appropriate, incorporated into the process. Two competing chemical pathways to the drug substance were considered. The more attractive

10. Mitigation Measures (Cont.)

environmental profile of the current process was a major reason this pathway was selected. Additionally, the cumulative effect of many small process improvements resulted in substantial yield improvement which implies less raw material usage per unit of product and less waste generated.

Specifically, the current process avoids the use of tributyl-tin chloride, an environmentally toxic compound used in the original process. The current process also uses less solvent and the solvents used are generally more environmentally benign (more biodegradable and less toxic). Methylene chloride was used in an earlier process. The current process avoids the use of methylene chloride, a priority pollutant, or other suspect carcinogens. The original process used larger quantities of solvents and included a greater number of SARA 313 solvents compared to the current process. Overall, 50% less aqueous waste is generated and these are biodegradable and of low aquatic toxicity.

In addition, a number of process changes were introduced during the course of the laboratory and pilot plant development; many of which further improved the environmental profile of the current process. Particularly noteworthy in this regard are the use of a sequestrant and mixed solvent system. Use of a sequestrant to remove a transition metal catalyst eliminated a recrystallization step and resulted in reduced solvent usage and a 5% overall waste reduction. In another step, a mixed solvent system is used to carry

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10. Mitigation Measures (Cont.)

out the desired reaction rather than sequential use of the two pure solvents. This facilitates cost effective recovery and reuse of the mixed solvent. Increased productivity in the crystallization procedure resulted in 30% less solvent usage. Productivity improvements in the final synthesis step also resulted in substantially reduced solvent usage. The overall process yield improvement achieved by the accumulation of multiple enhancements to the process was 25%. This provided the added benefit of reducing the amount of waste generated by the process.

11. Alternatives to the Proposed Action

The use of COZAAR will directly benefit patients by providing patients safe and effective therapy necessary for the management of hypertension.

Approval of COZAAR is justified from an environmental perspective and is preferable to non-approval.

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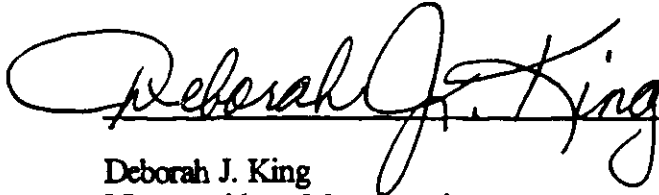
2/3/95

Date

Tablets Losartan Potassium
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The undersigned certifies that the information presented is true, accurate, and complete to the best of my knowledge and that of the DuPont Merck Pharmaceutical Company.



Deborah J. King
Vice President, Manufacturing
The DuPont Merck Pharmaceutical Company

2/3/95
Date

14. References

1. Methods for Measuring the Acute Toxicity of Effluents to Freshwater and Marine Organisms, EPA/600/4-85/013, 1985.

ATTACHMENT II

REGULATORY AFFAIRS

MAR 09 1995

LARRY P. BELL, M.D

NDA 20-386

COZAAR Tablets

Non-Confidential Addendum to February 1, 1995

Environmental Assessment for COZAAR

Item a. Contract Packaging Sites

Alternate Packaging Facilities

1. PACO Pharmaceutical Services, Inc., Lakewood, New Jersey

Packaging of the drug product will occur at the PACO facility located at 1200 PACO Way, Lakewood, NJ-08701. The type of environment present at this location specific to the drug product packaging operation is described in the following sections. The Lakewood site environment is described in the following section.

a. Geographic Condition

The PACO plant is located on approximately 11 acres of land in the Township of Lakewood, Ocean County, New Jersey. The plant is near latitude 40°3'32"N; longitude 74°11'7"W; about 60 miles south of Newark, NJ.

The site consists of one building covering approximately 150,000 sq. ft. and employing an average workforce of about 800-900 people. Lakewood has a population of approximately 11,000. The surrounding neighborhood includes light industry, wooded area and residential homes.

b. Air Resources

Air quality in this area is in compliance with the National Air Quality Standards (NAAQS) of the Clean Air Act for total particulates, sulfur oxides and nitrogen oxides. The entire state of New Jersey is in non-attainment with the NAAQS for ozone. New

b. Air Resources (Cont.)

Jersey is part of the EPA Region II and NJDEPE is responsible for implementing the state implementation plan. The mean summer temperature is 70°F (21°C) and the mean winter temperature is 37°F (28°C). Annual rainfall is about 42 inches (107 cm).

c. Water Resources

All potable water used at the PACO plant is supplied by the "Englishtown Raritan Aquifer" and the town of Lakewood public water supply. It is estimated that the daily average use is 19,178 gallons with an annual consumption of approximately 7 million gallons. Process waters are directly discharged into the Ocean County Sewage Treatment Plant in compliance with the Ocean County Utility Authority and local ordinances. Storm water from the roof drains and parking areas run off to Cedar Creek which eventually flows to the Metedeconk River. The plant is located in a 100 year flood zone.

d. Land Resources

The 11 acre site is level terrain covered by one building, driveways, walkways, parking and landscaped areas. It is surrounded by light industry, woods and residential communities. Prior to 1979, the land was a pinewood forest. The mean elevation above sea level is 120 feet. The soil is sandy loam and sandy gravel. The water table is between 14 to 18 ft.

e. Identification of Chemical Substances that are subject to proposed action

Information concerning the chemical name, empirical formula, molecular weight, chemical structure, laboratory codes, generic name, trade name, and CAS (Chemical Abstract Substance Registry) number can be found in Appendix I.

f. Introduction of Substance into the Environment

1) Substances Expected to be Emitted

a) Bulk Drug Synthesis

No bulk synthesis of losartan potassium will occur at the PACO, Lakewood, NJ facility.

b) Dosage Form Production

No dosage form production will occur at the PACO, Lakewood, NJ facility.

2) Control Procedures for Expected Emissions

a) Air Emission Controls

Air emissions from drug product packaging operations may include trace levels of particulates as described in Appendix II for emitted substances from dosage form production. In general, particulate emissions generated from packaging of film-coated tablets is extremely low.

As there is a virtual absence of particulates generated during packaging, specific air emissions controls are preventative or precautionary by design. Local exhaust ventilation is provided in the tablet packaging area to provide protection from incidental occupational exposure (e.g. as might result from a broken tablet).

2) Control Procedures for Expected Emissions(Cont.)

a) Air Emission Controls (Cont.)

Dry vacuuming conducted as part of the equipment clean-up during changeover of the packaging line will capture loose or broken tablets. With the exception of an alcohol solution used to sanitize the equipment, no organic solvents are used in the packaging operation. Air emissions resulting from this practice are expected to be negligible.

b) Liquid Emission Controls

Wastewater releases will be generated only during clean-up and changeover of the packaging equipment. Dry vacuum clean-up of the filling equipment during product changeover is supplemented with a water rinse. The film-coated tablet itself provides a measure of containment because of the film-coat and the reduced friability imparted to the tablet. Liquid emission controls are preventative in nature with little wastewater generation expected.

c) Solid Waste Controls

Non-hazardous wastes resulting from packaging may consist of paper, aluminum, plastic, drums and Tyvek® suits and product filter solids. Product filter solids and chemical contaminated wastes are sent to an off-site permitted incineration facility. Other non-hazardous wastes which cannot be recycled are disposed of at a state licensed landfill. In order to minimize the amount of material for disposal, excess raw materials may be returned to the customer for further use.

d) Employee Protection

Material Safety Data Sheets are available on-site for all chemicals as required by the Occupational Safety Act of 1971, the Hazards Communication act of 1985 and Title 29 Code of Federal Regulations (CFR) Part 1910. Employees associated with the manufacture of drug product have appropriate MSDSs available for their review. Employee protective clothing, such as gloves, uniforms and safety glasses are used during the packaging process to assure compliance with the Occupational Safety Act of 1971 and the Hazard Communication Act of 1985 and Title 29 CFR, Subpart I.

3) Applicable Emission Citations and Statements of Compliance

a) Lakewood, New Jersey

(1) Air Citations and Statements of Compliance

Air emissions and controls in place for the manufacture of drug product meet the requirements of the New Jersey Administrative Code, Title 7, Chapter 27 governing air pollution control. In all instances where particulate emissions are expected, the plant will be in compliance with the associated regulatory limits. No permits are required and no new permits are expected as a result of the proposed action. No incineration takes place at the PACO Lakewood, NJ facility.

(2) Liquid Citations and Statements of Compliance

Discharge of process wastewater to the Ocean County Utilities Authority is subject to, and in compliance with, the local authorities rules and regulations.

(2) Liquid Citations and Statements of Compliance (Cont.)

Wastewater discharges from packaging will consist of aqueous equipment washouts as discussed above, which will be further combined with sanitary wastes for the site. Currently no wastewater permit is required for this building, and none will be necessary as a result of packaging of the drug product at PACO.

(3) Solid Citations and Statements of Compliance

Solid waste management at the Lakewood, NJ site requires overall conformance with the requirements of New Jersey Administrative Code, Title 7, Department of Environmental Protection and Energy, Chapter 26 and all other applicable rules and regulations governing solid and hazardous waste management. The facility waste generator number is NJ009722257. The Lakewood site is in compliance with these rules and the proposed action will not impact the facility's ability to comply with such requirements. The site is not governed by any solid or hazardous waste permits and no permits are expected to be required as a result of packaging Tablets Losartan Potassium.

4) Effect of Application Approval on Compliance with Current Emission Requirements

PACO Pharmaceutical Services, Inc. of Lakewood, NJ states that it will be in compliance with all emission requirements set forth in permits, consent decrees and administrative orders applicable to the packaging of Tablets Losartan Potassium at its facility in Lakewood, NJ as well as emission regulations applicable to the packaging of Tablets Losartan Potassium at its facility in Lakewood, NJ.

2. Packaging Coordinators, Inc., Philadelphia, PA

The future packaging of the drug product will occur at the PCI facility located at K Street and Erie Avenue, Philadelphia, PA 19124. The type of environment present at this location specific to the drug product packaging operation is described in the following section.

a. Geographic Condition

The PCI plant is located on approximately 3 acres of land in the City of Philadelphia, Pennsylvania. The plant is near latitude 40° N; longitude 75° W. The site consists of a five story building covering approximately 164,000 square feet with the packaging area occupying four floors. All rooms are self-contained and completely enclosed. The facility employs approximately 450 people. Philadelphia has a population of approximately 1,680,000. The surrounding neighborhood includes retail business, light industry and residential homes.

b. Air Resources

Air quality in the area is in compliance with the National Ambient Air Quality Standards (NAAQS) of the Clean Air Act for suspended particulates, sulfur oxides and nitrogen oxides. This compliance is based on monitoring and reporting by the Pennsylvania Department of Environmental Resources (PADER) under the requirements of the state implementation plan, as required by the Clean Air Act. The area is in non-attainment with the NAAQS for ozone. Pennsylvania is part of the EPA Region III and PADER is responsible for implementing the State Implementation Plan which may require new stationary source permits for manufacturing. Meteorological data for the region is

b. Air Resources (Cont.)

collected at the Philadelphia International Airport located 20 miles from the PCI facility. Annual rainfall is approximately 42 inches (107 cm) and the mean ambient temperature varies between 33 and 77°F (0.5 - 25°C). Predominant winds are from west to southeast.

c. Water Resources

All potable water used at the PCI plant is supplied by the Philadelphia Water Authority. It is estimated that the daily average use is 2068 gallons with an annual consumption of approximately 517,000 gallons. Process waters are directly discharged into the Philadelphia Municipal Sewerage Treatment Plant in compliance with the sewage authority limits.

d. Land Resources

The 3 acre site is level terrain covered by 1 building, 5 stories high. It is surrounded by light industry, commercial establishments and residential communities. The facility, built in 1930, has no green areas. The mean elevation above sea level is 121 ft.

e. Identification of Chemical Substances that are Subject to Proposed Action

Information concerning the chemical name, empirical formula, molecular weight, chemical structure, laboratory codes, generic name, trade name, and CAS Registry number are in Appendix I.

f. Introduction of Substance into the Environment

1) Substances Expected to be Emitted

a) Bulk Drug Synthesis

No bulk drug synthesis of losartan potassium will occur at the PCI, Philadelphia facility.

b) Dosage Form Production

No dosage form production will occur at the PCI, Philadelphia facility.

2) Control Procedures for Expected Emissions

a) Air Emission Controls

Air emissions from drug product packaging operations may include trace levels of particulates as described in Appendix II for emitted substances from dosage form production. In general, particulate emissions generated during packaging of film-coated tablets are extremely low.

As there is a virtual absence of particulates generated during packaging, specific air emissions controls are preventative or precautionary by design. Product retention filters are employed on the equipment handling substances for packaging. These filters provide for an average of 72% arrestance for particulates. Local exhaust ventilation is provided in the tablet packaging area to provide protection from incidental occupational exposure (e.g. as might result from a broken tablet). Dry vacuuming conducted as part of the equipment clean-up during changeover of the packaging line will capture loose or broken tablets. With the exception of an alcohol solution used to sanitize the equipment, no organic solvents are used in the packaging operation. Air emissions resulting from this practice are expected to be negligible.

b) Liquid Emission Controls

Waste water releases will be generated only during clean-up and changeover of the packaging equipment. Dry vacuum clean-up of the filling equipment during product changeover is supplemented with a water rinse. The film-coated tablet itself provides a measure of containment because of the film-coat and the reduced friability imparted to the tablet. Liquid emission controls are preventative in nature with little wastewater generation expected.

c) Solid Waste Controls

Non-hazardous wastes resulting from packaging may consist of paper, aluminum, plastic, drums and Tyvek® suits and product filter solids. Product filter solids and chemical contaminated wastes are sent to a permitted incineration facility. Other non-hazardous waste which cannot be recycled are disposed of at a state licensed landfill. In order to minimize the amount of material for disposal, excess raw materials may be returned to the customer for further use.

d) Employee Protection

Material Safety Data Sheets are available on-site for all chemicals as required by the Occupational Safety Act of 1971, the Hazards Communication Act of 1985 and Title 29 Code of Federal Regulations (CFR) Part 1910. Employees associated with the manufacture of drug product have appropriate MSDSs available for their review. Employee protective coating, such as gloves, uniforms and safety glasses are used during the packaging process to assure compliance with the Occupational Safety Act of 1971 and the Hazard Communication Act of 1985 and Title 29 CFR, Subpart I.

3) Applicable Emission Citations and Statements of Compliance

a) Philadelphia, PA

(1) Air Citations and Statements of Compliance

The site is not governed by any air permits and no permits are expected to be required as a result of packaging losartan potassium at this location.

No on-site incineration takes place at the PCI Philadelphia, PA facility.

(2) Liquid Citations and Statements of Compliance

Discharge of process wastewater to the Philadelphia Water Treatment Authority is subject to, and in compliance with, the local authorities rules and regulations.

Wastewater discharges from packaging will consist of aqueous equipment washouts as discussed above, which will be further combined with sanitary wastes for the site. Compliance with these regulatory limits will not be impacted by the proposed action.

(3) Solid Citations and Statements of Compliance

Solid waste management at the Philadelphia, PA site requires overall conformance with the requirements of all applicable rules and regulations governing solid and hazardous waste management. The Philadelphia site is in compliance with these rules and proposed action will not impact the facility's ability to comply with such requirements. The site is not governed by any solid or hazardous waste permits and no permits are expected to be required as a result of packaging Tablets Losartan Potassium at this location.

4) Effects of Application Approval on Compliance with Current Emission Requirements

PCI of Philadelphia, Inc. states that it is in compliance with all emissions requirements set forth in permits, consent decrees and administrative orders applicable to the packaging of Tablets Losartan Potassium at its facility in Philadelphia, PA as well as emission regulations applicable to the packaging of Tablets Losartan Potassium at its facility in Philadelphia, PA.

Item b. Drug Substance Information

A. Drug Substance Information Summary

1. Nomenclature

International Non-Proprietary Name:

Losartan potassium

U. S. Adopted Name:

Losartan potassium

Chemical Name:

1H-Imidazole-5-methanol,2-butyl-4-chloro-1-
[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-
yl]methyl]-,monopotassium salt

2-n-Butyl-4-chloro-1-(2'-tetrazol-5-yl)-1,1'-
biphenyl-4-yl-methyl)-1H-imidazole-5-
methanol,potassium salt

Laboratory Codes:

L-158,086-005H

MK0954

DUP-753

Other Names:

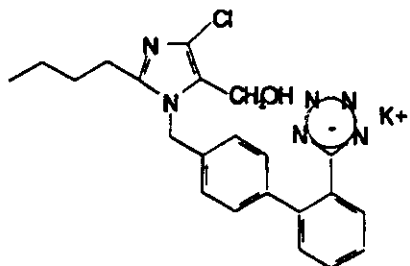
COZAAR

Chemical Abstracts Service (CAS) Registry No.:

124750-99-8

2. Description

Structural Formula



Molecular Formula



Molecular Weight

461.0

3. Environmental Fate

a. Solubility, aqueous

> 500 mg/mL at ambient (~25°C)

b. Dissociation Constant

pKa = 4.1 (1% methanol)

c. n-Octanol - Water Partitioning

log P = 1.19 @ pH 7.0

d. Thermal Behavior

$$T_f = 272^\circ\text{C}$$

$$H_f = 85.8 \text{ J/g}$$

In an oxidizing environment, exothermic pyrolysis occurs between 300 - 515°C. Above 550°C, combustion of char proceeds, leaving ~20% ash.

Vapor pressure

$$< 10^{-7} \text{ torr @ } 59^\circ\text{C}$$

e. UV - Vis Spectrum

Absorbance shoulders observed:

$$\sim 250 \text{ nm (A1\% 1cm } \sim 320)$$

$$\sim 228 \text{ nm (A1\% 1cm } \sim 574)$$

f. Biodegradation

Losartan potassium is not readily biodegradable when exposed to an unacclimated mixed microbial population (activated sludge). Exposure to a well-acclimated periphyton (algal) culture resulted in ~ 29% loss of parent compound in 28 days.

g. Hydrolysis

Losartan potassium is not susceptible to hydrolysis in aqueous solution.

@50°C

pH 5	(acetate buffer)	<10% (5 days)
pH 7	(phosphate buffer)	<10% (5 days)
pH 9	(borate buffer)	<10% (5 days)

h. Photolysis

Losartan potassium is susceptible to photolysis and degrades rapidly under clear sky conditions.

		t _{1/2}
pH 5	(acetate buffer)	10.9 hr.
pH 7	(phosphate buffer)	11.8 hr.
pH 9	(borate buffer)	17.6 hr.

4. Environmental Effects

a. Aquatic Toxicity

- 1) *Daphnia magna* (water flea)
48-hour LC₅₀ = 331 mg/L
NOEC = 80 mg/L
- 2) *Pimephales promelas* (Fathead Minnow)
48-hour LC₅₀ > 1000 mg/L
NOEC = 100 mg/L
- 3) *Oncorhynchus mykiss* (Rainbow trout)
96-hour LC₅₀ > 929 mg/L
NOEC > 929 mg/L

b. Microbial Inhibition

<i>Azotobacter paspali</i>	MIC > 1000 mg/L
<i>Scenedesmus quadricauda</i>	MIC > 1000 mg/L
<i>Fusarium acuminatum</i>	MIC > 1000 mg/L
<i>Aspergillus niger</i>	MIC > 1000 mg/L
<i>Pseudomonas putida</i>	MIC > 1000 mg/L
<i>Anabaena flos-aquae</i>	MIC > 1000 mg/L
<i>Paramecium caudatum</i>	MIC > 1000 mg/L

b. Microbial Inhibition (Cont.)*Photobacterium phosphoreum* (Microtox™)EC₅₀ (30 min, 15°C) ≥ 1000 mg/Lc. Maximum Non-Inhibitory Effect Concentration (Activated Sludge)

≥ 1000 mg/L

d. Algal Toxicity (10 day)

<u>Algae</u>	<u>End Point</u>	<u>NOEC</u> <u>(mg/L)</u>	<u>MIC</u> <u>(mg/L)</u>
<i>S. capricornutum</i>	cell growth	143	245
(green algae)	growth rate	245	245
<i>M. aeruginosa</i>	cell growth	556	949
(blue-green algae)	growth rate	≥ 949	≥ 949

Item c. Site Permit Information**Site Permit Information**

Permit Name	Permit Number	Expiration Date	Issuing Agency
Ballydine, Ireland *			
Air Permit - Solvent Incinerator	#ENV/A.P/2/91 #ENV/D/3	None	Tipperary County Council
Wastewater Treatment Plant Operation	#ENV/W/36/80	None	Tipperary County Council
Albany, Georgia			
Air Quality Permit	#2833-047-10356	NA	Georgia Department of Natural Resources, Environmental Protection Division (EPD)
Air Quality Permit	#2833-047-11517	NA	Georgia Department of Natural Resources, EPD
NPDES Permit Wastewater	GA0001619	September, 1999	Georgia Department of Natural Resources, EPD
Hazardous Waste Permit	HW0008(S)	December 29, 1999	Georgia Department of Natural Resources, EPD
Ground Water Permit	047-0003	March, 2005	Georgia Department of Natural Resources, EPD
Drinking Water	PG0950023	March, 2004	Georgia Department of Natural Resources, EPD
Garden City, NY			
Air - Dust Collection Equipment	C-282011-0886-00001 W-CA & CB	October, 1995	Nassau County Health Department
Air - Main Building	C-282011-0886-00007 W-CA, CB & CC	October, 1995	Nassau County Health Department
Air - R&D Building	C-282011-0886-00008 W-CA, CB	October, 1995	Nassau County Health Department
Air	C-282011-0886-00021 W through C-282011-0886-00023 W	October, 1995	Nassau County Health Department
Wastewater - Sewer Discharge Permit	#33	June 14, 1996	Cedar Creek Water Pollution Control Plant, Nassau County

* The Ballydine, Ireland facility applied for an Integrated Pollution Control License from the Irish EPA in August 1994. Once this license is granted, the license numbers listed above will be superseded.

Site Permit Information (Continued)

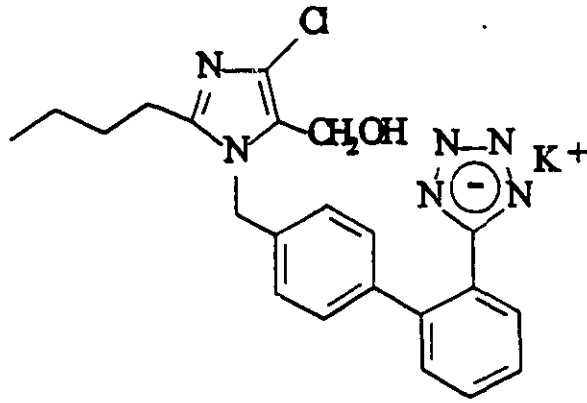
Permit Name	Permit Number	Expiration Date	Issuing Agency
West Point, PA - Permits Applicable to the Incineration of Returned Goods			
Air - Operating Permit for Rotary Kiln Incinerator with a tray scrubber and the Waste Heat Incinerator	#46-301-191B	August 8, 1998	Pennsylvania Department of Environmental Resources
Solid Waste - Waste Heat Incinerator Permit	PA No. 400459	None	Pennsylvania Department of Environmental Resources
Solid Waste - Rotary Kiln Incinerator Permit	PA No. 300501	January 1, 1997	Pennsylvania Department of Environmental Resources
West Point - Permits Not Applicable to the Incineration of Returned Goods			
UGTA - Merck Wastewater Contract	Contract	September 30, 1998	Upper Gwynedd Township Authority (UGTA)
Catalytic Oxidizer Plan Approval -	#46-313-117 (previous permit number 46-313-090B)	February 28, 1995	Pennsylvania Department of Environmental Resources
Solid Waste - Waste Crusher Permit	PA No. 300437	None	Pennsylvania Department of Environmental Resources
Wilson, NC			
Wastewater Permit	#8406	June 30, 1996	City of Wilson, Department of Public Works
Air Permit	#4884R9	March 31, 1997	North Carolina Department of Natural Resources & Community Development
Hazardous Waste	NCD980798839	August 31, 2001	North Carolina Department of Environmental Health & Natural Resources

ATTACHMENT III

Tablets Losartan Potassium
Chemical and Pharmaceutical Manufacturing and
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Appendix IV

Material Safety Data Sheet for Losartan Potassium



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MENCK SHARP AND BOWEN (IRL) LTD.; BALLINTEDE, KILSHILLAN,
 CLOMEL, COUNTY TIPPERRARY, IRELAND

***** MATERIAL SAFETY DATA SHEET *****

LABEL NAME: LOSARTAN POTASSIUM PLANT MENS CODE
BA-055
 Emergency Telephone Number: 051-40411

SECTION 1 - MATERIAL IDENTIFICATION

Chemical Name----- 2-s-Butyl-4-chloro-1-(2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-ylmethyl)-1H-imidazole-5-methanol, potassium salt
 Synonyms (Common)----- L-158,086; MK-954; DUP-753
 (Chemical)----- Not available
 Material Statistics Number----- 2-48692 (dry; 2-48693 (milled);
 2-48694 (blended)
 Material Product Number----- SP2240
 Chemical Classification----- Imidazole
 Intended Use----- Highly specific, non-peptide angiotensin II receptor antagonist

SECTION 2 - PRINCIPAL HAZARDOUS COMPONENT(S)

Component	Molecular Formula	Molecular Weight	CAS Number	Percent (%)
Losartan	C ₂₂ H ₂₂ ClN ₆ OK	461.0	124750-99-8	greater than 98

SECTION 3 - PHYSICAL PROPERTY DATA

Appearance----- White to off white crystalline powder
 Odor/Threshold Level (ppm)----- Not available
 Boiling Point (°C/°F)----- Not applicable
 Freezing Point (°C/°F)----- Not applicable
 Melting Range (°C/°F)----- 265°C (509°F)
 pH ----- 8.2 (1% aqueous solution)
 Solubility in water----- Soluble, greater than 500 mg/ml
 Specific Gravity (Water = 1)----- Not applicable
 Vapor Density (Air=1)----- Not applicable

*** Continued on next page ***

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MERCK SERONO INC. BORDA (IREL) LTD.; BALLINAHINE, KILSHOCKLAW,
 CLONSILLA, COUNTY DUBLIN, IRELAND

***** MATERIAL SAFETY DATA SHEET *****

LABEL NAME: LOSARTAN POTASSIUM

PLANT MFGS CODE
BA-055

Emergency Telephone Number: 051-48411

Vapor Pressure (mm Hg @ °C/°F)---Not applicable

Volatile Components (g w/w)-----0%

SECTION 4 - FIRE AND EXPLOSION HAZARD DATA

Flash Point (°C/°F)-----Not applicable

Flash Point Test Method-----Not applicable

Autoignition Temperature (°C/°F)-Not available

Flammable Limits -LEL (g)-----Not applicable

-UEL (g)-----Not applicable

Combustibility Information-----Upon application of a match flame, the material blackened in the area of flame impingement, but did not ignite. When subjected to a Meker burner flame application, the material ignited and burned in the area of the Meker burner producing blackish gray smoke and a crusty residue. The fire was not self-supporting.

Dust Explosivity Information-----The unvented pressure was 8 psig. Pressure developed under all venting ratios was less than 1 psig.

Shock Sensitivity Information-----Not known to be shock sensitive

Extinguishing Media-----If material is involved in fire, fight fire with water, dry chemical or CO₂ extinguishers.

Special Fire Fighting Procedures- Firefighters should wear self-contained breathing apparatus and full protective gear.

Fire/Explosion Hazards-----Material may ignite when impinged upon by heat and flames producing blackish gray smoke. Fire was not self-supporting in tests.

*** Continued on next page ***

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MENCK STAFF AND DOMES (IREL) LTD.; BALLINAHIN, KILSHENKILAN,
 CLONMEL, COUNTY TIPPERARY, IRELAND

***** MATERIAL SAFETY DATA SHEET *****

LABEL NAME: LOSARTAN POTASSIUM

PLANT MSDS CODE
 BA-655

Emergency Telephone Number: 831-66411

Hazardous Decomposition Products Resulting From A Fire- May release
 nitrogen oxides, CO₂, CO, phosgene and
 smoke.

SECTION 5 - REACTIVITY DATA

Stability (Normal Storage Conditions)- Stable under normal temperatures
 and storage conditions.

Storage Conditions to Avoid-----Not available

Thermal Stability/Instability Information- ARC testing detected a very
 large exotherm initiating at approximately
 225°C with a heat release in excess of
 86 cal/gm. Decomposes with heat.

Incompatibilities (Chemical Entities)- None reasonably foreseeable

Incompatibilities (Materials of Construction)- None reasonably foreseeable

Hazardous Polymerizations-----Will not occur

SECTION 6 - EMERGENCY AND FIRST AID PROCEDURES

Eye Contact-----Immediately flush eyes with plenty of
 water for 15 minutes. Seek medical
 attention immediately.

Skin Contact-----Wash with soap and water. Seek medical
 attention if symptoms appear.

Inhalation-----If inhaled, remove to fresh air. Seek
 medical attention if symptoms appear. If
 not breathing, give artificial
 respiration. If breathing is difficult,
 give oxygen.

Ingestion-----Seek medical attention if symptoms appear.
 Induce vomiting ONLY as directed by
 medical personnel. Never give anything by
 mouth to an unconscious person.

*** Continued on next page ***

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MERCK SHARP AND DOHME (IPL) LTD., BALLINAHINE, KILSHURLEN,
 CLOSHEL, COUNTY TIPPERRARY, IRELAND

***** MEDICAL SAFETY DATA SHEET *****

LABEL NAME: LOSARTAN POTASSIUM

PLANT MEDS CODE
 MA-033

Emergency Telephone Number: 061-40411

Notes to Physician----- Losartan potassium is under evaluation for use as an antihypertensive agent. Hypotension may be an adverse effect of overexposure. Supportive measures may be considered. No specific antidote for overexposure has been identified.

SECTION 7 - HEALTH HAZARD DATA

Component	OSHA Permissible Exposure Limit (PEL)	ACGIH-1992-93 Threshold Limit Value (TLV)	Merck Exposure Control Limit (ECL)
Losartan Potassium	Not established	Not established	0.1 mg/m ³ (8-hr TWA)

Carcinogen Designation----- Not listed as a carcinogen by the International Agency for Research on Cancer, the National Toxicology Program, or the Occupational Safety and Health Administration.

Effects of Acute Exposure

Eye Contact----- Severe eye irritant.
 Skin Contact----- Mild skin irritant. Mild contact sensitizer in guinea pigs.
 Inhalation----- Not available
 Ingestion----- Slightly toxic by ingestion. An adverse reaction observed in clinical use is temporary tachycardia (rapid heart rate).

Effects of Chronic Exposure

Sub-chronic and chronic animal bioassays resulted in observation of a number of minimal, pharmacologically mediated effects (e.g., changes in clinical and erythroid parameters, hypotension, gastric mucosal lesions and renal changes). Based upon developmental and reproductive toxicity tests in animals, inadvertent exposure to ME-934

*** Continued on next page ***

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MERCK SHARP AND DOHME (IPL) LTD., BALLINADINE, KILGERHELEN,
 CLOONEL, COUNTY TIPPERRARY, IRELAND

***** MATERIAL SAFETY DATA SHEET *****

LABEL NAME: LOSARTAN POTASSIUM

PLANT MFG CODE
 HA-655

Emergency Telephone Number: 051-60411

During the first trimester of pregnancy should not pose increased risk of adverse effects. In a fertility study in rats adverse effects on the fetus/newborn were noted suggesting that late gestation and lactation were critical periods. Losartan, like ACE inhibitors such as enalapril, is not recommended for use during the later stages of pregnancy. Losartan potassium is not considered to be genotoxic.

Quantitative Toxicity Data

SPECIES	ROUTE	TEST	LD50/NOEL/RESULT
Mouse	Oral	LDLo	400 mg/kg
Mouse	Oral	LD50	1257-1590 mg/kg
Rat	Oral	LDLo	200 mg/kg

SECTION 8 - SPILL/LEAK/DISPERSAL PROCEDURES

Steps to be taken in case materials released:

Immediately contact emergency response personnel. Keep unnecessary persons away. If emergency response personnel are unavailable, vacuum, shovel, or sweep up spilled material and place in an appropriate container for disposal. Use suitable protective equipment (Section 9). Follow all fire prevention procedures (Section 4).

For additional assistance in the U.S., CHEMTREC provides a toll-free hotline for chemical emergencies regarding spills, leaks, exposure or accidents: 1-800-424-9300.

Environmental Data-----Compound degrades rapidly in aqueous media under natural light conditions. Hydrolytically and biologically stable in aqueous media. Compound is non-inhibitory to activated sludge or other microbial species representative of the natural

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MERCK SHARP AND DOHME (UK) LTD.; BALLINTEEN, KILBARNEILAN,
CLONSILLA, COUNTY TIPPERARY, IRELAND

*** MATERIAL SAFETY DATA SHEET ***

LABEL NAME: LOSARTAN POTASSIUM

PLANT CODE
BA-455

Emergency Telephone Number: 011-40411

environment. Has low order of toxicity to representative aquatic organisms including daphnia, fish and algae.

TEST	SPECIES	RESULTS
LC50 (48 hr.)	Daphnia Magna	331 mg/L
LC50 (48 hr.)	Fathead minnow	Greater than 1000 mg/L
EC50 (96 hr.)	Rainbow trout	Greater than 929 mg/L

Waste Disposal Information-----Avoid contact of spilled materials and runoff with soil and surface waterways. Dispose of or treat all spill residues including contaminated soils following all applicable regulations.

SECTION 9 - SPECIAL PROTECTION INFORMATION

Respiratory-----An approved and properly fitted, full-face, negative pressure, HEPA filtered respirator or respirator of equivalent or greater protection is recommended to control employee exposure below the exposure limit if handling chemical without engineered controls.

Hands/Arms-----Latex gloves for the powder. If handling a solution, contact site safety for recommendation of gloves impervious to the solvent used.

Eye/Face-----Wear safety glasses. Full-face protection required if potential exists for direct exposure to dust.

Additional Protective Equipment--Not available

Ventilation-----Local exhaust ventilation is recommended where chemical may enter the workplace.

SECTION 10 - SPECIAL PRECAUTIONS

Special Precautions to be taken when:

Handling-----Avoid direct contact with skin and eyes.

*** Continued on next page ***

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MERCK SERUP AND DOBBI (IRL) LTD.; WALLINGTON, KILBOURNE,
CLONMEL, COUNTY TIPPERARY, IRELAND

***** MATERIAL SAFETY DATA SHEET *****

LABEL NAME: LOSARTAN POTASSIUM

PLANT MMS CODE
BA-655

Emergency Telephone Number: 051-40411

Storing----- Keep container closed. Store in a cool
dry place.

Other----- No special recommendations

SECTION 11 - BASIC INFORMATION DESCRIPTION

U.S. DOT----- Not available

ICAO/IATA----- Not available

IMO----- Not available

Hazardous Substance-Reportable Quantity (RQ)-- Not available

SECTION 12 - INTER-PLANT COMMUNICATION

List all other MSD plants requiring a copy of this MSDS: None

SECTION 13 - MSDS PREPARATION

H. DePaar
Safety----- Date: August 8, 1993

D. Barry-Walsh
Technical Operations----- Date: August 25, 1993

B. Newman, Ph.D.
Central Safety & Industrial Hygiene----- Date: September 1, 1993

SECTION 14 - MERCK DISCLAIMER

While this information and recommendations set forth are believed
to be accurate as of the date hereof, MERCK & CO., INC. makes no
warranty with respect hereto and disclaims all liability from
reliance thereon.

END

A handwritten signature in black ink, consisting of several loops and a trailing stroke, positioned above a horizontal line.

J.H.M. RESEARCH & DEVELOPMENT, INC. 5776 SECOND STREET, N.E. WASH. DC 20011