

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-387/37

Trade Name: Hyzaar

Generic Name: Losartan/potassium hydrochlorothiazide

Sponsor: Merck Research Laboratories

Approval Date: October 20, 2005

Indications: The treatment of hypertension.

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APPLICATION NUMBER:

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-387/37

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-387/S-037

Merck Research Laboratories
Attention: Jeffrey R. Tucker, M.D.
Director, Regulatory Affairs
BLA-20, P.O. Box 4
West Point, PA 19486

Dear Dr. Tucker:

Please refer to your supplemental new drug application dated 17 December, 2004, received 20 December 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for HYZAAR (losartan/potassium hydrochlorothiazide) 50-12.5, 100-12.5, and 100-25 mg Tablets.

We acknowledge receipt of your submissions dated 19 and 25 July 2005, 15 and 30 August 2005.

This supplemental new drug application provides for registration of a losartan 100 mg and hydrochlorothiazide 12.5 mg fixed-dose combination tablet.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the electronic final printed labeling (FPL) submitted on 30 August 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the requirement for pediatric studies for all age groups for this application.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Cardiovascular and Renal Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions please call:

Cheryl Ann Borden, MSN, RN, CCRN, CCNS
LCDR, United States Public Health Service
Regulatory Health Project Manager
(301) 796 1046.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Electronic Labeling

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Norman Stockbridge
10/20/2005 08:09:09 AM

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RESEARCH**

APPLICATION NUMBER:

20-387/37

LABELING

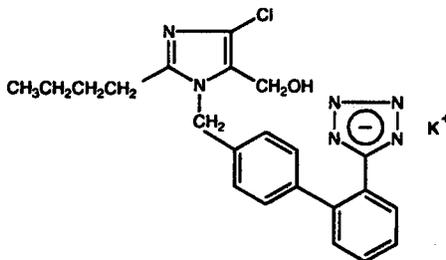
HYZAAR® 50-12.5**(LOSARTAN POTASSIUM-HYDROCHLOROTHIAZIDE TABLETS)****HYZAAR® 100-12.5****(LOSARTAN POTASSIUM-HYDROCHLOROTHIAZIDE TABLETS)****HYZAAR® 100-25****(LOSARTAN POTASSIUM-HYDROCHLOROTHIAZIDE TABLETS)****USE IN PREGNANCY**

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, HYZAAR should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality*.

DESCRIPTION

HYZAAR® 50-12.5 (losartan potassium-hydrochlorothiazide), HYZAAR® 100-12.5 (losartan potassium-hydrochlorothiazide) and HYZAAR® 100-25 (losartan potassium-hydrochlorothiazide), combine an angiotensin II receptor (type AT₁) antagonist and a diuretic, hydrochlorothiazide.

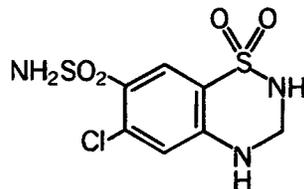
Losartan potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt. Its empirical formula is C₂₂H₂₂ClKN₆O, and its structural formula is:



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.

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is C₇H₈ClN₃O₄S₂ and its structural formula is:



Hydrochlorothiazide is a white, or practically white, crystalline powder with a molecular weight of 297.74, which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

HYZAAR is available for oral administration in three tablet combinations of losartan and hydrochlorothiazide. HYZAAR 50-12.5 contains 50 mg of losartan potassium and 12.5 mg of hydrochlorothiazide. HYZAAR 100-12.5 contains 100 mg of losartan potassium and 12.5 mg of hydrochlorothiazide. HYZAAR 100-25 contains 100 mg of losartan potassium and 25 mg of hydrochlorothiazide. Inactive ingredients are microcrystalline cellulose, lactose hydrous, pregelatinized starch, magnesium stearate, hydroxypropyl cellulose, hypromellose, and titanium dioxide. HYZAAR 50-12.5 and HYZAAR 100-25 also contain D&C yellow No. 10 aluminum lake. HYZAAR 100-12.5 may also contain carnauba wax.

HYZAAR 50-12.5 contains 4.24 mg (0.108 mEq) of potassium, HYZAAR 100-12.5 contains 8.48 mg (0.216 mEq) of potassium, and HYZAAR 100-25 contains 8.48 mg (0.216 mEq) of potassium.

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.

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.

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

The mechanism of the antihypertensive effect of thiazides is unknown.

Pharmacokinetics**General****Losartan Potassium**

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 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 ^{14}C -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 ^{14}C -labeled losartan, about 35% of radioactivity is recovered in the urine and about 60% in the feces. Following an intravenous dose of ^{14}C -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.

Race: Pharmacokinetic differences due to race have not been studied (see also PRECAUTIONS, Race and CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects, Losartan Potassium, Reduction in the Risk of Stroke, Race*).

Renal Insufficiency:

Losartan: Following oral administration, plasma concentrations and AUCs of losartan and its active metabolite are increased by 50-90% in patients with mild (creatinine clearance of 50 to 74 mL/min) or moderate (creatinine clearance 30 to 49 mL/min) renal insufficiency. In this study, renal clearance was reduced by 55-85% for both losartan and its active metabolite in patients with mild or moderate renal insufficiency. Neither losartan nor its active metabolite can be removed by hemodialysis.

Hydrochlorothiazide: Following oral administration, the AUC for hydrochlorothiazide is increased by 70 and 700% for patients with mild and moderate renal insufficiency, respectively. In this study, renal clearance of hydrochlorothiazide decreased by 45 and 85% in patients with mild and moderate renal impairment, respectively.

The usual regimens of therapy with HYZAAR may be followed as long as the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so HYZAAR is not recommended. (See 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. The lower starting dose of losartan recommended for use in patients with hepatic impairment cannot be given using HYZAAR. Its use in such patients as a means of losartan titration is, therefore, not recommended (see DOSAGE AND ADMINISTRATION).

Drug Interactions

Losartan Potassium

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. There is no pharmacokinetic interaction between losartan and hydrochlorothiazide. 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. A somewhat greater interaction (approximately 40% reduction in the AUC of active metabolite and approximately 30% reduction in the AUC of losartan) has been reported with rifampin. Fluconazole, an inhibitor of cytochrome P450 2C9, decreased the AUC of the active metabolite by approximately 40%, but increased the AUC of losartan by approximately 70% following multiple doses. Conversion of losartan to its active metabolite after intravenous administration is not affected by ketoconazole, an inhibitor of P450 3A4. The AUC of active metabolite following oral losartan was not affected by erythromycin, another inhibitor of P450 3A4, but the AUC of losartan was increased by 30%.

Hydrochlorothiazide

After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose is

eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Pharmacodynamics and Clinical Effects

Losartan Potassium

Hypertension: 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- to 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 losartan were demonstrated principally in 4 placebo-controlled, 6- to 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 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 (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.

Analysis of age, gender, and race subgroups of patients showed that men and women, and patients over and under 65, had generally similar responses. Losartan was effective in reducing blood pressure regardless of race, although the effect was somewhat less in Black patients (usually a low-renin population).

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.

Reduction in the Risk of Stroke: The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a multinational, double-blind study comparing losartan and atenolol in 9193 hypertensive patients with ECG-documented left ventricular hypertrophy. Patients with myocardial infarction or stroke within six months prior to randomization were excluded. Patients were randomized to receive once daily losartan 50 mg or atenolol 50 mg. If goal blood pressure (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was

added first and, if needed, the dose of losartan or atenolol was then increased to 100 mg once daily. If necessary, other antihypertensive treatments (e.g., increase in dose of hydrochlorothiazide therapy to 25 mg or addition of other diuretic therapy, calcium channel blockers, alpha-blockers, or centrally acting agents, but not ACE inhibitors, angiotensin II antagonists, or beta-blockers) were added to the treatment regimen to reach the goal blood pressure.

In efforts to control blood pressure, the patients in both arms of the LIFE study were coadministered hydrochlorothiazide the majority of time they were on study drug (73.9% and 72.4% of days in the losartan and atenolol arms, respectively).

Of the randomized patients, 4963 (54%) were female and 533 (6%) were Black. The mean age was 67 with 5704 (62%) age ≥ 65 . At baseline, 1195 (13%) had diabetes, 1326 (14%) had isolated systolic hypertension, 1469 (16%) had coronary heart disease, and 728 (8%) had cerebrovascular disease. Baseline mean blood pressure was 174/98 mmHg in both treatment groups. The mean length of follow-up was 4.8 years. At the end of study or at the last visit before a primary endpoint, 77% of the group treated with losartan and 73% of the group treated with atenolol were still taking study medication. Of the patients still taking study medication, the mean doses of losartan and atenolol were both about 80 mg/day, and 15% were taking atenolol or losartan as monotherapy, while 77% were also receiving hydrochlorothiazide (at a mean dose of 20 mg/day in each group). Blood pressure reduction measured at trough was similar for both treatment groups but blood pressure was not measured at any other time of the day. At the end of study or at the last visit before a primary endpoint, the mean blood pressures were 144.1/81.3 mmHg for the group treated with losartan and 145.4/80.9 mmHg for the group treated with atenolol [the difference in SBP of 1.3 mmHg was significant ($p < 0.001$), while the difference of 0.4 mmHg in DBP was not significant ($p = 0.098$)].

The primary endpoint was the first occurrence of cardiovascular death, nonfatal stroke, or nonfatal myocardial infarction. Patients with nonfatal events remained in the trial, so that there was also an examination of the first event of each type even if it was not the first event (e.g., a stroke following an initial myocardial infarction would be counted in the analysis of stroke). Treatment with losartan resulted in a 13% reduction ($p = 0.021$) in risk of the primary endpoint compared to the atenolol group; this difference was primarily the result of an effect on fatal and nonfatal stroke. Treatment with losartan reduced the risk of stroke by 25% relative to atenolol ($p = 0.001$).

For additional details on the LIFE study see the label for COZAAR.

Race: In the LIFE study, Black patients treated with atenolol were at lower risk of experiencing the primary composite endpoint compared with Black patients treated with losartan. In the subgroup of Black patients ($n = 533$, 6% of the LIFE study patients), there were 29 primary endpoints among 263 patients on atenolol (11%, 26 per 1000 patient-years) and 46 primary endpoints among 270 patients (17%, 42 per 1000 patient-years) on losartan. This finding could not be explained on the basis of differences in the populations other than race or on any imbalances between treatment groups. In addition, blood pressure reductions in both treatment groups were consistent between Black and non-Black patients. Given the difficulty in interpreting subset differences in large trials, it cannot be known whether the observed difference is the result of chance. However, the LIFE study provides no evidence that the benefits of losartan on reducing the risk of cardiovascular events in hypertensive patients with left ventricular hypertrophy apply to Black patients.

Losartan Potassium-Hydrochlorothiazide

The 3 controlled studies of losartan and hydrochlorothiazide included over 1300 patients assessing the antihypertensive efficacy of various doses of losartan (25, 50 and 100 mg) and

concomitant hydrochlorothiazide (6.25, 12.5 and 25 mg). A factorial study compared the combination of losartan/hydrochlorothiazide 50/12.5 mg with its components and placebo. The combination of losartan/hydrochlorothiazide 50/12.5 mg resulted in an approximately additive placebo-adjusted systolic/diastolic response (15.5/9.0 mmHg for the combination compared to 8.5/5.0 mmHg for losartan alone and 7.0/3.0 mmHg for hydrochlorothiazide alone). Another study investigated the dose-response relationship of various doses of hydrochlorothiazide (6.25, 12.5 and 25 mg) or placebo on a background of losartan (50 mg) in patients not adequately controlled (sitting diastolic blood pressure [SiDBP] 93-120 mmHg) on losartan (50 mg) alone. The third study investigated the dose-response relationship of various doses of losartan (25, 50 and 100 mg) or placebo on a background of hydrochlorothiazide (25 mg) in patients not adequately controlled (SiDBP 93-120 mmHg) on hydrochlorothiazide (25 mg) alone. These studies showed an added antihypertensive response at trough (24 hours post-dosing) of hydrochlorothiazide 12.5 or 25 mg added to losartan 50 mg of 5.5/3.5 and 10.0/6.0 mmHg, respectively. Similarly, there was an added antihypertensive response at trough when losartan 50 or 100 mg was added to hydrochlorothiazide 25 mg of 9.0/5.5 and 12.5/6.5 mmHg, respectively. There was no significant effect on heart rate.

There was no difference in response for men and women or in patients over or under 65 years of age.

Black patients had a larger response to hydrochlorothiazide than non-Black patients and a smaller response to losartan. The overall response to the combination was similar for Black and non-Black patients.

Severe Hypertension (Sitting Diastolic Blood Pressure [SiDBP] \geq 110 mmHg)

The safety and efficacy of HYZAAR as initial therapy for severe hypertension (defined as a mean SiDBP \geq 110 mmHg confirmed on 2 separate occasions off all antihypertensive therapy) was studied in a 6-week double-blind, randomized, multicenter study. Patients were randomized to either losartan and hydrochlorothiazide (50-12.5 mg, once daily) or to losartan (50 mg, once daily) and followed for blood pressure response. Patients were titrated at 2-week intervals if their SiDBP did not reach goal (<90 mmHg). Patients on combination therapy were titrated from losartan 50 mg/hydrochlorothiazide 12.5 mg to losartan 50 mg/hydrochlorothiazide 12.5 mg (sham titration to maintain the blind) to losartan 100 mg/hydrochlorothiazide 25 mg. Patients on monotherapy were titrated from losartan 50 mg to losartan 100 mg to losartan 150 mg, as needed. The primary endpoint was a comparison at 4 weeks of patients who achieved goal diastolic blood pressure (trough SiDBP <90 mmHg).

The study enrolled 585 patients, including 264 (45%) females, 124 (21%) blacks, and 21 (4%) \geq 65 years of age. The mean blood pressure at baseline for the total population was 171/113 mmHg. The mean age was 53 years. After 4 weeks of therapy, the mean SiDBP was 3.1 mmHg lower and the mean SiSBP was 5.6 mmHg lower in the group treated with HYZAAR. As a result, a greater proportion of the patients on HYZAAR reached the target diastolic blood pressure (17.6% for HYZAAR, 9.4% for losartan; $p=0.006$). Similar trends were seen when the patients were grouped according to gender, race or age (<, \geq 65).

After 6 weeks of therapy, more patients who received the combination regimen reached target diastolic blood pressure than those who received the monotherapy regimen (29.8% versus 12.5%).

During the study period, there were no reported cases of syncope in either treatment group. There were 2 (0.6%) and 0 (0.0%) cases of hypotension reported in the group treated with HYZAAR and the group treated with losartan, respectively. The overall pattern of adverse events reported for patients treated with HYZAAR as initial therapy was similar to the

adverse event profile for patients treated with losartan as initial therapy. For information on the specific adverse events observed during the study period, see ADVERSE REACTIONS, *Severe Hypertension*.

INDICATIONS AND USAGE

Hypertension

HYZAAR is indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy of hypertension, except when the hypertension is severe enough that the value of achieving prompt blood pressure control exceeds the risk of initiating combination therapy in these patients (see CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects*, and DOSAGE AND ADMINISTRATION).

Hypertensive Patients with Left Ventricular Hypertrophy

HYZAAR is indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy, but there is evidence that this benefit does not apply to Black patients. (See PRECAUTIONS, *Race*, CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects, Losartan Potassium, Reduction in the Risk of Stroke, Race*, and DOSAGE AND ADMINISTRATION.)

CONTRAINDICATIONS

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

Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

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, HYZAAR 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 HYZAAR 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 intra-amniotic environment.

If oligohydramnios is observed, HYZAAR 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.

There was no evidence of teratogenicity in rats or rabbits treated with a maximum losartan potassium dose of 10 mg/kg/day in combination with 2.5 mg/kg/day of hydrochlorothiazide. At these dosages, respective exposures (AUCs) of losartan, its active metabolite, and hydrochlorothiazide in rabbits were approximately 5, 1.5, and 1.0 times those achieved in humans with 100 mg losartan in combination with 25 mg hydrochlorothiazide. AUC values for losartan, its active metabolite and hydrochlorothiazide, extrapolated from data obtained with losartan administered to rats at a dose of 50 mg/kg/day in combination with 12.5 mg/kg/day of hydrochlorothiazide, were approximately 6, 2, and 2 times greater than those achieved in humans with 100 mg of losartan in combination with 25 mg of hydrochlorothiazide. Fetal toxicity in rats, as evidenced by a slight increase in supernumerary ribs, was observed when females were treated prior to and throughout gestation with 10 mg/kg/day losartan in combination with 2.5 mg/kg/day hydrochlorothiazide. As also observed in studies with losartan alone, adverse fetal and neonatal effects, including decreased body weight, renal toxicity, and mortality, occurred when pregnant rats were treated during late gestation and/or lactation with 50 mg/kg/day losartan in combination with 12.5 mg/kg/day hydrochlorothiazide. Respective AUCs for losartan, its active metabolite and hydrochlorothiazide at these dosages in rats were approximately 35, 10 and 10 times greater than those achieved in humans with the administration of 100 mg of losartan in combination with 25 mg hydrochlorothiazide. When hydrochlorothiazide was administered without losartan to pregnant mice and rats during their respective periods of major organogenesis, at doses up to 3000 and 1000 mg/kg/day, respectively, there was no evidence of harm to the fetus.

Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

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 HYZAAR. This condition should be corrected prior to administration of HYZAAR (see DOSAGE AND ADMINISTRATION).

Impaired Hepatic Function

Losartan Potassium-Hydrochlorothiazide

HYZAAR is not recommended for patients with hepatic impairment who require titration with losartan. The lower starting dose of losartan recommended for use in patients with hepatic impairment cannot be given using HYZAAR.

Hydrochlorothiazide

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Hypersensitivity Reaction

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

Systemic Lupus Erythematosus

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

Lithium Interaction

Lithium generally should not be given with thiazides (see PRECAUTIONS, *Drug Interactions, Hydrochlorothiazide, Lithium*).

PRECAUTIONS

General

Hypersensitivity: Angioedema. See ADVERSE REACTIONS, *Post-Marketing Experience*.

Losartan Potassium-Hydrochlorothiazide

In double-blind clinical trials of various doses of losartan potassium and hydrochlorothiazide, the incidence of hypertensive patients who developed hypokalemia (serum potassium <3.5 mEq/L) was 6.7% versus 3.5% for placebo; the incidence of hyperkalemia (serum potassium >5.7 mEq/L) was 0.4%. No patient discontinued due to increases or decreases in serum potassium. The mean decrease in serum potassium in patients treated with various doses of losartan and hydrochlorothiazide was 0.123 mEq/L. In patients treated with various doses of losartan and hydrochlorothiazide, there was also a dose-related decrease in the hypokalemic response to hydrochlorothiazide as the dose of losartan was increased, as well as a dose-related decrease in serum uric acid with increasing doses of losartan.

Hydrochlorothiazide

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when

the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy. Because losartan decreases uric acid, losartan in combination with hydrochlorothiazide attenuates the diuretic-induced hyperuricemia.

In diabetic patients, dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been reported in susceptible individuals treated with losartan; in some patients, these changes in renal function were reversible upon discontinuation of therapy.

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. Similar outcomes have been reported with losartan.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or BUN have been reported. Similar effects have been reported with losartan; in some patients, these effects were reversible upon discontinuation of therapy.

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

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.

Symptomatic Hypotension: A patient receiving HYZAAR should be cautioned that lightheadedness can occur, especially during the first days of therapy, and that it should be reported to the prescribing physician. The patients should be told that if syncope occurs, HYZAAR should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Potassium Supplements: A patient receiving HYZAAR should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician (see PRECAUTIONS, *Drug Interactions, Losartan Potassium*).

Drug Interactions

Losartan Potassium

No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, cimetidine and phenobarbital. Rifampin, an inducer of drug metabolism, decreased the concentrations of losartan and its active metabolite. (See CLINICAL PHARMACOLOGY, *Drug Interactions*.) In humans, two inhibitors of P450 3A4 have been studied. Ketoconazole did not affect the conversion of losartan to the active metabolite after intravenous administration of losartan, and erythromycin had no clinically significant effect after oral administration. Fluconazole, an inhibitor of P450 2C9, decreased active metabolite concentration and increased losartan concentration. The pharmacodynamic consequences of concomitant use of losartan and inhibitors of P450 2C9 have not been examined. Subjects who do not metabolize losartan to active metabolite have been shown to have a specific, rare defect in cytochrome P450 2C9. These data suggest that the conversion of losartan to its active metabolite is mediated primarily by P450 2C9 and not P450 3A4.

As with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium (see PRECAUTIONS, *Information for Patients, Potassium Supplements*).

As with other antihypertensive agents, the antihypertensive effect of losartan may be blunted by the non-steroidal anti-inflammatory drug indomethacin.

Hydrochlorothiazide

When administered concurrently, the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics — potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin) — dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs — additive effect or potentiation.

Cholestyramine and colestipol resins — Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroids, ACTH — intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine) — possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine) — possible increased responsiveness to the muscle relaxant.

Lithium — should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with HYZAAR.

Non-steroidal Anti-inflammatory Drugs — In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when HYZAAR and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Losartan Potassium-Hydrochlorothiazide

No carcinogenicity studies have been conducted with the losartan potassium-hydrochlorothiazide combination.

Losartan potassium-hydrochlorothiazide when tested at a weight ratio of 4:1, was negative in the Ames microbial mutagenesis assay and the V-79 Chinese hamster lung cell mutagenesis assay. In addition, there was no evidence of direct genotoxicity in the *in vitro* alkaline elution assay in rat hepatocytes and *in vitro* chromosomal aberration assay in Chinese hamster ovary cells at noncytotoxic concentrations.

Losartan potassium, coadministered with hydrochlorothiazide, had no effect on the fertility or mating behavior of male rats at dosages up to 135 mg/kg/day of losartan and 33.75 mg/kg/day of hydrochlorothiazide. These dosages have been shown to provide respective systemic exposures (AUCs) for losartan, its active metabolite and hydrochlorothiazide that are approximately 60, 60 and 30 times greater than those achieved in humans with 100 mg of losartan potassium in combination with 25 mg of hydrochlorothiazide. In female rats, however, the coadministration of doses as low as 10 mg/kg/day of losartan and 2.5 mg/kg/day of hydrochlorothiazide was associated with slight but statistically significant decreases in fecundity and fertility indices. AUC values for losartan, its active metabolite and hydrochlorothiazide, extrapolated from data obtained with losartan administered to rats at a dose of 50 mg/kg/day in combination with 12.5 mg/kg/day of hydrochlorothiazide, were approximately 6, 2, and 2 times greater than those achieved in humans with 100 mg of losartan in combination with 25 mg of hydrochlorothiazide.

Losartan Potassium

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 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. 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).

Hydrochlorothiazide

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of

hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 µg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation.

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. Thiazides appear in human 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.

Geriatric Use

In a controlled clinical study for the reduction in the combined risk of cardiovascular death, stroke and myocardial infarction in hypertensive patients with left ventricular hypertrophy, 2857 patients (62%) were 65 years and over, while 808 patients (18%) were 75 years and over. In an effort to control blood pressure in this study, patients were coadministered losartan and hydrochlorothiazide 74% of the total time they were on study drug. No overall differences in effectiveness were observed between these patients and younger patients. Adverse events were somewhat more frequent in the elderly compared to non-elderly patients for both the losartan-hydrochlorothiazide and the control groups (see CLINICAL PHARMACOLOGY, *Special Populations*).

Race

In the LIFE study, Black patients with hypertension and left ventricular hypertrophy had a lower risk of stroke on atenolol than on losartan (both cotreated with hydrochlorothiazide in the majority of patients). Given the difficulty in interpreting subset differences in large trials, it cannot be known whether the observed difference is the result of chance. However, the LIFE study does not provide evidence that the benefits of losartan on reducing the risk of cardiovascular events in hypertensive patients with left ventricular hypertrophy apply to Black patients. (See CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects; Losartan Potassium, Reduction in the Risk of Stroke*.)

ADVERSE REACTIONS

Losartan potassium-hydrochlorothiazide has been evaluated for safety in 858 patients treated for essential hypertension and 3889 patients treated for hypertension and left ventricular hypertrophy. In clinical trials with losartan potassium-hydrochlorothiazide, no adverse experiences peculiar to this combination have been observed. Adverse experiences have been limited to those that were reported previously with losartan potassium and/or hydrochlorothiazide. The overall incidence of adverse experiences reported with the combination was comparable to placebo.

In general, treatment with losartan potassium-hydrochlorothiazide was well tolerated. For the most part, adverse experiences have been mild and transient in nature and have not required discontinuation of therapy. In controlled clinical trials, discontinuation of therapy due to clinical adverse experiences was required in only 2.8% and 2.3% of patients treated with the combination and placebo, respectively.

In these double-blind controlled clinical trials, the following adverse experiences reported with losartan-hydrochlorothiazide occurred in ≥ 1 percent of patients, and more often on drug than placebo, regardless of drug relationship:

	Losartan Potassium- Hydrochloro- thiazide (n=858)	Placebo (n=173)
<i>Body as a Whole</i>		
Abdominal pain	1.2	0.6
Edema/swelling	1.3	1.2
<i>Cardiovascular</i>		
Palpitation	1.4	0.0
<i>Musculoskeletal</i>		
Back pain	2.1	0.6
<i>Nervous/Psychiatric</i>		
Dizziness	5.7	2.9
<i>Respiratory</i>		
Cough	2.6	2.3
Sinusitis	1.2	0.6
Upper respiratory infection	6.1	4.6
<i>Skin</i>		
Rash	1.4	0.0

The following adverse events were also reported at a rate of 1% or greater, but were as, or more, common in the placebo group in studies of essential hypertension: asthenia/fatigue, diarrhea, nausea, headache, bronchitis, pharyngitis.

Adverse events occurred at about the same rates in men and women. Adverse events were somewhat more frequent in the elderly compared to non-elderly patients and somewhat more frequent in Blacks compared to non-Blacks for both the losartan-hydrochlorothiazide and the control groups.

A patient with known hypersensitivity to aspirin and penicillin, when treated with losartan potassium, 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 were reported in one subject treated with losartan potassium.

Losartan Potassium

Other adverse experiences that have been reported with losartan, without regard to causality, are listed below:

Body as a Whole: chest pain, facial edema, fever, orthostatic effects, syncope; **Cardiovascular:** angina pectoris, arrhythmias including atrial fibrillation, sinus bradycardia, tachycardia, ventricular tachycardia and ventricular fibrillation, CVA, hypotension, myocardial infarction, second degree AV block; **Digestive:** anorexia, constipation, dental pain, dry mouth, dyspepsia, flatulence, gastritis, vomiting; **Hematologic:** anemia; **Metabolic:** gout; **Musculoskeletal:** arm pain, arthralgia, arthritis, fibromyalgia, hip pain, joint swelling, knee pain, leg pain, muscle cramps, muscle weakness, musculoskeletal pain, myalgia, shoulder pain, stiffness; **Nervous System/Psychiatric:** anxiety, anxiety disorder, ataxia, confusion, depression, dream abnormality, hypesthesia, insomnia, libido decreased, memory impairment, migraine, nervousness, panic disorder, paresthesia, peripheral neuropathy, sleep disorder, somnolence, tremor, vertigo; **Respiratory:** dyspnea, epistaxis, nasal congestion, pharyngeal discomfort, respiratory congestion, rhinitis, sinus disorder; **Skin:** alopecia, dermatitis, dry skin, ecchymosis, erythema, flushing, photosensitivity, pruritus, sweating, urticaria; **Special Senses:** blurred vision, burning/stinging in the eye, conjunctivitis, decrease in visual acuity, taste perversion, tinnitus; **Urogenital:** impotence, nocturia, urinary frequency, urinary tract infection.

Hydrochlorothiazide

Other adverse experiences that have been reported with hydrochlorothiazide, without regard to causality, are listed below:

Body as a Whole: weakness; **Digestive:** pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation; **Hematologic:** aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia; **Hypersensitivity:** purpura, photosensitivity, urticaria, necrotizing angitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema; **Metabolic:** hyperglycemia, glycosuria, hyperuricemia; **Musculoskeletal:** muscle spasm; **Nervous System/Psychiatric:** restlessness; **Renal:** renal failure, renal dysfunction, interstitial nephritis; **Skin:** erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis; **Special Senses:** transient blurred vision, xanthopsia.

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.

Cases of cough, including positive re-challenges, have been reported with the use of losartan in post-marketing experience.

Severe Hypertension: In a clinical study in patients with severe hypertension (SiDBP ≥ 110 mmHg), the overall pattern of adverse events reported through six weeks of follow-up was similar in patients treated with HYZAAR as initial therapy and in patients treated with losartan as initial therapy. There were no reported cases of syncope in either treatment group. There were 2 (0.6%) and 0 (0.0%) cases of hypotension reported in the group treated with HYZAAR and the group treated with losartan, respectively. There were 3 (0.8%) and 2 (1.2%) cases of increased serum creatinine (>0.5 mg/dL) in the group treated with HYZAAR and the group treated with losartan, respectively, during the same time period. (See CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects, Severe Hypertension.*)

Post-Marketing Experience

The following additional adverse reactions have been reported in post-marketing experience:

Digestive: Hepatitis has been reported rarely in patients treated with losartan.

Hemic: Thrombocytopenia has been reported rarely with losartan.

Hypersensitivity: Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue has been reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Vasculitis, including Henoch-Schönlein purpura, has been reported with losartan. Anaphylactic reactions have been reported.

Metabolic and Nutrition: Hyperkalemia, hyponatremia have been reported with losartan.

Musculoskeletal: Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

Respiratory: Dry cough (see above) has been reported with losartan.

Laboratory Test Findings

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

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in 0.6 and 0.8 percent, respectively, of patients with essential hypertension treated with HYZAAR alone. No patient discontinued taking HYZAAR due to increased BUN. One patient discontinued taking HYZAAR due to a minor increase in serum creatinine.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.14 grams percent and 0.72 volume percent, respectively) occurred frequently in patients treated with HYZAAR 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 HYZAAR alone, no patients were discontinued due to these laboratory adverse experiences.

Serum Electrolytes: See PRECAUTIONS.

OVERDOSAGE

Losartan Potassium

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.

Hydrochlorothiazide

The oral LD₅₀ of hydrochlorothiazide is greater than 10 g/kg in both mice and rats. The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

DOSAGE AND ADMINISTRATION

Hypertension

Dosing must be individualized. The usual starting dose of losartan is 50 mg once daily, with 25 mg recommended for patients with intravascular volume depletion (e.g., patients treated with diuretics) (see WARNINGS, *Hypotension — Volume-Depleted Patients*) and patients with a history of hepatic impairment (see WARNINGS, *Impaired Hepatic Function*). Losartan can be administered once or twice daily at total daily doses of 25 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.

Hydrochlorothiazide is effective in doses of 12.5 to 50 mg once daily and can be given at doses of 12.5 to 25 mg as HYZAAR.

To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.

The side effects (see WARNINGS) of losartan are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent (primarily hypokalemia) and dose-independent phenomena (e.g., pancreatitis), the former much more common than the latter. Therapy with any combination of losartan and hydrochlorothiazide will be associated with both sets of dose-independent side effects.

Replacement Therapy: The combination may be substituted for the titrated components.

Dose Titration by Clinical Effect: A patient whose blood pressure is not adequately controlled with losartan monotherapy (see above) or hydrochlorothiazide alone, may be switched to HYZAAR 50-12.5 (losartan 50 mg/hydrochlorothiazide 12.5 mg) once daily. If blood pressure remains uncontrolled after about 3 weeks of therapy, the dose may be increased to two tablets of HYZAAR 50-12.5 once daily or one tablet of HYZAAR 100-25 (losartan 100 mg/hydrochlorothiazide 25 mg) once daily. A patient whose blood pressure is not adequately controlled with losartan 100 mg monotherapy (see above) may be switched to HYZAAR 100-12.5 once daily. If blood pressure remains uncontrolled after about 3 weeks of therapy, the dose may be increased to two tablets of HYZAAR 50-12.5 once daily or one tablet of HYZAAR 100-25 (losartan 100 mg/hydrochlorothiazide 25 mg) once daily.

A patient whose blood pressure is inadequately controlled by 25 mg once daily of hydrochlorothiazide, or is controlled but who experiences hypokalemia with this regimen, may be switched to HYZAAR 50-12.5 (losartan 50 mg/hydrochlorothiazide 12.5 mg) once daily, reducing the dose of hydrochlorothiazide without reducing the overall expected antihypertensive response. The clinical response to HYZAAR 50-12.5 should be subsequently evaluated, and if blood pressure remains uncontrolled after about 3 weeks of therapy, the dose may be increased to two tablets of HYZAAR 50-12.5 once daily or one tablet of HYZAAR 100-25 (losartan 100 mg/hydrochlorothiazide 25 mg) once daily.

The usual dose of HYZAAR is one tablet of HYZAAR 50-12.5 once daily. More than two tablets of HYZAAR 50-12.5 once daily or more than one tablet of HYZAAR 100-25 once daily is not recommended. The maximal antihypertensive effect is attained about 3 weeks after initiation of therapy.

Use in Patients with Renal Impairment: The usual regimens of therapy with HYZAAR may be followed as long as the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so HYZAAR is not recommended.

Patients with Hepatic Impairment: HYZAAR is not recommended for titration in patients with hepatic impairment (see WARNINGS, *Impaired Hepatic Function*) because the appropriate 25 mg starting dose of losartan cannot be given.

Severe Hypertension

The starting dose of HYZAAR for initial treatment of severe hypertension is one tablet of HYZAAR 50-12.5 once daily (see CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects*). For patients who do not respond adequately to HYZAAR 50-12.5 after 2 to 4 weeks of therapy, the dosage may be increased to one tablet of HYZAAR 100-25 once daily. The maximum dose is one tablet of HYZAAR 100-25 once daily. HYZAAR is not recommended as initial therapy in patients with hepatic impairment (see WARNINGS, *Impaired Hepatic Function*) because the appropriate 25 mg starting dose of losartan cannot be given. It is also not recommended for use as initial therapy in patients with intravascular volume depletion (e.g., patients treated with diuretics, see WARNINGS, *Hypotension—Volume-Depleted Patients*).

Hypertensive Patients with Left Ventricular Hypertrophy

Treatment should be initiated with COZAAR 50 mg once daily. Hydrochlorothiazide 12.5 mg should be added or HYZAAR 50-12.5 substituted if the blood pressure reduction is inadequate. If additional blood pressure reduction is needed, COZAAR 100 mg and hydrochlorothiazide 12.5 mg or HYZAAR 100-12.5 may be substituted, followed by COZAAR 100 mg and hydrochlorothiazide 25 mg or HYZAAR 100-25. For further blood pressure reduction other antihypertensives should be added (see CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects, Losartan Potassium, Reduction in the Risk of Stroke*).

HYZAAR may be administered with other antihypertensive agents.

HYZAAR may be administered with or without food.

HOW SUPPLIED

Description	50 – 12.5 mg	100 – 12.5 mg	100 – 25 mg
Product No.	3502	6729	3793
Color	Yellow	White	Light Yellow
Shape	Teardrop	Oval	Teardrop
Obverse code	HYZAAR	Blank	HYZAAR
Reverse code	MRK 717	745	MRK 747
NDC			
Bottle: 30 tablets	0006-0717-31	0006-0745-31	0006-0747-31

Bottle: 90 tablets	0006-0717-54	0006-0745-54	0006-0747-54
Unit dose packs of 100	0006-0717-28	0006-0745-28	0006-0747-28
Bottle: 1000 tablets	0006-0717-82	0006-0745-82	0006-0747-82
Bottle: 4000 tablets	----	----	0006-0747-81
Bottle: 5000 tablets	0006-0717-86	0006-0745-86	----

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed. Protect from light.

Manufactured for:
 **MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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20-387/37

MEDICAL REVIEW

CLINICAL REVIEW

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Established Name losartan potassium-
hydrochlorothiazide
(Proposed) Trade Name Hyzaar™
Therapeutic Class antihypertensives
Applicant Merck & Co., Inc.

Priority Designation S

Formulation tablets
Dosing Regimen once daily
Indication treatment of hypertension
Intended Population hypertensives

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Clinical Review
Thomas A. Marciniak, M.D.
NDA 20-387 Serial 000
Hyzaar™ losartan potassium-hydrochlorothiazide

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical perspective I recommend approval of this supplement for the Hyzaar losartan 100 mg / hydrochlorothiazide (HCTZ) 12.5 mg formulation. The applicant has submitted previously (January 26, 2004) evidence establishing that this combination has more antihypertensive efficacy than its components used alone. There are no safety issues because this formulation is a lower dosage than the approved formulations and comparable dosages have been used safely in the LIFE study and in post-marketing use.

1.2 Recommendation on Postmarketing Actions

I do not recommend any postmarketing actions.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The new clinical data in this submission consist of a bioequivalence study of losartan 100 mg and HCTZ 12.5 mg taken alone and in combination. The applicant submitted previously (January 26, 2004) a summary of the evidence that combining losartan 100 mg and HCTZ 12.5 mg increases their hypertensive effects compared to solo administration.

1.3.2 Efficacy

The prior submission (January 26, 2004) provided substantial evidence that adding HCTZ 12.5 mg to losartan 100 mg adds to the blood pressure reduction of both components. The evidence consisted of the following:

- An open-label follow-on study of HCTZ 12.5 mg added to losartan demonstrating an additional reduction in DBP of about 4 mm Hg
- Modeling of the blood pressure reductions with losartan and HCTZ alone and combined in three other sponsor conducted studies, estimating an effect on DBP of adding HCTZ 12.5 mg to losartan 100 mg of about -3.9 mm Hg and an effect of adding losartan 100 mg to HCTZ 12.5 mg of about -6.4 mm Hg
- A review of the literature of blood pressure lowering effects of HCTZ combined with other angiotensin receptor blockers and ACE inhibitors. The mean DBP effect of adding HCTZ 12.5 mg to an ACEI is about -3.6 mm Hg and to an ARB about -3.7 mm Hg.

These three sets of analyses appear reasonably consistent and provide substantial evidence that the combination losartan 100 mg/HCTZ 12.5 is effective. Because these analyses are based on

the use of separate losartan and HCTZ formulations, the Study 306 showing the bioequivalence of the combination product to the separate formulation provides the link to apply these analyses to the combination.

1.3.3 Safety

This submission does not add substantially to the safety information regarding Hyzaar. The safety of Hyzaar is supported by the original NDA submission, by the use of HCTZ with losartan in the LIFE study reviewed specifically in conjunction with Serial 033 adding the LIFE study description and indication to the Hyzaar label, and by extensive post-marketing use. This submission adds an intermediate dosage (the highest approved dosage is 100/25), so the new formulation should not present any unique safety problems.

1.3.4 Dosing Regimen and Administration

This application adds a dosage form used in the titration scheme for the LIFE study, the outcome study supporting the indication for reducing the risk of stroke in patients with hypertension and LVH. There are no other issues regarding the dosing regimen or administration.

1.3.5 Drug-Drug Interactions

This submission does not provide any information on drug-drug interactions other than the lack of pharmacokinetic interaction between losartan and HCTZ in the 100/12.5 mg dosages. There are no outstanding issues regarding drug-drug interactions for Hyzaar.

1.3.6 Special Populations

The bioequivalence study was performed including both males and females. It appears to have been conducted in a Hispanic population. I reviewed the efficacy and safety of losartan/HCTZ by gender, age, and race in conjunction with Serial 033 for adding the LIFE study to the Hyzaar label. Please see my review of that submission for details on effects in special populations.

This submission does not provide any data regarding pediatric use. The safety and effectiveness in pediatric patients has not been established. The Division granted a waiver of pediatric studies in a letter dated September 29, 2004.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Hyzaar™ (losartan potassium-hydrochlorothiazide) is an approved combination product for the treatment of hypertension, severe hypertension, and to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy. It consists of an angiotensin receptor blocker (losartan) combined with a thiazide diuretic (hydrochlorothiazide [HCTZ]) in tablet formulations of 50/12.5 and 100/25 mg for once daily administration. This application is for a tablet formulation of 100/12.5 mg.

2.2 Currently Available Treatment for Indications

There are many other products available for the treatment of hypertension. One of the components of this combination (losartan) was approved on April 1, 2003, to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy (LVH). The approval for this indication was based on the results of one large, international study, the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study. Because the protocol for the LIFE study specified that patients whose blood pressure was inadequately controlled on losartan were to be given HCTZ and because the majority of patients in the losartan arm also received HCTZ, this indication was added to the Hyzaar label earlier this year. Losartan (Cozaar) and Hyzaar are the only products that have this indication. In the LIFE study patients were started on losartan 100 mg alone. If their blood pressure was inadequately controlled, the next titration step was adding HCTZ 12.5 mg. This application requests approval for marketing of the 100/12.5 combination of losartan and HCTZ.

2.3 Availability of Proposed Active Ingredient in the United States

Hyzaar and its components losartan and HCTZ are approved products in widespread use in the United States.

2.4 Important Issues with Pharmacologically Related Products

There are no important outstanding issues with pharmacologically related products, i.e., angiotensin receptor blockers or thiazide diuretics.

2.5 Presubmission Regulatory Activity

The Division discussed with the sponsor requirements for approval of the 100/12.5 combination at a teleconference on December 23, 2003. The Division Director discussed that there should be evidence that adding HCTZ 12.5 mg to losartan 100 mg augments the blood pressure effect. The sponsor replied that they did have a limited amount of data from a controlled ABPM study (Study 021) that showed that HCTZ 12.5 mg resulted in a significant blood pressure decrease when added to patients not controlled on losartan alone. The Division Director said that this study plus other data may be enough to demonstrate that HCTZ 12.5 mg does have an additional benefit in lowering blood pressure when added to losartan monotherapy. Alternatively, the

sponsor could make a 'modeling' argument that HCTZ 12.5 mg always augments blood pressure reduction when added to ACE Inhibitors, angiotensin II blockers, and other drugs. There is certainly a sense that HCTZ always contributes an additive blood pressure-lowering effect in hypertension, but we have some data to suggest that this may not always be true.

The sponsor submitted a proposal for concurrence dated January 26, 2004, that HCTZ always contributes to blood pressure lowering when added to losartan and other antihypertensive agents that are renin-angiotensin system (RAS) inhibitors. The sponsor's argument was based on three pieces:

1. The ABPM Study 021 mentioned above. In an open-label, two-week follow-on to this 4-week, double-blind study of losartan 50 and 100 mg QD and 50 mg BID vs placebo adding HCTZ 12.5 mg to the regimen of patients whose DBP remained above 85 mm HG reduced their DBP by an additional 4 mm Hg.
2. Statistical dose-response modeling utilizing data from previous Merck studies. Data from earlier Merck studies 048, 049, 054 were used to fit the model. Figure 1 below shows the results of the sponsor's modeling exercise on diastolic blood pressure reductions using various combinations of losartan and hydrochlorothiazide. The effect of adding HCTZ 12.5 mg to losartan 100 mg is about -3.9 mm Hg and the effect of adding losartan 100 mg to HCTZ 12.5 mg is about -6.4 mm Hg. Although not shown, a similar pattern was seen for effects on systolic blood pressure.

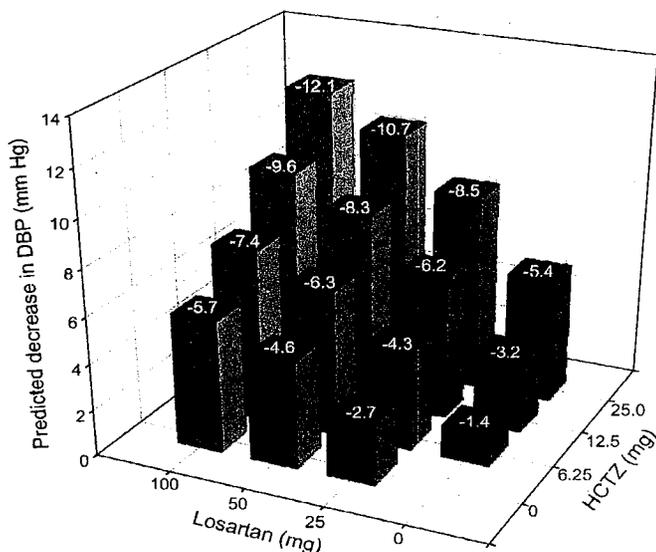


Figure 1: Sponsor's Model of DBP Decreases with Losartan and HCTZ

3. Published clinical data from ACE inhibitors (ACEI) and angiotensin II receptor blockers (ARB) demonstrating that HCTZ 12.5 mg always contributes to blood pressure lowering when added to RAS inhibitors. The sponsor's analysis of the peer reviewed medical literature for ACEIs is summarized in Table 1 and for ARBs Table 2. The Division medical reviewer found two inconsistencies in the ACEI analysis: First, for enalapril, the blood pressure changes don't account for a placebo effect and therefore the change of 8.8/6.4 mm Hg is exaggerated. Second, with regard to the moexipril reference, systolic blood pressure effects were not reported. The remainder of values cited in the table are accurate and consistent with what is in the references. The mean DBP effect of adding HCTZ 12.5 mg to an ACEI is about -3.6 mm Hg and to an ARB about -3.7 mm Hg.

Table 1: Sponsor's Incremental Blood Pressure Lowering of HCTZ 12.5 mg on Top of Various ACEI Doses from Literature References

	Enalapril 20 mg [1]	Lisinopril 20 mg [2]	Moexipril 7.5 mg [3]	Quinapril 20 mg [4]	Mean
SBP	-8.8	-5.4	-3.8	-4.4	-5.60
DBP	-6.4	-3.0	-2.5	-2.3	-3.55
[] See references.					

Table 2: Sponsor's Incremental Blood Pressure Lowering of HCTZ 12.5 mg on Top of Various ARB Doses from Literature References

	Candesartan 32 mg [5]	Eprosartan 600 mg [6]	Irbesartan 300 mg [7]	Valsartan 160 mg [8]	Telmisartan 40 mg [9]	Olmesartan 40 mg [10]	Mean
SBP	-13.5	-6.4	-1	-5.6	-7.4	-4.6	-6.4
DBP	-3.9	-2.9	-4.8	-4.1	-3.5	-2.7	-3.7
[] See references.							

The conclusion of the Division medical reviewer was the following: "The composite of the data, despite the limitations I have cited, do suggest that the addition of hydrochlorothiazide 12.5 mg would give incremental blood pressure lowering when added on top of maximally labeled doses of losartan. While it is always nice to have well designed controlled clinical studies to answer such questions, I do not feel strongly that the sponsor needs to conduct such a trial to show that HCTZ 12.5 mg adds incremental blood pressure lowering on top of maximally labeled doses of losartan."

COMMENT: I concur that the sponsor has provided substantial evidence that the combination of losartan 100 mg/HCTZ 12.5 mg has a greater antihypertensive effect than either component used alone. I do not believe that it is necessary to demonstrate such an effect in a more traditional blinded, placebo-controlled study.

2.6 Other Relevant Background Information

None.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The Division CMC review, Dr. William Timmer, recommends approval of this supplement. He does not note any deficiencies or issues in his review dated July 28, 2005.

3.2 Animal Pharmacology/Toxicology

There are no animal pharmacology or toxicology studies included in this submission. The new dosage is lower than the currently approved dosages so that additional preclinical studies are not needed.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The single clinical study included in this submission Study 306, a bioequivalence study of Hyzaar 100/12.5 to its components. The primary review of this study was done by the FDA clinical pharmacology and biopharmaceutics review. I summarize her review in Section 5.1.

The sponsor submitted a proposal for concurrence dated January 26, 2004, that HCTZ always contributes to blood pressure lowering when added to losartan and other antihypertensive agents that are renin-angiotensin system (RAS) inhibitors. That submission was reviewed by Dr. Mehul Desai and I have summarized the findings from his review in Section 2.5.

4.2 Table of Clinical Studies

Study	Nature	N
Protocol 306	Bioequivalence of Hyzaar 100/12.5 to its components	77

4.3 Review Strategy

For the primary analyses for efficacy I relied upon Dr. Desai's review of evidence submitted on January 26, 2004, that HCTZ contributes to blood pressure lowering when added to losartan and

the FDA biopharmaceutist's review of Study 306 from this submission. I summarize and critique the findings from these two reviews in Sections 2.5 and 5.1 respectively.

4.4 Data Quality and Integrity

The FDA biopharmaceutist's review of Study 306 has not raised any issues regarding data quality and integrity for that study.

4.5 Compliance with Good Clinical Practices

Study 306 was conducted in compliance with Good Clinical Practices.

4.6 Financial Disclosures

_____ holds sponsor stock with an estimated value of about _____ 2004. The sponsor has not made any financial arrangements with the investigators contingent upon results of the study.

b(6)

COMMENT: The financial disclosures and arrangements are acceptable.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The pharmacokinetics of both active components of Hyzaar have been characterized adequately in the original Cozaar and Hyzaar NDAs. The one issue for this submission is the bioequivalence of the 100/12.5 formulation to its components. This submission includes the report and data for Study 306 that provides evidence for the bioequivalence of these formulations. Please see the FDA biopharmaceutist's review for the details. The FDA biopharmaceutist's reviewer, Dr. Elena Mishina, recommends approval in her review dated July 29, 2005. The pertinent comments from that review are the following:

- The sponsor used potency adjusted pharmacokinetic parameters in the evaluation of bioequivalence. The use of the potency adjusted pharmacokinetic parameters is not allowed for the evaluation of the bioequivalence. The sponsor clarified that the potency adjusted and unadjusted results are similar. The sponsor is advised in a future that all calculations of the bioequivalence parameters should be performed according to the FDA Guidance for Industry on bioequivalence.
- The losartan 100-mg/HCTZ 12.5-mg combination tablet was bioequivalent to the coadministration of a currently marketed COZAAR (losartan 100 mg) tablet and a MICROZIDE (HCTZ 12.5 mg) capsule with respect to losartan AUC₀₋₈. However, the bioequivalence of these treatments with respect to losartan C_{max} was not established.

- The losartan 100-mg/ HCTZ 12.5-mg combination tablet was bioequivalent to the coadministration of a currently marketed COZAAR (losartan 100 mg) tablet and a MICROZIDE (HCTZ 12.5 mg) capsule with respect to the _____

- The losartan 100-mg/ HCTZ 12.5-mg combination tablet was bioequivalent to the coadministration of a currently marketed COZAAR (losartan 100 mg) tablet and a MICROZIDE (HCTZ 12.5 mg) capsule with respect to HCTZ.

b(4)

b(4)

COMMENT: I agree that the difference in C_{max} for losartan is not clinically important given the potency and exposure of the active metabolite.

5.2 Pharmacodynamics

This submission does not provide data regarding pharmacodynamics. Pharmacodynamics are adequately described in the original Hyzaar NDA submission.

5.3 Exposure-Response Relationships

This submission does not provide data regarding exposure-response relationships. Exposure-response relationships are adequately described in the original Hyzaar NDA submission.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The current indications for Hyzaar are for the treatment of hypertension and severe hypertension and to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy. This submission does not change these indications. It does add a dosage formulation with dosages used in the titration scheme for the last indication. The primary analyses for efficacy are found in Dr. Desai's review of evidence submitted on January 26, 2004, that HCTZ contributes to blood pressure lowering when added to losartan. The pharmacokinetic evidence establishing the bioequivalence of the new formulation to its individual components and supporting linkage to the clinical studies referenced by the sponsor and Dr. Desai is reviewed in the FDA biopharmaceutist's review of Study 306 from this submission. I summarize and critique the findings from these two reviews in Sections 2.5 and 5.1 respectively.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This submission does not add substantially to the safety information regarding Hyzaar. The safety of Hyzaar is supported by the original NDA submission, by the use of HCTZ with losartan in the LIFE study reviewed specifically in conjunction with Serial 033 adding the LIFE study description and indication to the Hyzaar label, and by extensive post-marketing use. This submission adds an intermediate dosage (the highest approved dosage is 100/25), so the new formulation should not present any unique safety problems.

There are limited safety data available from Study 306, the bioequivalence study. Of the 77 subjects in this study 21 reported a total of 25 adverse events (AEs). There were no serious AEs or deaths. All of the AEs were headache or dizziness except for two cases of vomiting about six hours after dosing. One subject had ALT and AST increases to about 4-5 fold on day six.

COMMENT: Nothing is added to the safety information regarding Hyzaar.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

This application adds a dosage form used in the titration scheme for the LIFE study, the outcome study supporting the indication for reducing the risk of stroke in patients with hypertension and LVH. There are no other issues regarding the dosing regimen or administration.

8.2 Drug-Drug Interactions

This submission does not provide any information on drug-drug interactions other than the lack of pharmacokinetic interaction between losartan and HCTZ in the 100/12.5 mg dosages. There are no outstanding issues regarding drug-drug interactions for Hyzaar.

8.3 Special Populations

The bioequivalence study was performed including both males and females. It appears to have been conducted in a Hispanic population. I reviewed the use of losartan/HCTZ by gender, age, and race in conjunction with Serial 033 for adding the LIFE study to the Hyzaar label. Please see my review of that submission.

8.4 Pediatrics

This submission does not provide any data regarding pediatric use. The safety and effectiveness in pediatric patients has not been established. The Division granted a waiver of pediatric studies in a letter dated September 29, 2004.

8.5 Advisory Committee Meeting

This submission is not and will not be the subject of an advisory committee meeting.

8.6 Literature Review

The sponsor reviewed the literature for HCTZ use with ACEIs and ARBs for the January 26, 2004, submission. I did not perform a literature review.

8.7 Postmarketing Risk Management Plan

There is no postmarketing risk management plan proposed or needed.

8.8 Other Relevant Materials

I did not identify any other relevant materials.

9 OVERALL ASSESSMENT

9.1 Conclusions

The sponsor's submission from January 26, 2004, provides substantial evidence that combining losartan 100 mg with HCTZ 12.5 mg adds to the antihypertensive effect of each component. The bioequivalence study in this submission supports using data from the individual component use to draw this conclusion. Because the dosage formulation is an intermediate dosage level compared to the approved dosages and because losartan use with HCTZ has been studied extensively and Hyzaar post-marketing experience is extensive without major concerns, the safety of the 100/12.5 combination is well established.

9.2 Recommendation on Regulatory Action

I recommend approval of the 100/12.5 formulation.

9.3 Recommendation on Postmarketing Actions

I do not recommend any postmarketing actions.

9.4 Labeling Review

The original proposed labeling is based on the label prior to approval the indication for reducing the risk of stroke in patients with hypertension and LVH. It did not change any clinical information in the label but merely adds the existence of the 100/12.5 formulation. A revised

proposed labeling was provided that incorporates the indication for reducing the risk of stroke. The one change needed for this new proposed label is to change the titration directions in the Dosage and Administration subsection for Hypertensive Patients with Left Ventricular Hypertrophy to include the new formulation.

9.5 Comments to Applicant

The proposed label should be changed to include the new formulation in the titration directions in the Dosage and Administration subsection for Hypertensive Patients with Left Ventricular Hypertrophy.

Currently proposed:

Treatment should be initiated with COZAAR 50 mg once daily. Hydrochlorothiazide 12.5 mg should be added or HYZAAR 50-12.5 substituted if the blood pressure reduction is inadequate. If additional blood pressure reduction is needed, COZAAR 100 mg and hydrochlorothiazide 12.5 mg may be substituted, ~~_____~~

~~_____~~ For further blood pressure reduction other antihypertensives should be added (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Losartan Potassium, Reduction in the Risk of Stroke).

b(4)

Recommended change (underlined):

Treatment should be initiated with COZAAR 50 mg once daily. Hydrochlorothiazide 12.5 mg should be added or HYZAAR 50-12.5 substituted if the blood pressure reduction is inadequate. If additional blood pressure reduction is needed, COZAAR 100 mg and hydrochlorothiazide 12.5 mg or Hyzaar 100-12.5 may be substituted, followed by COZAAR 100 mg and hydrochlorothiazide 25 mg or HYZAAR 100-25. For further blood pressure reduction other antihypertensives should be added (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Losartan Potassium, Reduction in the Risk of Stroke).

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/s/

Thomas Marciniak
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MEDICAL OFFICER

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-387/37

CHEMISTRY REVIEW(S)

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA#: 20-387 **CHEM.REVIEW#:** 1 **REVIEW DATE:** 25 May 2005

SUBMISSION/TYPE **DOCUMENT DATE** **CDER DATE** **ASSIGNED DATE**

N20387 SE2 037 20-DEC-04 30-DEC-04 12-JAN-05

NAME & ADDRESS OF APPLICANT: Merck & Co., Inc.
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, PA 19486

Jeffery R. Tucker, M.D.
Director, Regulatory Affairs
484-344-7788

DRUG PRODUCT NAME: HYZAAR™
Losartan Potassium / Hydrochlorothiazide

PHARMACOLOGICAL INDICATION: Hypertension.

Dosage form: Tablet
Rte. of Admin.: Oral
Strength(s): losartan potassium : hydrochlorothiazide
100 mg : 12.5 mg
Dispensed: x Rx OTC

REMARKS/COMMENTS:

This PAS SE2 Supplement was submitted in support of an additional strength of the losartan potassium : hydrochlorothiazide drug product combination. The approved combinations of the losartan potassium / hydrochlorothiazide drug product are, respectively,

50 mg / 12.5 mg and 100 mg / 25 mg

The current supplement seeks approval for a 100 mg / 12.5 mg dosage combination.

CONCLUSIONS & RECOMMENDATIONS:

This supplement is recommended for APPROVAL from a CMC perspective under section 505 of the FFD&C Act.

NDA 20-387 / SE2 – 037

Page 2 of 33

HYZAAR®

Losarten Potassium / Hydrochlorothiazide 100 mg / 12.5 mg

/s/ William C. Timmer, Ph.D.

cc: Orig. NDA 20-387
HFD-110/Division File
HFD-110/PM/CBorden

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_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
20-387/37

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA: 20,387 SE8 037

Submission Dates: December 17, 2004, July 19, and 25, 2005

Drug Name: HYZAAR™ (Losartan Potassium – Hydrochlorothiazide)

Formulation: 100-12.5 mg tablet

Applicant: Merck &Co., Inc.

Priority: 3S

Submission: Supplemental NDA, Labeling Changes

Reviewer: Elena V. Mishina, Ph.D.

BACKGROUND

In this supplemental NDA, the sponsor describes the changes in the Clinical and Statistical Section of the Label of the approved New Drug Application for HYZAAR™ (Losartan Potassium – Hydrochlorothiazide). Specifically, the sponsor is proposing to add a new intermediate strength, fixed-dose combination that contains losartan 100 mg and HCTZ 12.5 mg. The availability of the HYZAAR™ 100-12.5-mg strength will allow for a step-wise titration from losartan 100-mg monotherapy in patients that require the addition of a low dose diuretic for further blood pressure lowering.

HYZAAR 50-12.5 and 100-25 (losartan potassium-hydrochlorothiazide) combine an angiotensin II receptor (type AT1) antagonist and a diuretic, hydrochlorothiazide. 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). Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. Hydrochlorothiazide is not metabolized; at least 61 percent of the oral dose is eliminated unchanged by the kidney within 24 hours.

With this supplemental NDA 20,387 (SE8-037), the sponsor submitted for review the results of one study. The purpose of this study was to evaluate an intermediate strength

fixed-dose combination that contains losartan potassium-HCTZ-100-12.5 mg and evaluate bioequivalence to the concomitant administration.

RESULTS

Study 306 compared the combination tablet of losartan 100-mg/HCTZ 12.5-mg (Treatment A) to the coadministration of a currently marketed COZAAR (losartan 100 mg) tablet and MICROZIDE (HCTZ 12.5 mg) capsule, Treatment B. _____

b(4)

Losartan:

The combination tablet of losartan 100-mg/HCTZ 12.5-mg was bioequivalent to the coadministration of a currently marketed COZAAR (losartan 100 mg) tablet and MICROZIDE (HCTZ 12.5 mg) capsule with respect to AUC; however the Treatment A was not bioequivalent to Treatment B with respect to C_{max}. The losartan geometric mean AUC_{0-∞} ratio (A/B) and 90% CI was 0.993 (0.950, 1.039) and fell within the pre-specified bioequivalence bounds (0.80, 1.25). The losartan geometric mean C_{max} ratio (A/B) and 90% CI was 0.835 (0.749, 0.931), the confidence interval was skewed with the lower bound of the 90% CI being lower than the bioequivalence limit (0.80, 1.25).

b(4)

HCTZ:

The losartan 100-mg/HCTZ 12.5-mg combination tablet was bioequivalent to the MICROZIDE (HCTZ 12.5 mg) capsule with respect to the HCTZ component. The HCTZ geometric mean AUC_{0-∞} ratio (A/B) and 90% CI was 0.924 (0.825, 1.035) and the HCTZ geometric mean C_{max} ratio (A/B) and 90% CI was 0.931 (0.836, 1.037).

The urinary recoveries of HCTZ (percent dose) were 52% and 59% following the losartan 100-mg/HCTZ 12.5-mg combination tablet and the coadministration of a currently marketed COZAAR (losartan 100 mg) tablet and a MICROZIDE (HCTZ 12.5 mg) capsule, respectively.

Table 1: Summary of Pharmacokinetic Variables of Losartan Following Single Dose Administration of a Losartan 100-mg/ HCTZ 12.5-mg Combination Tablet or Following Coadministration of a Losartan 100-mg Tablet with an HCTZ 12.5-mg Capsule

PK Variable [†]	N	Geometric Mean [‡] for Treatment		Geometric Mean Ratio [§] (A/B)	90% Confidence Interval for Geometric Mean Ratio [§]	MSE
		A	B			
Losartan AUC _{0-∞} (ng•hr/mL)	75	1018.1	1024.9	0.993	(0.950, 1.039)	0.0275
Losartan C _{max} (ng/mL)	75	532.7	637.9	0.835	(0.749, 0.931)	0.1602
Losartan AUC _{0-t} (ng•hr/mL)	75	1008.4	1015.2	0.993	(0.949, 1.039)	0.0278
Losartan T _{max} (hr)	75	1.50 [‡]	1.25 [‡]	0.25 [§]	(0.125, 0.500) [§]	
Losartan Half-Life (hr)	75	3.06 [‡]	3.20 [‡]			

[†] PK variables AUC_{0-∞}, C_{max}, and AUC_{0-t} are potency-adjusted.
[‡] Least squares estimate for geometric means are based on an ANOVA performed on the natural-log transformed values and are then back-transformed to the original scale. Median used for T_{max} and Harmonic Mean used for Half Life.
[§] For T_{max}, represents Hodges-Lehman estimate of median treatment difference, with corresponding 90% CI about Hodges-Lehman estimate for median difference.
^{||} Mean Square Error (MSE) on the natural-log scale.
 Treatment A: 100 mg Losartan / 12.5 mg HCTZ Combination Tablet.
 Treatment B: 100 mg COZAAR[™] and 12.5 mg MICROZIDE[™] Coadministered.

Table 2: Summary of Pharmacokinetic Variables of HCTZ Following Single Dose Administration of a Losartan 100-mg/ HCTZ 12.5-mg Combination Tablet or Following Coadministration of a Losartan 100-mg Tablet with an HCTZ 12.5-mg Capsule

PK Variable [†]	N	Geometric Mean [‡] for Treatment		Geometric Mean Ratio [§] (A/B)	90% Confidence Interval for Geometric Mean Ratio [§]	MSE
		A	B			
HCTZ AUC _{0-∞} (ng•hr/mL)	20	462.08	499.90	0.924	(0.825, 1.035)	0.0426
HCTZ C _{max} (ng/mL)	20	76.15	81.76	0.931	(0.836, 1.037)	0.0386
HCTZ AUC _{0-t} (ng•hr/mL)	20	418.16	459.01	0.911	(0.811, 1.024)	0.0452
HCTZ Renal Clearance (mL/min)	20	250.43	260.72	0.961	(0.910, 1.014)	0.0097
HCTZ Cum. Ur. Rec. 0-48hr (%Dose)	20	52.01	58.92	0.883	(0.788, 0.988)	0.0425
HCTZ T _{max} (hr)	20	3.00 [‡]	2.00 [‡]	0.75 [§]	(0.500, 1.250) [§]	
HCTZ Half-Life (hr)	20	9.62 [‡]	9.78 [‡]			

[†] PK variables AUC_{0-∞}, C_{max}, and AUC_{0-t} are potency-adjusted.
[‡] Least squares estimate for geometric means are based on an ANOVA performed on the natural-log transformed values and are then back-transformed to the original scale. Median used for T_{max} and Harmonic Mean used for Half Life.
[§] For T_{max}, represents Hodges-Lehman estimate of median treatment difference, with corresponding 90% CI about Hodges-Lehman estimate for median difference.
^{||} Mean Square Error (MSE) on the natural-log scale.
 Treatment A: 100 mg Losartan / 12.5 mg HCTZ Combination Tablet.
 Treatment B: 100 mg COZAAR[™] and 12.5 mg MICROZIDE[™] Coadministered.



COMMENTS:

1. In Tables 1-3 the sponsor referred to the potency adjusted PK parameters. To clarify this, the teleconference with the sponsor was held on July 7, 2005. The FDA reviewer asked the following questions:

1. What was the reason for the potency adjustment for the PK parameters calculation?
2. How was this adjustment made?
3. What were the coefficients for the potency adjustment?
4. Was it performed for the reference or/ and test formulation?
5. Please recalculate the ANOVA based on non- adjusted PK parameters.

Sponsor' Response.

During release testing of the formulation batch, the assay content was determined. For bioequivalence comparisons, minor assay content differences were taken into account when comparing the in vivo performance of the dosage forms. With this correction, the in vivo exposure parameters (Cmax and AUC) are reflective of the dosage form performance and not confounded by assay content variations between batches. Potency adjustments have been made for previous bioequivalence studies submitted for COZAAR and HYZAAR.

b(4)

The AUC and Cmax of losartan, ——— and hydrochlorothiazide (HCTZ) were potency adjusted to 100 mg and 12.5 mg based on the assay potencies of the formulations for losartan potassium and HCTZ, respectively. The losartan potassium assay content in the 100 mg tablet was 99.8 mg, and was 100.1 mg for the HYZAAR 100- 12.5 mg tablet. The HCTZ assay content in the 12.5 mg MICROZIDE capsule was 12.15 mg and was 12.09 mg for the HYZAAR 100- 12.5 mg tablet.

The potency adjustment for losartan potassium and HCTZ PK parameters (Cmax and AUC) was determined by the following relationship:

Adjusted PK parameter = PK parameter x (nominal potency/ assay potency)

This potency adjustment was applied to both the test and reference formulations.

, the PK parameters (C_{max} and AUC) were similarly adjusted based on losartan potassium potencies.

The potency unadjusted data for losartan, HCTZ, and are provided in Tables 4-6, respectively.

Table 4: Summary of Unadjusted Pharmacokinetic Variables of Losartan Following Single Dose Administration of a Losartan 100-mg/ HCTZ 12.5-mg Combination Tablet or Following Coadministration of a Losartan 100-mg Tablet with an HCTZ 12.5-mg Capsule

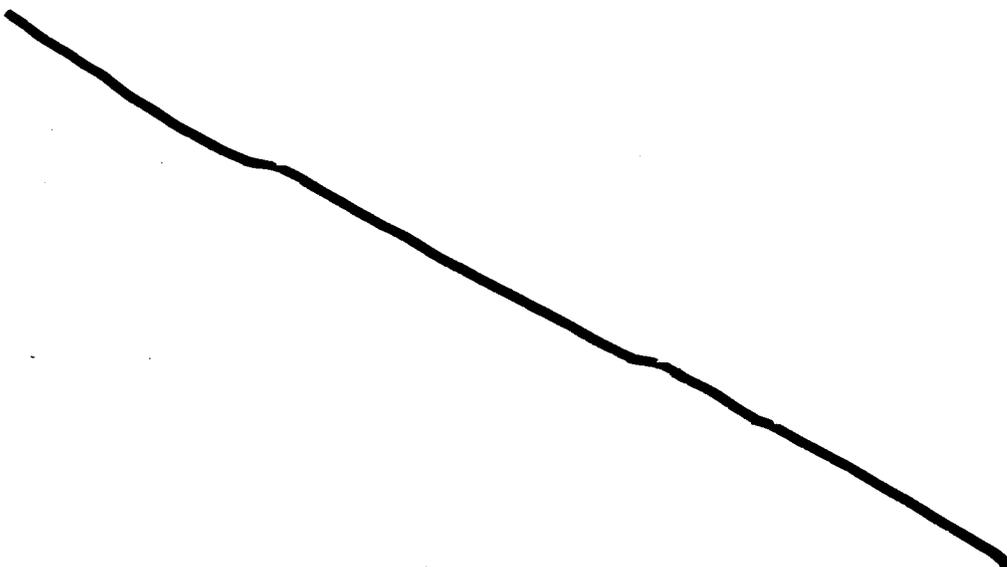
PK Variable	N	Geometric Mean ¹ For Treatment		Geometric Mean Ratio ² (A/B)	90% Confidence Interval for Geometric Mean Ratio ²	MSE ³
		A	B			
Losartan AUC _{0-∞} (ng•hr/mL)	75	1019.1	1022.8	0.996	(0.952, 1.042)	0.0275
Losartan C _{max} (ng/mL)	75	533.2	636.6	0.838	(0.751, 0.934)	0.1602
Losartan AUC ₀₋₆ (ng•hr/mL)	75	1009.4	1013.2	0.996	(0.952, 1.042)	0.0278
Losartan T _{max} (hr)	75	1.50	1.25	0.25	(0.125, 0.500)	
Losartan Half-Life (hr)	75	3.06	3.20			

¹ Least squares estimate for geometric means are based on an ANOVA performed on the natural-log transformed values. Median used for T_{max} and Harmonic Mean used for Half Life.
² For T_{max}, represents Hodges-Lehman estimate of median treatment difference, with corresponding 90% CI about Hodges-Lehman estimate for median difference.
³ Mean Square Error (MSE) on the natural-log scale.
 Treatment A: 100 mg Losartan / 12.5 mg HCTZ Combination Tablet
 Treatment B: 100 mg COZAAR and 12.5 mg MICROZIDE Coadministered

Table 5: Summary of Unadjusted Pharmacokinetic Variables of HCTZ Following Single Dose Administration of a Losartan 100-mg/ HCTZ 12.5-mg Combination Tablet or Following Coadministration of a Losartan 100-mg Tablet with an HCTZ 12.5-mg Capsule

PK Variable	N	Geometric Mean ¹ For Treatment		Geometric Mean Ratio ² (A/B)	90% Confidence Interval for Geometric Mean Ratio ²	MSE ³
		A	B			
HCTZ AUC _{0-∞} (ng•hr/mL)	20	446.92	485.90	0.920	(0.821, 1.030)	0.0426
HCTZ C _{max} (ng/mL)	20	73.65	79.47	0.927	(0.832, 1.032)	0.0386
HCTZ AUC ₀₋₆ (ng•hr/mL)	20	404.44	446.16	0.907	(0.807, 1.019)	0.0452
HCTZ Renal Clearance (mL/min)	20	250.43	260.72	0.961	(0.910, 1.014)	0.0097
HCTZ Cum. Ur. Rec. 0-48hr (%Dose)	20	52.01	58.92	0.883	(0.788, 0.988)	0.0425
HCTZ T _{max} (hr)	20	3.00	2.00	0.75	(0.500, 1.250)	
HCTZ Half-Life (hr)	20	9.62	9.78			

¹ Least squares estimate for geometric means are based on an ANOVA performed on the natural-log transformed values. Median used for T_{max} and Harmonic Mean used for Half Life.
² For T_{max}, represents Hodges-Lehman estimate of median treatment difference, with corresponding 90% CI about Hodges-Lehman estimate for median difference.
³ Mean Square Error (MSE) on the natural-log scale.
 Treatment A: 100 mg Losartan / 12.5 mg HCTZ Combination Tablet
 Treatment B: 100 mg COZAAR and 12.5 mg MICROZIDE Coadministered



In conclusion, in this study the potency unadjusted values were very similar to the adjusted values and did not change the conclusions of the study.

COMMENTS, continued.

2. The use of the potency adjusted pharmacokinetic parameters is not allowed for the evaluation of the bioequivalence. The sponsor is advised in a future that all calculations of the bioequivalence parameters should be performed according to the FDA Guidance for Industry on bioequivalence.
3. The losartan 100-mg/HCTZ 12.5-mg combination tablet was bioequivalent to the coadministration of a currently marketed COZAAR (losartan 100 mg) tablet and a MICROZIDE (HCTZ 12.5 mg) capsule with respect to losartan AUC_{0-∞}. However, the bioequivalence of these treatments with respect to losartan C_{max} was not established.
4. The losartan 100-mg/ HCTZ 12.5-mg combination tablet was bioequivalent to the coadministration of a currently marketed COZAAR (losartan 100 mg) tablet and a MICROZIDE (HCTZ 12.5 mg) capsule with respect to the _____
5. The losartan 100-mg/ HCTZ 12.5-mg combination tablet was bioequivalent to the coadministration of a currently marketed COZAAR (losartan 100 mg) tablet and a MICROZIDE (HCTZ 12.5 mg) capsule with respect to HCTZ.

b(4)



b(4)

7. The submitted data in NDA 20,387 (SE2 037) are acceptable in meeting the OCPB requirements.

RECOMMENDATIONS:

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation I recommends the approval of the proposed labeling changes in the package insert. The application is acceptable for meeting the recommendations of the Office of Clinical Pharmacology and Biopharmaceutics. The conclusion of the Comment 1 should be conveyed to the sponsor.

The dissolution acceptance criteria for the new tablet strength recommended as was adopted for the other strength marketed products.

The dissolution method and specifications are as follows:

Condition	Recommendation
Dissolution Medium	Water at 37°C
USP Apparatus I	100 rpm
Basket Speed	
Volume	900 mL
Specifications	
losartan potassium	Q
HCTZ	Q

b(4)

Elena Mishina, Ph. D.
Clinical Pharmacology Reviewer

Date _____

Patrick Marroum, Ph. D.
Cardio-Renal Team Leader

cc list: NDA 20,387, MehulM, MarroumP, MishinaE, HFD 110 BIOPHARM

APPENDIX

**APPEARS THIS WAY
ON ORIGINAL**

20 Page(s) Withheld

 Trade Secret / Confidential (b4)

~~X~~ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

11 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Elena Mishina
7/29/05 03:05:53 PM
BIOPHARMACEUTICS

Patrick Marroum
7/29/05 03:44:01 PM
BIOPHARMACEUTICS

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-387/37

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 07/31/06	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER 20-387	
		NAME OF APPLICANT / NDA HOLDER Merck & Co., Inc.	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) HYZAAR			
ACTIVE INGREDIENT(S) Losartan potassium and hydrochlorothiazide		STRENGTH(S) 100mg/12.5mg	
DOSAGE FORM Film Coated tablets			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by the FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
<i>FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.</i>			
<i>For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment or supplement, complete above section and sections 5 and 6.</i>			
1. GENERAL			
a. United States Patent Number 5,138,069		b. Issue Date of Patent August 11, 1992	c. Expiration Date of Patent August 11, 2009
d. Name of Patent Owner E.I. Du Pont de Nemours and Company		Address (of Patent Owner) 1007 Market Street	
		City/State Wilmington, Delaware	
		ZIP Code 19898	FAX Number (if available)
		Telephone Number (302) 992-4926	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1 e.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input type="checkbox"/> Yes <input type="checkbox"/> No
--	---

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
--	--

5. No Relevant Patents

For this pending NDA, amendment or supplement, there are no relevant patents that claim the approved drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use or sale of the drug product Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

Richard S. Parr



October 26, 2004

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Richard S. Parr

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Rahway, NJ

ZIP Code

07065-0907

Telephone Number

(732) 594-4958

FAX Number (if available)

(732) 594-4720

E-Mail Address (if available)

richard_parr@merck.com

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 07/31/06	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER 20-387	
		NAME OF APPLICANT / NDA HOLDER Merck & Co., Inc.	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) HYZAAR			
ACTIVE INGREDIENT(S) Losartan potassium and hydrochlorothiazide		STRENGTH(S) 100mg/12.5mg	
DOSAGE FORM Film Coated tablets			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by the FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
<i>FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.</i>			
<i>For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment or supplement, complete above section and sections 5 and 6.</i>			
1. GENERAL			
a. United States Patent Number 5,153,197		b. Issue Date of Patent October 6, 1992	c. Expiration Date of Patent October 6, 2009
d. Name of Patent Owner E.I. Du Pont de Nemours and Company		Address (of Patent Owner) 1007 Market Street	
		City/State Wilmington, Delaware	
		ZIP Code 19898	FAX Number (if available)
		Telephone Number (302) 992-4926	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
1	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product	Use: (Submit indication or method of use information as identified specifically in the proposed labeling)
	HYZAAR is indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy of hypertension, except when the hypertension is severe enough that the value of achieving prompt blood pressure control exceeds the risk of initiating combination therapy in these patients.

5. No Relevant Patents

For this pending NDA, amendment or supplement, there are no relevant patents that claim the approved drug substance (active ingredient), drug product (formulation or composition) or methods(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use or sale of the drug product. Yes

6. Declaration Certification	
<p>6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.</p> <p>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</p>	
<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</p>  <p>Richard S Parr</p>	<p>Date Signed</p> <p>October 26, 2004</p>
<p>NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).</p>	
<p>Check applicable box and provide information below.</p>	
<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<p>Name</p> <p>Richard S. Parr</p>	
<p>Address</p> <p>P.O. Box 2000, RY60-30</p>	<p>City/State</p> <p>Rahway, NJ</p>
<p>ZIP Code</p> <p>07065-0907</p>	<p>Telephone Number</p> <p>(732) 594-4958</p>
<p>FAX Number (if available)</p> <p>(732) 594-4720</p>	<p>E-Mail Address (if available)</p> <p>richard_parr@merck.com</p>

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 07/31/06	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER 20-387	
		NAME OF APPLICANT / NDA HOLDER Merck & Co., Inc.	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) HYZAAR			
ACTIVE INGREDIENT(S) Losartan potassium and hydrochlorothiazide		STRENGTH(S) 100mg/12.5mg	
DOSAGE FORM Film Coated tablets			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by the FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number 5,608,075		b. Issue Date of Patent March 4, 1997	c. Expiration Date of Patent March 4, 2014
d. Name of Patent Owner Merck & Co., Inc. E.I. Du Pont de Nemours and Company The Du Pont Merck Pharmaceutical Company		Address (of Patent Owner) P.O. BOX 2000, RY 60-30	
		City/State RAHWAY, NEW JERSEY	
		ZIP Code 07065-0907	FAX Number (if available) (732) 594-4720
		Telephone Number (732) 594-3902	E-Mail Address (if available)
e. <u>Name of agent or representative</u> who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3
 The patent claims the form of the active ingredient described in NDA 20-387 (namely, losartan Form I) and is submitted for listing on that basis. The patent claims are not limited to that particular form and claim as well, for example, losartan Form II. Because the patent is being submitted on the basis that it claims the form of the active ingredient described in the approved NDA and pending supplement, additional testing of other forms is not required.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input type="checkbox"/> Yes <input type="checkbox"/> No
--	---

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
---	--

5. No Relevant Patents

For this pending NDA, amendment or supplement, there are no relevant patents that claim the approved drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use or sale of the drug product. Yes

6. Declaration Certification	
<p>6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.</p> <p>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</p>	
<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</p>  <p>Richard S. Parr</p>	<p>Date Signed</p> <p>December 9, 2004</p>
<p>NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).</p>	
<p>Check applicable box and provide information below.</p>	
<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<p>Name</p> <p>Richard S. Parr</p>	
<p>Address</p> <p>P.O. Box 2000, RY60-30</p>	<p>City/State</p> <p>Rahway, NJ</p>
<p>ZIP Code</p> <p>07065-0907</p>	<p>Telephone Number</p> <p>(732) 594-4958</p>
<p>FAX Number (if available)</p> <p>(732) 594-4720</p>	<p>E-Mail Address (if available)</p> <p>richard_parr@merck.com</p>

EXCLUSIVITY SUMMARY

NDA # 20-387

SUPPL # 037

HFD # 110

Trade Name Hyzaar

Generic Name losartan/ hydrochlorothiazide

Applicant Name Merck Research Laboratories

Approval Date, If Known Oct 1995

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES

NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

SE2

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES

NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

Refer to Dr Elena Mishina's review.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

Yes

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # YES ! NO
! Explain:

Investigation #2 !
IND # YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES
Explain:

!
! NO
! Explain:

Investigation #2

YES
Explain:

!
! NO
! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====
Name of person completing form: LCDR Cheryl Ann Borden
Title: Regulatory Health Project Manager
Date: 11 October 2005

Name of Office/Division Director signing form: Norman Stockbridge, M.D., PhD.
Title: Acting Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Norman Stockbridge
10/12/2005 04:57:42 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 20-387 Supplement Type (e.g. SE5): SE2 Supplement Number: 037

Stamp Date: 20 December 2004 Action Date: 20 October 2005

HFD 110 Trade and generic names/dosage form: Hyzaar (losartan/ hydrochlorothiazide 50-12.5, 100-12.5, and 100-25 mg Tablets)

Applicant: Merck Research Laboratories Therapeutic Class: 6

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: This application supports the registration of a losartan 100 mg and HCTZ 12.5 mg fixed-dose combination tablet.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. Tanner Stage _____
Max _____ kg _____ mo. _____ yr. Tanner Stage _____

Reason(s) for partial waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Adult studies ready for approval

Formulation needed

Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

LCDR Cheryl Ann Borden, MSN, RN
{See appended electronic signature page}

Regulatory Health Project Manager

cc: NDA 20-387/ S-037
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Cheryl Borden
8/2/05 12:51:11 PM



NDA 20-387/S-037

PRIOR APPROVAL SUPPLEMENT

Merck & Co., Inc.
Attention: Jeffrey R. Tucker, M.D.
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. Tucker:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Hyzaar™ (losartan potassium/hydrochlorothiazide) 50/12.5
and 100/25 mg Tablets

NDA Number: 20-387

Supplement number: 037

Date of supplement: December 17, 2004

Date of receipt: December 20, 2004

This supplemental application proposes a new 100-12.5 mg strength of Hyzaar™ tablets.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 18, 2005, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 20, 2005.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
5600 Fishers Lane
Rockville, Maryland 20857

NDA 20-387/S-037

Page 2

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, please call:

Cheryl Ann Borden, MSN, RN, CCRN, CCNS
Regulatory Health Project Manager
(301) 594-5311

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Edward Fromm
12/30/04 11:43:04 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 20-387/S-037

MERCK & Co., Inc.
Attention: Jeffrey R. Tucker, M.D.
Director, Regulatory Affairs
P.O. Box 4
West Point, PA 19486

Dear Dr. Tucker:

Please refer to your 20 December 2004 supplemental new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for HYZAAR (Losartan Potassium Hydrochlorothiazide) 50-12.5 mg and 100-25 mg Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on 4 March 2005 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions please call:

Cheryl Ann Borden, MSN, RN, CCRN, CCNS
Regulatory Health Project Manager
(301) 594 5312.

Sincerely,

{See appended electronic signature page}
Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Norman Stockbridge
3/4/05 10:56:00 AM