CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20-387/S-008

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NOV 10 1998

NDA 20-387/S-008

Merck Research Laboratories
Attention: Jeffery R. White, M.D.
Sumneytown Pike, P.O. Box 4
BLA-25
West Point, PA 19486

Dear Dr. White:

Please refer to your supplemental new drug application dated February 10, 1998, received February 11, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hyzaar (losartan potassium/hydrochlorothiazide) 50-12.5 mg Tablets.

We acknowledge receipt of your submissions dated September 11 and October 23, 1998.

This supplemental new drug application provides for a new tablet strength, 100 mg losartan potassium/25 mg hydrochlorothiazide. Included with the submission is final printed labeling revised as follows:

DESCRIPTION:

Instead of "HYZAAR" followed by the generic name, the labeling now reads:

> HYZAAR 50-12.5 (losartan potassium-hydrochlorothiazide tablets)
> HYZAAR 100-25 (losartan potassium-hydrochlorothiazide tablets)

The first sentence now begins, "HYZAAR 50-12.5 (losartan potassium-hydrochlorothiazide tablets) and HYZAAR 100-25 . . .."

The next-to-last paragraph now begins, "HYZAAR is available for oral administration in two tablet combinations of losartan and hydrochlorothiazide. HYZAAR 50-12.5 contains 50 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 . . .."

The single sentence in the last paragraph has been revised to "HYZAAR 50-12.5 contains 4.24 mg (0.108 mEq) of potassium and HYZAAR 100-25 contains 8.48 mg (0.216 mEq) of potassium."

ADVERSE REACTIONS:

In the third paragraph, "HYZAAR" has been changed to "losartan-hydrochlorothiazide."

DOSAGE AND ADMINISTRATION, Dose Titration by Clinical Effect:

This subsection has been revised to read as follows:

> A patient whose blood pressure is not adequately controlled with losartan monotherapy (see above) 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 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.

HOW SUPPLIED:

Information on HYZAAR 100-25 has been added. The first sentence of the **Storage** subsection has been revised to read, "Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]."

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the final printed labeling included in your October 23, 1998 submission. Accordingly, the supplemental application is approved effective on the date of this letter.

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

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

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

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

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

If you have any questions, please contact:

Ms. Kathleen Bongiovanni
Regulatory Health Project Manager
(301) 594-5334

signed 11/10/98
KBong 11-16-98

Sincerely yours,

/S/ 4/10/98

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Archival NDA 20-387
~~HFD-110/Div. Files~~
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-101/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-95/DDMS (with labeling)
HFD-810/DNDC Division Director
DISTRICT OFFICE
HFD-110/K.Bongiovanni
sb/10/30/98;11/9/98
Initialed by: R Mittal/11/2/98
K Srinivasachar/11/2/98
A Proakis/11/2/98
C Resnick/11/3/98
K Knudsen/11/4/98
N Stockbridge/11/4/98
N Morgenstern/11/6/98
G Buehler for N Morgenstern/11/9/98
filename: 20387s008ap.doc

Approval Date – 4/28/95

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-387/S-008

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-387/S-008

AUG 10 1998

Merck Research Laboratories
Attention: Jeffrey R. White, M.D.
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. White:

Please refer to your supplemental new drug application dated February 10, 1998, received February 11, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hyzaar (losartan potassium/hydrochlorothiazide) 50-12.5 mg Tablets.

We acknowledge receipt of your submissions dated April 20, June 19, and July 15 and 20, 1998.

The user fee goal date is August 11, 1998.

This supplemental application provides for a new tablet strength, 100 mg losartan potassium/25 mg hydrochlorothiazide, with draft labeling revised under **DESCRIPTION, DOSAGE AND ADMINISTRATION,** and **HOW SUPPLIED.**

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit revised draft labeling for the drug. The labeling should be identical in content to the submitted labeling (package insert submitted July 15, 1998 and immediate container and carton labels submitted July 19, 1998) with the following exceptions:

Please delete from the proprietary name in the package insert and all carton and container labeling. The is unnecessary and crowds an already cluttered abbreviation list. Listing the strengths (100/25) is adequate and succinctly provides a health-care practitioner with the essential information. Furthermore, by using the product is tied to a reference strength that may at some future time not be available. Also, terms like forte, and strong convey a therapeutic message of enhanced activity that may not be merited by the available data.

Please delete the letters from the logo on the carton and container labels for all strengths of Hyzaar. has an established meaning for bioequivalence concerns as listed in the Orange Book, and its inclusion as part of a logo may render the labeling misleading.

In addition to the above changes to your labeling, please consider using the following storage statement in the **HOW SUPPLIED** section of the package insert and on the immediate container labels:

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

If space on the immediate container is limited, either of the following statements would be acceptable, provided the full statement (as above) appears on the outer carton and in the package insert:

> Store at 25°C (77°F); excursions 15-30°C (59-86°F). Keep container tightly closed. Protect from light.

or

> Store at 25°C (77°F); (see insert). Keep container tightly closed. Protect from light.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

We note that the approved dissolution medium and specifications are as follows:

Medium:
Method:
Specification:

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change prior to approval of this supplemental application.

If you have any questions, please contact:

Ms. Kathleen Bongiovanni
Regulatory Health Project Manager
(301) 594-5334

Sincerely yours.

/S/ 3/10/98

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Archival NDA 20-387
HFD-110/Div. Files
HFD-95/DDMS
DISTRICT OFFICE
HFD-110/K.Bongiovanni
HFD-530/DBoring
sb/8/3/98;8/3/98
kb/8/6/98;sb/8/10/98
Initialed by: RMittal/8/6/98;
K Srinivasachar/8/6/98
A Proakis/8/6/98
C Resnick/8/6/98
E Fadiran/8/6/98
A Parekh/8/6/98
K Knudsen/8/10/98
R Fenichel/8/10/98
G Buehler for N Morgenstern
filename: 20387s008ae.doc

APPROVABLE (AE)

/S/ 8-10-98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-387/S-008

FINAL PRINTED LABELING

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

HYZAAR® 50-12.5
(LOSARTAN POTASSIUM-HYDROCHLOROTHIAZIDE TABLETS)

HYZAAR® 100-25
(LOSARTAN POTASSIUM-HYDROCHLOROTHIAZIDE TABLETS)

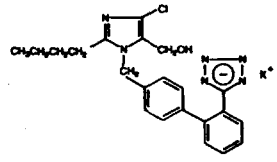
USE IN PREGNANCY

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) and HYZAAR® 100-25 (losartan potassium-hydrochlorothiazide), combine an angiotensin II receptor (type AT_1) antagonist and a diuretic, hydrochlorothiazide.

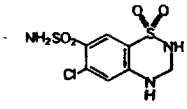
Losartan potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt. Its empirical formula is $C_{22}H_{22}ClKN_6O$, and its structural formula is:



Losartan potassium is a white to off-white free-flowing crystalline powder with a molecular weight of 461.01. It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone.

Oxidation of the 5-hydroxymethyl group on the imidazole ring results in the active metabolite of losartan.

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$ 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 two tablet combinations of losartan and hydrochlorothiazide. HYZAAR 50-12.5 contains 50 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, hydroxypropyl methylcellulose, titanium dioxide and D&C yellow No. 10 aluminum lake.

HYZAAR 50-12.5 contains 4.24 mg (0.108 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 AT_1 receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland). There is also an AT_2 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 AT_1 receptor and have much greater affinity (about 1000-fold) for the AT_1 receptor than for the AT_2 receptor. *In vitro* binding studies indicate that losartan is a reversible, competitive inhibitor of the AT_1 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 AT_1 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.

Renal Insufficiency: Plasma concentrations of losartan are not altered in patients with creatinine clearance above 30 mL/min. In patients with lower creatinine clearance, AUCs are about 50% greater and are doubled in hemodialysis patients. Plasma concentrations of the active metabolite are not significantly altered in patients with renal impairment or in hemodialysis patients. Neither losartan nor its active metabolite can be removed by hemodialysis.

Hepatic Insufficiency: Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite

were, respectively, 5 times and about 1.7 times those in young male volunteers. Compared to normal subjects the 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. 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. Conversion of losartan to its active metabolite after intravenous administration is not affected by ketoconazole, an inhibitor of P450 3A4. There is no pharmacokinetic interaction between losartan and hydrochlorothiazide.

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

Losartan inhibits the pressor effect of angiotensin II (as well as angiotensin I) infusions. A dose of 100 mg inhibits the pressor effect by about 85% at peak with 25-40% inhibition persisting for 24 hours. Removal of the negative feedback of angiotensin II causes a 2-3 fold rise in plasma renin activity and consequent rise in angiotensin II plasma concentration in hypertensive patients. Losartan does not affect the response to bradykinin, whereas 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 6-12 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. Black patients, however, had notably smaller responses to losartan monotherapy.

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

Persistent dry cough (with an incidence of a few percent) has been associated with ACE inhibitor use and in practice can be a cause of discontinuation of ACE inhibitor therapy. Two prospective, parallel-group, double-blind, randomized, controlled trials were conducted to assess the effects of losartan on the incidence of cough in hypertensive patients who had experienced cough while receiving ACE inhibitor therapy. Patients who had typical ACE inhibitor cough when challenged with lisinopril, whose cough disappeared on placebo, were randomized to losartan 50 mg, lisinopril 20 mg, or either placebo (one study, n=97) or 25 mg hydrochlorothiazide

HYZAAR® 50-12.5
(LOSARTAN POTASSIUM-HYDROCHLOROTHIAZIDE TABLETS)
HYZAAR® 100-25
(LOSARTAN POTASSIUM-HYDROCHLOROTHIAZIDE TABLETS)
Circular Number 7892809
6369-09

HYZAAR® 50-12.5
(LOSARTAN POTASSIUM-HYDROCHLOROTHIAZIDE TABLETS)
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7892809
6369-09

(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.

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 (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.

INDICATIONS AND USAGE

HYZAAR is indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy (see 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. (See CLINICAL PHARMACOLOGY, *Drug Interactions.*) Potent inhibitors of cytochrome P450 3A4 and 2C9 have not been studied clinically but *in vitro* studies show significant inhibition of the formation of the active metabolite by inhibitors of P450 3A4 (ketoconazole, troleandomycin, gestodene), or P450 2C9 (sulfaphenazole) and nearly complete inhibition by the combination of sulfaphenazole and ketoconazole. In humans, ketoconazole, an inhibitor of P450 3A4, did not affect the conversion of losartan to the active metabolite after intravenous administration of losartan. Inhibitors of cytochrome P450 2C9 have not been studied clinically. The pharmacodynamic consequences of concomitant use of losartan and inhibitors of P450 2C9 have not been examined.

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*).

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.

Use in the Elderly

Of the total number of patients in controlled clinical studies of hypertension with HYZAAR, 107 patients (12.5%) were 65 years and over, while 9 patients (1.0%) were 75 years and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Losartan potassium-hydrochlorothiazide has been evaluated for safety in 858 patients treated for essential hypertension. 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–Hydrochlorothiazide (n=858)	Placebo (n=173)
Body as a Whole		
Abdominal pain	1.2	0.6
Edema/swelling	1.3	1.2
Cardiovascular		
Palpitation	1.4	0.0
Musculoskeletal		
Back pain	2.1	0.6
Nervous/Psychiatric		
Dizziness	5.7	2.9
Respiratory		
Cough	2.6	2.3
Sinusitis	1.2	0.6
Upper respiratory infection	6.1	4.6
Skin		
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: asthenia/fatigue, diarrhea, nausea, headache, bronchitis, pharyngitis.

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

A patient with known hypersensitivity to aspirin and penicillin, when treated with 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 was 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 angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions; *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.

Post-Marketing Experience

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

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.

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

Hyperkalemia 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/m^2 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 LD_{50} 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

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) 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 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.

HYZAAR may be administered with other antihypertensive agents.

HYZAAR may be administered with or without food.

HOW SUPPLIED

No. 3502 — Tablets HYZAAR, 50-12.5 are yellow, teardrop shaped, film-coated tablets, coded MRK 717 on one side and HYZAAR on the other. Each tablet contains 50 mg of losartan potassium and 12.5 mg of hydrochlorothiazide. They are supplied as follows:

NDC 0006-0717-31 unit of use bottles of 30
NDC 0006-0717-54 unit of use bottles of 90
NDC 0006-0717-58 unit of use bottles of 100
(6505-01-416-4329, 50-12.5 100's)
NDC 0006-0717-28 unit dose packages of 100
NDC 0006-0717-82 unit of use bottles of 1,000.

No. 3793 — Tablets HYZAAR 100-25 are light yellow, teardrop shaped, film-coated tablets, coded MRK 747 on one side and HYZAAR on the other. Each tablet contains 100 mg of losartan potassium and 25 mg of hydrochlorothiazide. They are supplied as follows:

NDC 0006-0747-31 unit of use bottles of 30
NDC 0006-0747-58 unit of use bottles of 100
NDC 0006-0747-28 unit dose packages of 100.

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.

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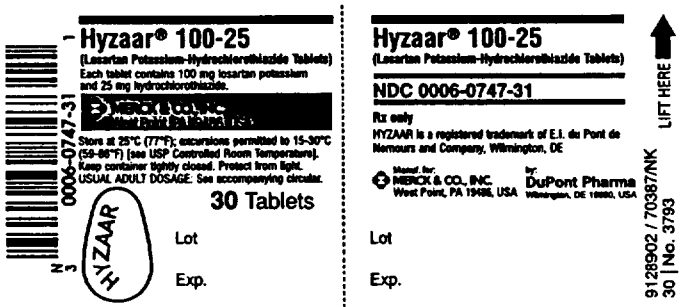

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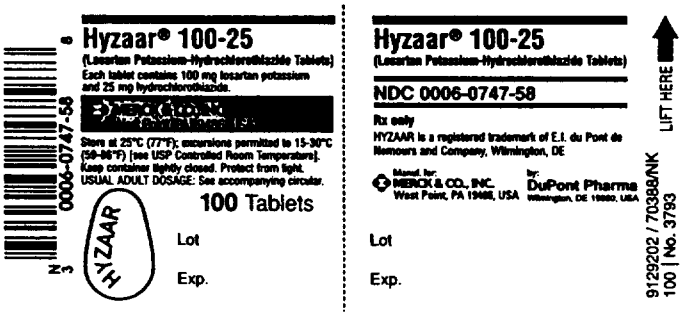

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NDA 20-387

Hyzaar® 100-25
(Losartan Potassium-Hydrochlorothiazide Tablets)

Each tablet contains 100 mg losartan potassium and 25 mg hydrochlorothiazide.
USUAL ADULT DOSAGE: See accompanying circular.
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.
This is a bulk package and not intended for dispensing.
HYZAAR is a registered trademark of
E.I. du Pont de Nemours and Company, Wilmington, DE

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HYZAAR
100 Tablets
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NDA 20-387

Hyzaar® 100-25

(Losartan Potassium-Hydrochlorothiazide Tablets)

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

DuPont Pharma
Wilmington, DE 19880, USA

Each tablet contains 100 mg losartan potassium and 25 mg hydrochlorothiazide.
USUAL ADULT DOSAGE: See accompanying circular.
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.
This is a bulk package and not intended for dispensing.
HYZAAR is a registered trademark of
E.I. du Pont de Nemours and Company, Wilmington, DE

9129601
70390/NK

HYZAAR

100 Tablets

N 3 0006-0747-28 1

Hyzaar® 100-25

(Losartan Potassium-Hydrochlorothiazide Tablets)

NDC 0006-0747-28

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

DuPont Pharma
Wilmington, DE 19880, USA

Each tablet contains 100 mg losartan potassium and 25 mg hydrochlorothiazide.
Rx only

HYZAAR

100 | No. 3793

100 Tablets

N 3 0006-0747-28 1

APPROVED
NOV 10 1998

Labeling: Original
NDA No. 20387 Rec'd: 10-26-98
Reviewed by: KSm

11-10-98

NDA 20-387

Hyzaar® 100-25

(Losartan Potassium-Hydrochlorothiazide Tablets)

Each tablet contains 100 mg losartan potassium and 25 mg hydrochlorothiazide.

MERCK & CO., Inc. / DuPont Pharma

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.

30 Tablets

Lot

Exp.

MRK 747

COMPLIMENTARY

USUAL ADULT DOSAGE:
See accompanying circular.

Rx only

HYZAAR is a registered trademark of E.I. du Pont de Nemours and Company, Wilmington, DE

5731

9152701 / 70420/NK
30 | No. 3793

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-387/S-008

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

MAY 1 1998

MAY - 4 1998

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-387 (Supplement SCF-008) **SUBMISSION DATES:** February 10, 1998
HYZAAR® (Losartan Potassium/Hydrochlorothiazide) April 20, 1998
Tablets (50-12.5 & 100-25 mg)

MERCK RESEARCH LABORATORIES. **REVIEWER:** Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: NDA SUPPLEMENT

BACKGROUND. HYZAAR® is a combination tablet consisting of losartan (an angiotensin II receptor antagonist) and hydrochlorothiazide (HCTZ) approved for the treatment of hypertension. The approved strength contains losartan 50 mg and HCTZ 12.5 mg but the sponsor has requested for the approval of a new strength (100-25 mg) of the combination tablet which is exactly compositionally proportional to the approved strength (see appendix). The sponsor was requested to submit comparative dissolution data in three media (water, acid and phosphate buffer) for the approved and the proposed strength of HYZAAR® tablets and this has now been submitted to the Agency. The labeling has been up-dated with the addition of the new strength of HYZAAR® tablet.

SYNOPSIS:
The dissolution data submitted by the sponsor are summarized in Tables 1-6 and Figures 1-6 while Figures 7-8 show the effect of pH on the solubility of losartan and HCTZ (attached).
The similarity values (f2) for the three media are:
Water - 45.6 for losartan and 45.9 for HCTZ
0.1N HCl - 52.3 for losartan and 57.3 for HCTZ
Phosphate Buffer, pH 6.5 - 45.3 for losartan and 44.5 for HCTZ
The lower f2 values for losartan and HCTZ in water and phosphate buffer may be due to the high variability of the dissolution data at 5, 15 and 20 minutes time points. The sponsor argues that the difference observed in the dissolution data at 5, 15, and 20 minutes in water and buffer is due to the lower surface area to mass ratio for the 100-25 mg tablet compared to the 50-12.5 mg tablet. The increase in time for dissolution in 0.1N HCl is due to pH-solubility characteristics of losartan which led to a decrease in the rate of erosion of the tablet in acid medium. The Tmax for losartan and its active metabolite are approximately 1 and 4 hours respectively while that of HCTZ is about 1 hour. The two tablet formulations are exactly compositionally proportional and the f2 value in 0.1N HCl (a physiologically more relevant medium) is greater than 50%. It is therefore unlikely that the difference in dissolution in the early time points (minutes) will have any significant impact on the in vivo bioavailability of the new strength of HYZAAR® tablet.

COMMENTS TO BE SENT TO THE FIRM:

DISSOLUTION: Based on the dissolution data submitted by the sponsor, the approved dissolution medium and specifications should be:
Medium:
Method:
Specifications:

CONCLUSION:
The Division of Pharmaceutical Evaluation I has reviewed the sponsor's supplement to the NDA and recommends the approval of a new strength of HYZAAR® tablets (100-25 mg) with the dissolution specifications of Q= % at min for losartan, Q= % at min for HCTZ.

/S/ 5/1/98

Emmanuel O. Fadiran, Ph.D.
Division of Pharmaceutical Evaluation I

/S/

FT Initialed by A. Parekh, Ph.D. ---------- 5/4/98

cc: NDA 20-387, HFD-110, HFD-860 (Fadiran), Short (Chemist Team Leader, HFD-110), CDR (Attn: Barbara Murphy).

COMPOSITION OF THE FORMULATIONS

Market Composition

Ingredient	mg/tablet 100/25	50/12.5
Tablet Core		
✓ Losartan Potassium		
✓ Hydrochlorothiazide USP		
✓ Microcrystalline Cellulose (Avicel PH102) NF		
✓ Lactose Hydrous (Fast Flo) NF		
✓ Pregelatinized Starch 1500 NF		
✓ Magnesium Stearate Impalpable Powder NF		
Uncoated Tablet Weight (mg)		
Tablet Coat[1]		
✓ Yellow Coating Color Concentrate Powder		
Purified Water USP[2]		
Film-coated Tablet Weight (mg)		

1 Excess prepared to account for losses during the film-coating process.
2 Removed during processing.

Table 1. Individual Losartan Potassium Dissolution Results for Tablets HYZAAR Using 0.1N HCl

Losartan Potassium, % Dissolved (of Label Claim)												
	50/12.5 mg Strength Tablet						100/25 mg Strength Tablet					
Sample	15 min	30 min	45 min	60 min	120 min	180 min	15 min	30 min	45 min	60 min	120 min	180 min
1												
2												
3												
4												
5												
6												
Mean	6	13	20	29	59	88	4	10	16	22	43	76

Table 2. Individual HCTZ Dissolution Results for Tablets HYZAAR Using 0.1N HCl

Hydrochlorothiazide, % Dissolved (of Label Claim)												
	50/12.5 mg Strength Tablet						100/25 mg Strength Tablet					
Sample	15 min	30 min	45 min	60 min	120 min	180 min	15 min	30 min	45 min	60 min	120 min	180 min
1												
2												
3												
4												
5												
6												
Mean	4	12	22	32	63	85	3	10	18	26	51	75

Figure 1 Comparative Dissolution Profile for Tablets HYZAAR - Losartan Potassium 0.1N HCl

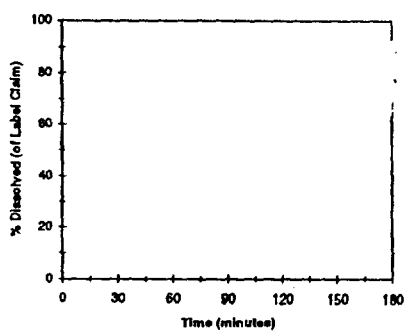
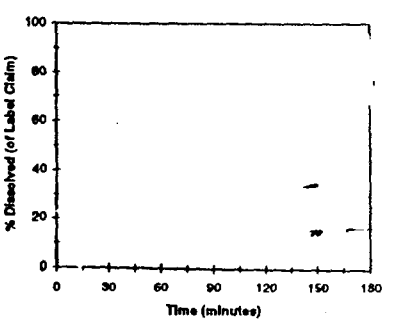


Figure 2 Comparative Dissolution Profile for Tablets HYZAAR - Hydrochlorothiazide 0.1N HCl



◆ 50/12.5 mg Tablet
□ 100/25 mg Tablet

Table 3 Individual Losartan Potassium Dissolution Results for Tablets HYZAAR Using Water

Losartan Potassium, % Dissolved (of Label Claim)												
	50/12.5 mg Strength Tablet						100/25 mg Strength Tablet					
Sample	5 min	15 min	20 min	30 min	45 min	60 min	5 min	15 min	20 min	30 min	45 min	60 min
1												
2												
3												
4												
5												
6												
Mean	15	77	96	99	99	99	8	55	77	99	100	99

Table 4 Individual HCTZ Dissolution Results for Tablets HYZAAR Using Water

Hydrochlorothiazide, % Dissolved (of Label Claim)												
	50/12.5 mg Strength Tablet						100/25 mg Strength Tablet					
Sample	5 min	15 min	20 min	30 min	45 min	60 min	5 min	15 min	20 min	30 min	45 min	60 min
1												
2												
3												
4												
5												
6												
Mean	10	66	85	91	93	94	5	46	65	87	90	90

Figure 3 Comparative Dissolution Profile for Tablets HYZAAR - Losartan Potassium Water

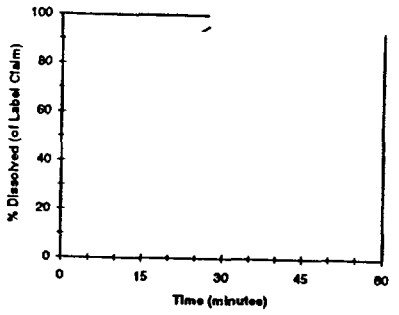
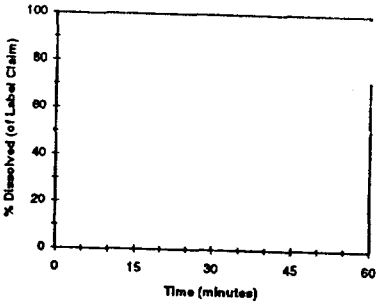


Figure 4 Comparative Dissolution Profile for Tablets HYZAAR - Hydrochlorothiazide Water



◆ 50/12.5 mg Tablet
□ 100/25 mg Tablet

Table 5 Individual Losartan Potassium Dissolution Results for Tablets HYZAAR Using USP Phosphate Buffer pH 6.5

Losartan Potassium, % Dissolved (of Label Claim)												
	50/12.5 mg Strength Tablet						100/25 mg Strength Tablet					
Sample	5 min	15 min	20 min	30 min	45 min	60 min	5 min	15 min	20 min	30 min	45 min	60 min
1												
2												
3												
4												
5												
6												
Mean	16	76	97	99	99	99	10	55	76	98	99	99

Table 6 Individual HCTZ Dissolution Results for Tablets HYZAAR Using USP Phosphate Buffer 6.5

Hydrochlorothiazide, % Dissolved (of Label Claim)												
	50/12.5 mg Strength Tablet						100/25 mg Strength Tablet					
Sample	5 min	15 min	20 min	30 min	45 min	60 min	5 min	15 min	20 min	30 min	45 min	60 min
1												
2												
3												
4												
5												
6												
Mean	11	65	84	90	91	92	6	44	63	84	86	87

Figure 5 Comparative Dissolution Profile for Tablets HYZAAR - Losartan Potassium USP Phosphate Buffer pH 6.5

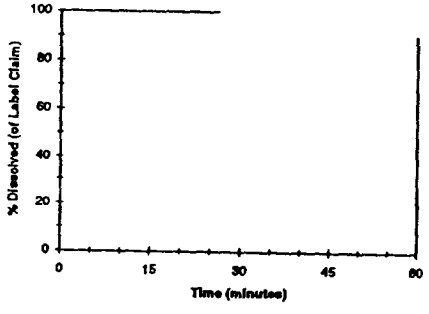
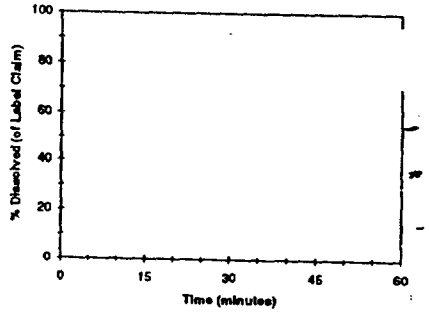


Figure 6 Comparative Dissolution Profile for Tablets HYZAAR - Hydrochlorothiazide USP Phosphate Buffer pH 6.5



◆ 50/12.5 mg Tablet
□ 100/25 mg Tablet

Figure 7 Dependence of Losartan Potassium Solubility on pH

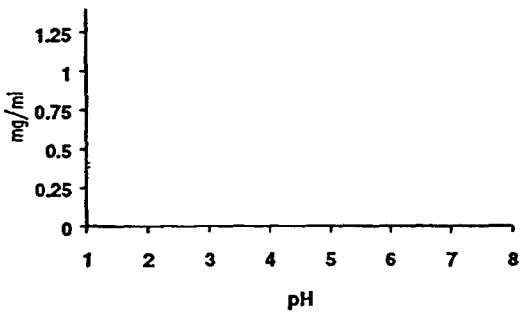
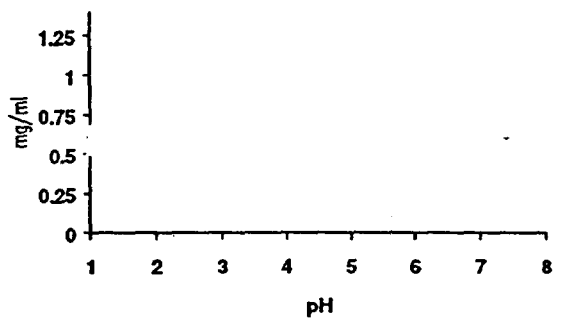


Figure 8 Dependence of Hydrochlorothiazide Solubility on pH



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-387/S-008

CHEMISTRY REVIEW(S)

OCT 26 1998

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-387/S-008 **REVIEW DATE:** 23-OCT-98

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SCF-008(AL) (Amendment)	11-SEP-98	15-SEP-98	15-SEP-98

NAME & ADDRESS OF APPLICANT

Merck Research Laboratories
Merck & Co. Inc.
West Point, PA 19486 **Telephone:** 610-397-2310

DRUG PRODUCT NAME

Proprietary:	HYZAAR
Nonproprietary/USAN:	Losartan Potassium Tablets/Hydrochlorothiazide
Code Name/#:	MK-954; DuP-753; 1-158,086; L-158,086-005H;E-3340
Chem.Type/Ther.Class:	1S

Amendment to Supplement Provides For:

dissolution specifications and revision of the labeling and storage statements in the package circular in response to the Agency's approvable letter of August 10, 1998.

PHARMACOL.CATEGORY/INDICATION:

An angiotensin II receptor agonist; said to reduce systolic and diastolic blood pressure in patients with mild to moderate essential hypertension.

DOSAGE FORM: Film coated tablets

STRENGTH: 50 mg Losartan Potassium Tablets/12.5 mg Hydrochlorothiazide

ROUTE OF ADMINISTRATION: ORAL

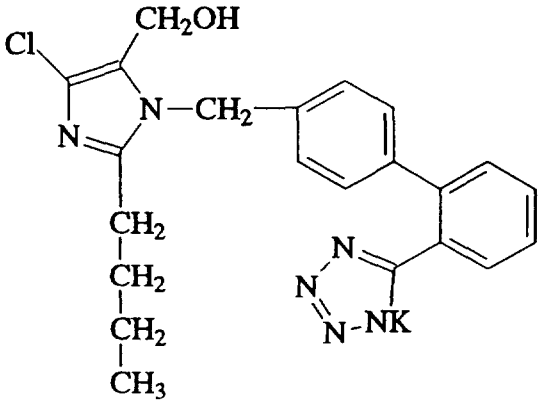
DISPENSED: Rx

DRUG SUBSTANCE 1. LOSARTAN POTASSIUM

CHEMICAL NAME: 2-butyl-4-chloro-1[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]-methyl]-1H-imidazole-5-methanol, monopotassium salt.

CAS #: 124750-99-8 **MOLECULAR FORMULA:** $C_{22}H_{22}ClKN_6O$ **MOLECULAR WEIGHT:** 461.01

STRUCTURAL FORMULA:

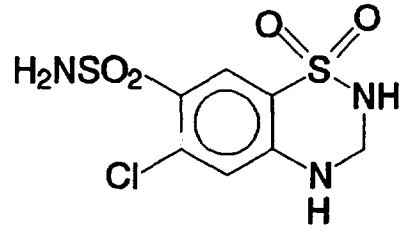


DRUG SUBSTANCE 2. HYDROCHLOROTHIAZIDE

CHEMICAL NAME: 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

CAS #: 58-93-5 **MOLECULAR FORMULA:** $C_7H_8ClN_3O_4S_2$ **MOLECULAR WEIGHT:** 297.74

STRUCTURAL FORMULA:



REMARKS/COMMENTS:

Storage statement in the Paste-up of the circular, carton and container labels is acceptable.

The circular has been revised as requested. The has been deleted from the proprietary name in the package insert and from all carton and container labeling. The has been deleted from the logo on the carton and container labels as requested.

CONCLUSIONS & RECOMMENDATIONS:

Satisfactory. The supplement may be approved.

cc:
Orig. NDA
HFD-110/Division File
HFD-110/Ram Mittal/date
HFD-110/CSO
R/D Init by: KS/ /S/ 10-23-98

/S/

Ramsharan D. Mittal Ph.D., Review Chemist
filename: C:\NDA\20387\20387AL.008

AUG - 6 1998

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-387/S-008 **REVIEW DATE:** 22-MAY-98 **REVISED DATE:** 04-AUG-98

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SCF-008	10-FEB-98	11-FEB-98	17-FEB-98
SCF-008(BC)	20-APR-98	21-APR-98	27-APR-98
SCF-008(BL)	19-JUN-98	22-JUN-98	24-JUN-98
SCF-008(BL)	15-JUL-98	22-JUL-98	27-JUL-98
SCF-008(BL)	20-JUL-98	21-JUL-98	27-JUL-98

NAME & ADDRESS OF APPLICANT

Merck Research Laboratories
Merck & Co. Inc.
West Point, PA 19486 **Telephone:** 610-397-2310

DRUG PRODUCT NAME

Proprietary:	HYZAAR
Nonproprietary/USAN:	Losartan Potassium Tablets/Hydrochlorothiazide
Code Name/#:	MK-954; DuP-753; 1-158,086; L-158,086-005H;E-3340
Chem.Type/Ther.Class:	1S

Supplement Provides For:

the approval of a new strength 100/25 mg of the combination tablet.

PHARMACOL.CATEGORY/INDICATION:

An angiotensin II receptor agonist; said to reduce systolic and diastolic blood pressure in patients with mild to moderate essential hypertension.

DOSAGE FORM: Film coated tablets

STRENGTH: 50 mg Losartan Potassium Tablets/12.5 mg Hydrochlorothiazide

ROUTE OF ADMINISTRATION: ORAL

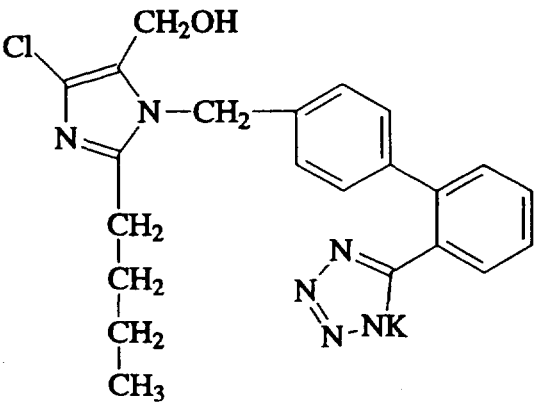
DISPENSED: Rx

DRUG SUBSTANCE 1. LOSARTAN POTASSIUM

CHEMICAL NAME: 2-butyl-4-chloro-1[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]-methyl]-1H-imidazole-5-methanol, monopotassium salt.

CAS #: 124750-99-8 **MOLECULAR FORMULA:** $C_{22}H_{22}ClKN_6O$ **MOLECULAR WEIGHT:** 461.01

STRUCTURAL FORMULA:

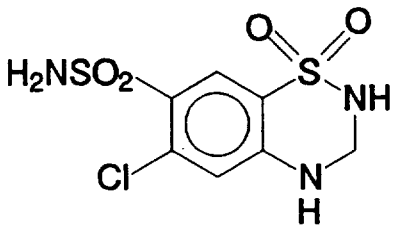


DRUG SUBSTANCE 2. HYDROCHLOROTHIAZIDE

CHEMICAL NAME: 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

CAS #: 58-93-5 **MOLECULAR FORMULA:** $C_7H_8ClN_3O_4S_2$ **MOLECULAR WEIGHT:** 297.74

STRUCTURAL FORMULA:



REMARKS/COMMENTS:

See comments and recommendations for storage statements. Regarding HYZAAR on the label and cartons the Labeling and Nomenclature Committee (LNC) has informed that as a proprietary name and on the labels is unacceptable.

CONCLUSIONS & RECOMMENDATIONS:

The applicant should be requested to consider using the following storage statement in the "How Supplied" section of the Package Insert and on the immediate container labels:

"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"

If space on the immediate container is limited, either of the following statements is acceptable provided the full statement (as above) appears on the outer carton and in the package insert:

"Store at 25°C(77°F); excursions 15-30°C(59-86°F). Keep container tightly closed. Protect from light"

or

"Store at 25°C(77°F); (see insert). Keep container tightly closed. Protect from light"

A review by Biopharm (Division of Pharmaceutical Evaluation I) has recommended the following dissolution specifications:

Based on the dissolution data submitted by the applicant, the approved dissolution medium and specifications should be:

Medium:
Method:
Specifications:

The application is approvable except for the use of "DS" and "AA" on the carton and labels.

cc:
Orig. NDA
HFD-110/Division File
HFD-110/Ram Mittal/date
HFD-110/CSO
R/D Init by: KS/

/S/
8-5-98

/S/

Ramsharan D. Mittal Ph.D., Review Chemist
filename: C:\NDA\20387\20387SCF.008

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-387/S-008

ADMINISTRATIVE DOCUMENTS

NOV 10 1998

RHPM Review of Labeling

NDA: 20-387/S-008 Hyzaar (losartan potassium/HCTZ) Tablets

Date of submission: October 23, 1998

Date of receipt: October 26, 1998

Applicant: Merck Research Laboratories

Background: In response to our August 1998, 1998 approvable letter, Merck submitted revised draft labeling and agreed to the revised dissolution specification in a submission dated September 11, 1998. I called Jeffrey White, M.D. on October 19, 1998, and asked him to send in final printed labeling. The FPL came in a submission dated October 23, 1998.

Review: The submitted final printed labeling has been revised as follows:

DESCRIPTION:

Instead of "HYZAAR" followed by the generic name, the labeling now reads, "HYZAAR 50-12.5 (losartan potassium-hydrochlorothiazide tablets) HYZAAR 100-25 (losartan potassium-hydrochlorothiazide tablets)"

The first sentence now begins, "HYZAAR 50-12.5 (losartan potassium-hydrochlorothiazide tablets) and HYZAAR 100-25 ..."

The next-to-last paragraph now begins, "HYZAAR is available for oral administration in two tablet combinations of losartan and hydrochlorothiazide. HYZAAR 50-12.5 contains 50 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 ..."

The single sentence in the last paragraph has been revised to "HYZAAR 50-12.5 contains 4.24 mg (0.108 mEq) of potassium and HYZAAR 100-25 contains 8.48 mg (0.216 mEq) of potassium."

ADVERSE REACTIONS:

In the third paragraph, "HYZAAR" has been changed to "losartan-hydrochlorothiazide."

DOSAGE AND ADMINISTRATION, Dose Titration by Clinical Effect:

This subsection has been revised as follows (changes underlined to illustrate):

A patient whose blood pressure is not adequately controlled with losartan monotherapy (see above) 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 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.

HOW SUPPLIED:

Information on HYZAAR 100-25 has been added. The first sentence of the Storage subsection has been revised to read, "Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]."

Recommendation: I will prepare an approval letter for this supplement for Dr. Lipicky's signature. This supplement falls under 21 CFR 314.70 (b)(3) Supplements requiring FDA approval before the change is made.

/S/

Kathleen F. Bongiovanni 10.30.98

cc: NDA 20-387/S-008
HFD-110
HF-2/MedWatch
HFD-110/KBongiovanni
HFD-110/SBenton
kb/10/30/98.