CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-387/S-010

Approval Letter
Dear Dr. White:

Please refer to your July 14, 1998 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hyzaar (losartan potassium/hydrochlorothiazide) 50/12.5 mg Tablets.

This supplemental new drug application provides for final printed labeling revised as follows:

**CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug Interactions, Losartan Potassium:**
"Conversion of losartan to its active metabolite after intravenous administration is not affected by ketoconazole, an inhibitor of P450 3A4" has been added before the last sentence of this subsection.

**PRECAUTIONS, Information for Patients, Potassium Supplements:** a cross reference, "(see PRECAUTIONS, Drug Interactions, Losartan Potassium)" has been added.

**PRECAUTIONS, Drug Interactions, Losartan Potassium:** "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" has been added before the last sentence of this subsection.

The last sentence of this subsection has been revised to read "The pharmacodynamic consequences of concomitant use of losartan and inhibitors of P450 2C9 have not been examined."

The following has been added to the end of this subsection: "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)."

We have completed the review of this supplemental application 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 with your July 14, 1998 submission. Accordingly, the supplemental application is approved effective on the date of this letter.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.
If you have any questions, please contact:

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

Sincerely yours,

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/8/14/98;8/21/98
Initialed by: R Mittal/8/17/98
K Srinivasachar/8/18/98
A Proakis/8/18/98
C Resnick/8/19/98
K Knudsen/8/20/98
N Morgenstern/8/21/98

APPROVAL (AP)
CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-387/S-010

Final Printed Labeling
HYZAAR® (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/Natalional Morbidity and Mortality.

**DESCRIPTION**

HYZAAR® (Losartan potassium-hydrochlorothiazide) combines an angiotensin II receptor type AT1 antagonist and a diuretic, hydrochlorothiazide. Losartan potassium, a non-peptide molecule, is chemically described as 2-butylnicotinonitrile-5-carboxylic acid 1-ethyl-5-sulfonylbenzimidazol 5-methanone monopotassium salt. Its empirical formula is C_{17}H_{17}N_{3}O_{5}K, and its structural formula is:

![Chemical Structure of Losartan](image)

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 alcohol, and slightly soluble in common organic solvents, such as acetone and methyl ethyl ketone.

Hydrochlorothiazide is 8-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamido-1,1-dioxide. Its empirical formula is C_{17}H_{12}ClN_{3}O_{3}S, and its structural formula is:

![Chemical Structure of Hydrochlorothiazide](image)

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 containing 50 mg of losartan potassium, 12.5 mg of hydrochlorothiazide and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, pregelatinized starch, magnesium stearate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, talc, titanium dioxide and DMC, yellow No. 10 dye.

**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 vasconstrictor, 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 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 (diuretic), 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 mechanism of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equal 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 renal 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 accumulates in plasma upon once-daily dosing.

Following oral administration, losartan is well absorbed (about 90%) on a meal. Losartan is extensively metabolized 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 concentration 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 small amount of unabsorbed losartan excreted in the urine increases its Cmax but has only minor effects on losartan AUC or on the AUC of the metabolite (about 10%).

Both losartan and its active metabolites are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1% and 0.2%, respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed. Following oral and intravenous administration of [14C]-labeled losartan potassium, circulating plasma radiolucency 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) is contributed 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 560 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. About 60% of the dose is eliminated in the feces following an intravenous dose of [14C]-labeled losartan. About 4% of radioactivity is recovered in the urine within 50 hours after oral administration.

**Special Populations**

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

Geriatric: Losartan pharmacokinetics have been investigated in 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. Plasma concentrations of losartan are lower in patients with lower creatinine clearance. Plasma concentrations of the active metabolite are similar in male and female.

Race: Losartan 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 slightly altered in patients with renal impairment or on hemodialysis patients. Neither losartan nor its active metabolite can be removed by hemodialysis.

Hepatic Insufficiency: Following first 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 lowest 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. Co-administration 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. Co-administration 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 CYP3A4. 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 5.1 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 II infusions. A dose of 100 mg inhibits the pressor effect by about 85% at peak with 25-40% inhibition persisting for 24 hours. Removal of the negative feedback of 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 or AII, whereas ACE inhibitors increase the responses 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 primarily 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 1975 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 5.5-10.0/3.5-7.5 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 55-80% 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
HYZAAR® (Losartan Potassium-Hydrochlorothiazide Tablets)

placebo (one study, n=9) to 25 mg hydrochlorothiazide (n=120). The double-blind treatment period lasted up to 8 weeks. The incidence of cough is shown below.

<table>
<thead>
<tr>
<th>Study 1</th>
<th>Placebo</th>
<th>Losartan</th>
<th>Lisinopril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>26%</td>
<td>17%</td>
<td>6%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study 2</th>
<th>Placebo</th>
<th>Losartan</th>
<th>Lisinopril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>36%</td>
<td>19%</td>
<td>6%</td>
</tr>
</tbody>
</table>

These studies demonstrate that the incidence of cough associated with Lisinopril, 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 2 controlled studies of Losartan and hydrochlorothiazide included over 1300 patients and did not indicate the antihypertensive efficacy of various doses of Losartan (25, 50 and 100 mg) and concomitant Hydrochlorothiazide (25, 12.5 and 25 mg).

A factorial study compared the combination of Losartan/ hydrochlorothiazide 25/12.5 mg vs. its components and placebo. The combination of Losartan/Hydrochlorothiazide 50/12.5 mg resulted in an approximately additive placebo-adjusted systolic blood pressure reduction of 5.7/0.3 mmHg for the combination compared to 8.5/0.6 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 (25, 12.5 and 25 mg) and placebo on a background of Losartan (50 mg) in patients not adequately controlled (SBP 95-120 mmHg) of Losartan (50 mg) alone.

The third study investigated the dose-response relationship of various doses of Losartan (25, 50 and 100 mg) and placebo on a background of hydrochlorothiazide (25 mg) in patients not adequately controlled (SBP 93-120 mmHg) of Losartan (50 mg) alone. These studies showed an added antihypertensive response at trough 24 hours post-dosing of hydrochlorothiazide 12.5 or 25 mg added to Lisartan 50 mg of 5.0/3.5 and 10.6/3.0 mmHg, respectively. Similarly, there was an added antihypertensive response at trough 24 hours post-dosing of losartan 50 or 100 mg added to hydrochlorothiazide 25 mg of 9.0/5.0 and 17.5/6.5 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 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 hypotension or to other sulfonamides derived drugs.

WARNING:

FetalNeonatal 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. Dipyridamolism has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios as this has been associated with fetal limb contractures, craniofacial deformations, and hypotrophic lung development. Prematurity, immature lung 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 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 pregnancy becomes apparent, physicians should have the patient discontinue the use of HYZAAR as soon as possible.

Maternal deaths have been reported in patients treated with angiotensin II receptor antagonists. While these reports suggest the potential for angiotensin II receptor antagonists to cause fetal harm, there is no evidence that this is the case with HYZAAR.

Hypersensitivity Reaction

HYZAAR may cause angioneurotic edema in patients with a history of angioneurotic edema.

Hypersensitivity to angiotensin II receptor antagonists may be caused either by direct exposure or by cross-reactivity with another angiotensin II receptor antagonist. However, the frequency of this type of reaction has been low. Patients who have experienced an anaphylactoid reaction to angiotensin II receptor antagonists should not be treated with HYZAAR.

Lithium Interaction

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

PRECAUTIONS

General

Losartan Potassium-Hydrochlorothiazide

In double-blind, placebo-controlled trials, the incidence of hyperkalemia in patients who received Losartan potassium and Hydrochlorothiazide, the incidence of hyperkalemia in patients who received Losartan potassium and Hydrochlorothiazide, was 0.1%. In patients treated with various doses of Losartan and hydrochlorothiazide, the incidence of hyperkalemia was 0.1%. In patients treated with various doses of Losartan and hydrochlorothiazide, there was also a dose-related decrease in the hyperkalemic response to hydrochlorothiazide as the dose of Losartan is increased. Following a single dose of Losartan, the response of serum potassium to a single dose of hydrochlorothiazide is reduced.

Periodic monitoring 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: hypokalemia, hyponatremia, hypochloremic alkalosis, and hyponatremia. Serum and urine electrolyte determinations are particularly important when the patient has been on a non-sodium-excessive diet, is taking diuretics, or is receiving parenteral fluids. Warning signs of symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness...
HYZAR® (Losartan Potassium-Hydrochlorothiazide Tablets)


drug of mouth, thirst, lethargy, drowsiness, restlessness, confusion, seizures, muscle pain or cramps, muscle fatigue, hypertension, oliguria, lactic acidosis, and gastrointesti- nal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brucellosis, when severe cuminum is present or after prolonged therapy. Isotonic glucose and electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmias and may also cause or exacerbate the sharing of the heart to the toxic effects of digitals (e.g., increased ven- tricular irritability).

Although any chloride deficiency 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 hypokalemia may occur in edematous patients in hot weather, appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hypernatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice—additive effect or potentiation

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of the heart to the toxic effects of digitals (e.g., increased ven- tricular irritability).
Dosage/Frequency
At 100 mg/day only a decrease in the number of corpus lutea was observed. The relationship of these findings to drug treatment is uncertain since there was no effect at these dosage levels on implantation, conceptus size, or live animal/ litter size. 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 male mice (at doses of up to approximately 500 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 hepatic adenocarcinoma 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 linked recessive lethality gene. Positive test results were obtained only in the in vitro CHO Sister Chromatid Exchange (SCE) test and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1200 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 Category 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 HYZAR, 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 drug 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 the therapy. In controlled clinical trials, discontinuation of therapy due to clinical adverse experiences was required in only 2.8% and 2.5% of patients treated with the combination and placebo, respectively.

In these double-blind controlled clinical trials, the following adverse experiences reported with HYZAR occurred in 24 percent of patients, and more often on drug than placebo, regardless of drug relationship:

<table>
<thead>
<tr>
<th>Losartan Potassium-Hydrochlorothiazide (n=858)</th>
<th>Placebo (n=173)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body as a Whole</strong></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1.2</td>
</tr>
<tr>
<td>Edema/edema swelling</td>
<td>1.3</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
</tr>
<tr>
<td>Palpitation</td>
<td>1.4</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>2.1</td>
</tr>
<tr>
<td>Nervous/Psychiatric</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5.7</td>
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<tr>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
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<td>1.2</td>
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<td>6.1</td>
</tr>
<tr>
<td>Infection</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>1.4</td>
</tr>
</tbody>
</table>
HYZAAPR (Lesotan Potassium-Hydrochlorothiazide Tablets)

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 penicil- lins, 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 events, 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, arthrythmia including atrial fibrillation, sinus bradycardia, tachycardia, venous tachycardia and venous tachycardia in ischemia, CHF, hypotension, myocardial infarction, second degree AV block, Digestive: anorexia, constipation, dental pain, dry mouth, dyspepsia, Retention, gas, vomiting; Hematologic: anemia, Metabolic: goit, Musculoskeletal: arm pain, arthralgia, arthritis, fibromyalgia, hip pain, joint swelling, knee pain, leg pain, muscle cramps, muscle weakness, musculocontractual pain, myalgia, shoulder pain, stiffness; Nervous: Systmnaic: Psychiatric: anxiety, anxiety disorders, ataxia, confusion, depression, dream abnormalities, hypotension, insomnia, sleep disorders, decreased memory impairment, migraine, nervousness, panic disorder, parasthesia, peripheral neuropathy, sleep disorders, somno-

- lence, tremor, vertigo; Respiratory: dyspnea, epistaxis, nasal congestion, pharyngodynia, respiratory depression, rhinitis, sinus disorder; Skin: alopecia, dermatitis, dry skin, eczema, pruritus, rash, flushing, photosensitivity, pruritus, sweating, urticaria, Special Senses: blurred vision, burning, stinging in the eye, conjunctivitis, decreased in visual acuity, taste perversion, tinnitus; Urogenital: impotence, nocturia, urinary frequency, urinary tract infection.

Hydrochlorothiazide

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

Body: As a Whole: weakness, Digestive: pancreatitis, jaun-


ice, diarreheic cholestatic hepatitis, ulcers, dyspepsia, cramp-


ing, gastric irritation; Hematologic: aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocyto-


penia, Hypersensitivity: purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cataracts, vascularitis), fever, respiratory distress including pneumonitis and pulmo-


nary edema, anaphylactic reactions, metabolic hyperglyce-


mia, glositis, hyperuricemia, Musculoskeletal: muscle spasm; Nervous System/Psychiatric: restlessness; Renal: renal failure, renal dysfunction, interstitial nephritis, skin: eczema 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 involving 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 HYZAAPR.

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in 0.6 to 1.0 percent, respectively, of patients with essential hypertension treated with HYZAAPR alone. No patient discontinued taking HYZAAPR due to increased BUN. One patient discontinued taking HYZAAPR due to a minor increase in serum creatine.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit levels were observed in 0.1 to 0.7 percent, respectively, of patients treated with HYZAAPR 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 HYZAAPR alone, no patients were discontinued due to these laboratory adverse experiences.

Serum Electrolytes: See PRECAUTIONS.

OVERDOSE

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 112 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 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, hyporetenional and dehydration resulting from excessive diuresis. It digitally has also been administered, hypokalemia may accentuate cardiac arrhyth-


mias. 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). Hypertension - Volume Depleted 'Patients' and patients with a history of hepatic impairment (see WARNINGS).

Losartan can be administered once or twice daily at total daily doses of 25 to 100 mg. If the antihypertensive effect was measured at trough using once a day dosing is inadequate, a twice a day regimen at the same antihypertensive dose may be given a more satisfactory response.

Hydrochlorothiazide is effective in doses of 12.5 to 100 mg once daily and can be given at doses of 12.5 to 25 mg as HYZAAPR. 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 hydrochlo-


rothiazide are a mixture of dose-dependent primarily hypokalemic and volume depletion, and volume independent (e.g., pancreatitis), the former 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 monother-


apy (see above) may be switched to HYZAAPR (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 100 mg/25 mg.

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 HYZAAPR (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 HYZAAPR should be dose-


quently evaluated and if blood pressure remains uncontrolled after 1 to 2 additional weeks of therapy, the dose may be increased to 100 mg/25 mg once daily.

The usual starting dose of HYZAAPR is one tablet once daily. More than two tablets 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 HYZAAPR 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 HYZAAPR is not recommended.

Patient Coadministration: Patients not taking HYZAAPR are not recom-


mended for titration in patients with hepatic impairment (see WARNINGS). Impaired Hepatic Function because the appro-


priate 25 mg starting dose of losartan cannot be given.

HYZAAPR may be administered with or without food.
CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-387/S-010

Administrative Documents
RHPM Review of Labeling

NDA: 20-387/S-010  Hyzaar (losartan potassium/HCTZ) Tablets

Date of submission: July 14, 1998

Date of receipt: July 16, 1998

Applicant: Merck Research Laboratories

**Background:** Merck has submitted final printed labeling as a "Special Supplement – Changes Being Effected." The cover letter notes that the revised labeling will be used on or before November 1, 1998.

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

CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug Interactions, Losartan Potassium: "Conversion of losartan to its active metabolite after intravenous administration is not affected by ketoconazole, an inhibitor of P450 3A4" has been added before the last sentence of this subsection.

PRECAUTIONS, Information for Patients, Potassium Supplements: a cross reference, "(see PRECAUTIONS, Drug Interactions, Losartan Potassium)" has been added.

PRECAUTIONS, Drug Interactions, Losartan Potassium: "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" has been added before the last sentence of this subsection. The last sentence of this subsection has been revised to read "The pharmacodynamic consequences of concomitant use of losartan and inhibitors of P450 2C9 have not been examined."

The following has been added to the end of this subsection: "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)."

**Recommendation:** I will prepare an approval letter for this supplement for Dr. Lipicky's signature, pending the Medical Officer's review of the acceptability of the revisions. This supplement falls under 21 CFR 314.70 (c), Supplements for changes that may be made before FDA approval.

Kathleen F. Bongiovanni

cc: NDA 20-386/S-014
    HFD-110
    HF-2/MedWatch
    HFD-110/KBongiovanni
    HFD-110/SBenton

kb/7/23/98.