CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 20386/S-007 AND 20387/S-005

Trade Name: COZAAR AND HYZAAR

Generic Name: LOSARTAN POTASSIUM
LOSARTAN POTASSIUM & HYDROCHLOROTHIAZIDE

Sponsor: MERCK RESEARCH LABORATORIES

Approval Date: NOVEMBER 7, 1997
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20386/S-007 AND 20387/S-005

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

Dear Dr. Bell:

Please refer to your April 17, 1997 supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cozaar (losartan potassium) 25 and 50 mg Tablets (NDA 20-386) and Hyzaar (losartan potassium/hydrochlorothiazide) 50/12.5 mg Tablets (NDA 20-387)

The supplemental applications provide for final printed labeling revised as follows:

ADVERSE REACTIONS, Post-Marketing Experience, Hypersensitivity: "pharynx" has been added to the following: "Angioedema (involving swelling of the face, lips, pharynx, and/or tongue) has been reported rarely in patients treated with losartan."

ADVERSE REACTIONS, Post-Marketing Experience: The sentence "Hyperkalemia has been reported." has been added to the end of this subsection.

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drugs are safe and effective for use as recommended in the final printed labeling included with your April 17, 1997 submission. Accordingly, the supplemental applications are 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:

Original NDA
HFD-110
HF-2/MedWatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-813/OGD (with labeling)
HFD-735/DPE (with labeling)
DISTRICT OFFICE
HFD-810/ONDG Division Director
HFI-20/Press Office (with labeling)
HFD-110/KBongiovanni
sb/10/27/97; 11/8/97
R/D: KKnüdser/10/28/97
NStockbridge/10/28/97
CGanley/10/29/97
RMittal/10/29/97
RWolters/10/29/97
AProskla/10/29/97
CResnick/10/29/97
NMorgenstern/11/5/97

Approval Date: 20-386 - 4/14/95
20-387 - 4/28/95

APPROVAL (AP)
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20386/S-007 AND
20387/S-005

FINAL PRINTED LABELING
COZAAR®

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 death to the developing fetus. When pregnancy is detected, COZAAR® should be discontinued as soon as possible. See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION
COZAAR® (losartan potassium), the first of a new class of angiotensin II receptor antagonist, is an angiotensin II receptor (type AT1) antagonist. Losartan potassium, a non-peptide molecule, is chemically described as 3,5-dihydroxy-2-(1-p-[1-(2-tetrazolyl)phenyl]ethylaminol)-4-methylphenylsulfonamide. The empirical formula is C25H28N4O5S, and its structural formula is:

\[
\text{CH}_3\text{COCH}_2\text{CH}(_2)\text{NH}(_2)\text{COOH}\]

Losartan potassium is a white to off-white, free-flowing crystalline powder, with a molecular weight of 465.5. It is freely soluble in water, soluble in ethanol, and slightly soluble in common organic solvents, such as methanol and ethyl acetate.

CLINICAL PHARMACOLOGY
Mechanism of Action
Angiotensin II (formed from angiotensin I) is a potent peptide vasoconstrictor of the renal-angiotensin system and an important component in the physiologic control of blood pressure. The renin-angiotensin system is the major regulatory mechanism for blood pressure. It is also an AT1 receptor antagonist. Losartan is not known to be associated with cardiovascular hemodynamics. Both losartan and its active metabolite block the vasoconstrictive and pressor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues, including vascular smooth muscle, atrial natriuretic factor, and adrenal gland. There is an AT1 receptor that is not known to be associated with cardiovascular hemodynamics. Both losartan and its active metabolite block the vasoconstrictive and pressor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues, including vascular smooth muscle, atrial natriuretic factor, and adrenal gland. Losartan also blocks the vasoconstrictive and pressor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues, including vascular smooth muscle, atrial natriuretic factor, and adrenal gland. Losartan also blocks the vasoconstrictive and pressor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues, including vascular smooth muscle, atrial natriuretic factor, and adrenal gland. Losartan also blocks the vasoconstrictive and pressor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues, including vascular smooth muscle, atrial natriuretic factor, and adrenal gland. Losartan also blocks the vasoconstrictive and pressor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues, including vascular smooth muscle, atrial natriuretic factor, and adrenal gland. Losartan also blocks the vasoconstrictive and pressor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues, including vascular smooth muscle, atrial natriuretic factor, and adrenal gland. Losartan also blocks the vasoconstrictive and pressor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues, including vascular smooth muscle, atrial natriuretic factor, and adrenal gland. Losartan also blocks the vasoconstrictive and pressor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues, including vascular smooth muscle, atrial natriuretic factor, and adrenal gland. Losartan also blocks the vasoconstrictive and pressor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues, including vascular smooth muscle, atrial natriuretic factor, and adrenal gland. Losartan also blocks the vasoconstrictive and pressor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues, including vascular smooth muscle, atrial natriuretic factor, and adrenal gland. Losartan also blocks the vasoconstrictive and pressor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues, including vascular smooth muscle, atrial natriuretic factor, and adrenal gland. Losartan also blocks the vasoconstrictive and pressor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues, including vascular smooth muscle, atrial natriuretic factor, and adrenal gland. Losartan also blocks the vasoconstrictive and pressor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues, including vascular smooth muscle, atrial natriuretic factor, and adrenal gland. Losartan also blocks the vasoconstrictive and pressor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues, including vascular smooth muscle, atrial natriuretic factor, and adrenal gland.

Effectiveness and Safety of the Active Metabolite
The effectiveness and safety of the active metabolite of losartan are similar to those of losartan. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).

Relevant Pharmacologic Differences due to Race
Relevant pharmacologic differences due to race have not been studied.

Drug Interactions
Losartan, administered alone or in combination with other antihypertensive agents, was well tolerated in patients with reduced renal function. Losartan can be administered concurrently with diuretics, beta blockers, calcium channel blockers, and other antihypertensive agents. Losartan was generally well tolerated in patients with impaired renal function. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).

Losartan, administered alone or in combination with other antihypertensive agents, was well tolerated in patients with reduced renal function. Losartan can be administered concurrently with diuretics, beta blockers, calcium channel blockers, and other antihypertensive agents. Losartan was generally well tolerated in patients with impaired renal function. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).
COZAAR® (Losartan Potassium Tablets)

Due to the effects 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 glomerular filtration fraction. In multiple dose studies in hypertensive patients, there were no notable effects on uric acid or renal prostaglandin concentrations, feeling tachycardia, total cholesterol or HDL-cholesterol or fasting glucose concentrations. There was a small uricosuric effect leading to a minimal decrease in serum uric acid (mean decrease 0.4 mg/dL) during chronic oral administration.

The antihypertensive effects of COZAAR were demonstrated 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 88-115. The studies allowed comparisons of two doses (50-100 mg) as once-daily or twice-daily regimens, comparisons of peak and trough effects, and comparisons of response by gender, age, and race. Three additional studies examined the antihypertensive effects of losartan and hydrochlorothiazide in combination.

The 4 studies of losartan monotherapy included a total of 1078 patients randomized to several doses of losartan and 86 to placebo. The 10 and 25 mg dose produced a peak 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 antihypertensive mean decreases in blood pressure, compared to placebo in the range of 5-10/5-8/5-7.2 mm Hg, 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 uniform, but moderately, larger than trough effects, with the trough-to-peak ratio for systolic and diastolic responses 50-65% and 50-60%, respectively.

Addition of a low dose of hydrochlorothiazide (12.5 mg) to losartan 80 mg once daily resulted in placebo-adjusted blood pressure reductions of 19.8/6.3 mm Hg.

Analyses 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 and 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 5 years. There is no apparent rebound effect after abrupt withdrawal of losartan. There was no evidence of change in average heart rate in losartan-treated patients in controlled trials.

Peripheral edema (with an incidence of a few percent) has been associated with ACE inhibitor use and in practice can be a source 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 80 mg, lisinopril 20 mg, or other placebo (one study, n=17) or 25 mg hydrochlorothiazide (0.125 mg). The double-blind treatment period lasted up to 6 weeks. The incidence of cough is shown below:

<table>
<thead>
<tr>
<th>Study 1</th>
<th>Cough</th>
<th>Cough</th>
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</thead>
<tbody>
<tr>
<td>HCTZ</td>
<td>25%</td>
<td>17%</td>
</tr>
<tr>
<td>Losartan</td>
<td>5%</td>
<td>9%</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>6%</td>
<td>3%</td>
</tr>
</tbody>
</table>

These studies demonstrate that the incidence of cough associated with losartan therapy, in a population that had cough associated with ACE inhibitor therapy, is similar to that associated with hydrochlorothiazide or placebo therapy.

INDICATIONS AND USAGE

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

In considering the use of monotherapy with COZAAR, it should be noted that in controlled trials COZAAR had an effect on blood pressure that was usually less in black patients than in non-blacks, a finding similar to the small effect of angiotensin converting enzyme inhibitors in blacks.

CONTRAINDICATIONS

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

WARNINGS

Fetal/Neonatal Morbidity and Mortality

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

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal death, and renal failure. Oral antihypertensive drugs should be discontinued at the first trimester of pregnancy.
COZAAR® (Losartan Potassium Tablets)

...also been reported, presumably resulting from decreased renal function; oligohydramnios in the setting has been associated with fetal limb contractures, cruciatio deformities, and hyperechogenic lung development. If oligohydramnios is noted and the patient is hemodynamically stable, serial ultrasound examinations should be performed to assess the intrauterine environment. If oligohydramnios is observed, COZAAR® should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), 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 irreparable 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, oliguria should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and substituting for dialyzed renal function.

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

Hypotension — Infants/Dependent Patients

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

PRECAUTIONS

General

Based on pharmacokinetic data that demonstrate significant lower urinary tract or kidney, and the evaluation of adverse effects in animal patients, a lower dose should be considered for patients with impaired liver function (see CLINICAL PHARMACOLOGY). COZAAR® is not recommended for use in patients with severe renal impairment (see CLINICAL PHARMACOLOGY). COZAAR® is contraindicated in patients with severe renal impairment (see CLINICAL PHARMACOLOGY).

Hypersensitivity: See ADVERSE REACTIONS, Post-Marketing Experience.

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-allele system, changes in renal function have been noted in patients taking COZAAR®. In susceptible individuals treated with COZAAR®, a decrease in glomerular filtration rate (GFR) and creatinine clearance have been observed (see CLINICAL PHARMACOLOGY). These decreases in GFR and creatinine clearance have been reversible upon discontinuation of therapy.

In patients whose renal function may depend on the activity of the renin-angiotensin-allele system (e.g., patients with severe congestive heart failure, treatment with angiotensin-converting enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and death. Similar experiences have been reported with COZAAR®. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or BUN have been reported. For patients already taking COZAAR® in some patients, these effects were reversible upon discontinuation of therapy.

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 advised to report pregnancy to their physicians as soon as possible.

Drug Interactions

No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, donepezil, and phenytoin. (See CLINICAL PHARMACOLOGY, Drug Interactions.) Potent inhibitors of cytochromes P450 3A4 and 2C19 have not been studied clinically, but in vitro studies show significant inhibition of the formation of the active metabolites by inhibitors of P450 3A4 (cyclosporin, tacrolimus, gabapentin, and P450 2C19 (fluconazole, sulfamethoxazole and trimethoprim, and ketoconazole). The pharmacodynamic consequences of concomitant use of losartan and these inhibitors have not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Losartan potassium was not carcinogenic when administered orally to rats and mice at dose levels up to 150 and 25 mg/kg, respectively. Female rats given the highest dose (770 mg/kg/day) had a slightly higher incidence of pulmonary tumors when compared with control animals and the differences were statistically significant only in females. No significant differences in body weight gain in rats. 250 mg/kg in mice) provided systemic exposures for losartan and its pharmacologically active metabolites that were approximately 100- and 50-times (based on AUC for the metabolite) the exposure of a 69 kg human given 100 mg per day.

Losartan potassium was negative in the microbial mutagenesis and in vitro mammalian cell mutation assays and in the in vivo male mouse micronucleus assay and in the in vivo rat and hamster chromosomal aberration assays. In addition, the active metabolites showed no evidence of genotoxicity in the in vitro bacterial and in vivo mammalian chromosome aberration assay.

Fertility and reproductive performance were not affected in studies with male rats given doses of losartan potassium up to approximately 100 mg/kg. The administration of losartan dose levels in females (500 mg/kg) resulted in a relatively small decrease in the number of corpora lutea, implantation sites, and live fetuses/females at 80 and 150 mg/kg. As an increase in the number of corpora lutea was observed. The relationship of these findings to drug-treatment is uncertain since there was no evidence of any effects on pregnancy in pregnant female, percent post-implantation loss, or the survival of rat pups at parturition. In neonatal pups, at 150 mg/kg for 7 days, systemic exposure (AUCa) for losartan and its metabolites were approximately 65 and 26 times the exposure achieved in man at the minimum recommended human daily dosage (100 mg).

Pregnancy Category C (first trimester) and D (second and third trimester). See Variable, 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 metabolites have been shown to be present in rat milk. Nursing mothers should be made aware 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.

Uses in the Elderly

Of the total number of patients receiving COZAAR® in controlled clinical studies, 281 patients (9%) were 65 years of age or older, with 57 patients (2%) were 75 years and over. No overall differences in effectiveness and safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

COZAAR® has been evaluated for safety in more than 3000 patients treated for essential hypertension and over 2000 patients with other subjects having a mean age of 59 years and over and over 200 patients given placebo. All adverse events reported with COZAAR® were similar to placebo.

In controlled clinical trials, discontinuation of therapy due to adverse events was required in 2.5% of patients treated with COZAAR® and 3.7% of placebo treated patients.

The following table of adverse events is based on adverse events reported in over 40-42 weekly placebo controlled trials involving over 1000 patients on various doses of COZAAR® and over 200 patients given placebo. All causes of losartan are grouped because none of the adverse events appeared to have a dose-related frequency. The table includes all adverse events, whether or not related to therapy, that occurred at a frequency of at least 1% in patients treated with losartan and that were more frequent than placebo.

<table>
<thead>
<tr>
<th>Losartan (n=1578)</th>
<th>Placebo (n=234)</th>
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<tbody>
<tr>
<td>Dizziness</td>
<td>3.3%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1.3%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1.3%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.1%</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>1.0%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>1.0%</td>
</tr>
<tr>
<td>Rash</td>
<td>1.0%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>1.0%</td>
</tr>
<tr>
<td>Upper respiratory</td>
<td>0.8%</td>
</tr>
<tr>
<td>Lower respiratory</td>
<td>0.8%</td>
</tr>
<tr>
<td>Cough</td>
<td>1.3%</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>1.3%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>1.3%</td>
</tr>
</tbody>
</table>
COZAAR® (Losartan Potassium Tablets)

The following adverse events were also reported at a rate of 1% or greater in patients treated with COZAAR, but were not, or more frequently, in the placebo group: asthenia, diarrhea, dizziness, flatulence, dyspepsia, headache, infection, influenza, lymphadenopathy, nasopharyngitis, nausea, pharyngitis, rhinitis, sinusitis, and upper respiratory tract infection.

Some of these adverse effects may be related to the antihypertensive effects of COZAAR, although they are believed to be due to a combination of factors. In addition, patients treated with COZAAR may have an increased frequency of these adverse events when compared to placebo, although a causal relationship has not been established.

If any of these conditions or other adverse reactions occur, the patient should be carefully monitored. In severe cases, the drug should be discontinued.

COZAAR may be administered with other antihypertensive agents.

COZAAR may be administered with or without food.

NOW SUPPLIED

No. 301-8 Tablets COZAAR, 50 mg, are light green, oval, film-coated tablets with code M84 on one side and M81 on the other. They are supplied as follows:

- RDC000-985-5641 100 tablets of 50 mg
- RDC000-985-5645 50 tablets of 50 mg
- RDC000-985-5654 60 tablets of 50 mg
- RDC000-985-5658 100 tablets of 50 mg
- RDC000-985-5662 30 tablets of 50 mg
- RDC000-985-5666 100 tablets of 50 mg
- RDC000-985-5670 40 tablets of 50 mg
- RDC000-985-5674 30 tablets of 50 mg
- RDC000-985-5678 100 tablets of 50 mg
- RDC000-985-5682 40 tablets of 50 mg
- RDC000-985-5686 30 tablets of 50 mg
- RDC000-985-5690 100 tablets of 50 mg
- RDC000-985-5694 40 tablets of 50 mg
- RDC000-985-5698 30 tablets of 50 mg
- RDC000-985-5702 100 tablets of 50 mg

Storage

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

Merk & Co., Inc., West Point, PA 19486, USA

Ismail February 1997

Printed in USA

by:

DuPont

Pharma

Wilmington, DE 19890 USA

THEMED
HYZAAR®
(LOXANTAN POTASSIUM-
HYDROCHLOROTHIAZIDE TABLETS)

DESCRIPTION

HYZAAR® (losartan potassium-hydrochlorothiazide) contains losartan potassium, a non-peptide, orally active antagonist which is structurally related to saralasin, and hydrochlorothiazide, a diuretic.

Losartan potassium, the non-peptide, orally active antagonist, is chemically described as 2-[1-[(2S)-2-[(1S)-1-phenyl-3-[(1S)-1-phenyl-3-sulfamoyl]propyl]amino]-2-methylpropyl]amino]ethan-1-ol. Its empirical formula is C₁₇H₁₉N₃O₅S and its molecular weight is 359.4.

Hydrochlorothiazide is a white, or practically white, crystalline powder with a molecular weight of 205.7. It is freely soluble in water, soluble in alcohol, and slightly soluble in common organic solvents, such as acetone or ethyl acetate.

Both losartan potassium and hydrochlorothiazide are administered with or without food.

HYZAAR® consists of 44.4 mg of losartan potassium and 12.5 mg of hydrochlorothiazide in tablets.

CLINICAL PHARMACOLOGY

Mechanism of Action

Angiotensin II is a potent pressor that is produced from angiotensin I by a substance known as renin. This molecule is formed from angiotensin I by the action of renin. Losartan blocks the action of renin by selectively blocking the binding of angiotensin II to the AT1 receptor.

ACE inhibitors block the production of angiotensin II by blocking the conversion of angiotensin I to angiotensin II. Losartan is not an ACE inhibitor.

Losartan is an AT1 receptor antagonist which can block the renin-angiotensin-aldosterone system. Losartan is not an ACE inhibitor.

Losartan has been shown to be effective in the treatment of hypertension in patients with renal impairment or in hypertensive patients with diabetes.

Because Losartan is not an ACE inhibitor, Losartan is not expected to cause hyperkalemia or coughing, which are commonly associated with ACE inhibitors.

Losartan is not expected to cause an increase in serum creatinine. However, patients with renal impairment or diabetes may be at risk for worsening renal function.

The effects of Losartan in patients with renal impairment or diabetes have not been studied. Losartan may be used in these patients with caution, especially in patients with a history of kidney disease.

Losartan has not been studied in patients with severe renal impairment or in hemodialysis patients. However, it is expected that Losartan would be effective in these patients.
HUZAM® (Losartan Potassium-Hydrochlorothiazide Tablets)

placebo (one study, n=471) or 25 mg hydrochlorothiazide (n=109). The double-blind treatment period lasted up to 8 weeks. The incidence of cough is shown below.

Study 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Losartan</th>
<th>Lioprel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>26%</td>
<td>17%</td>
</tr>
<tr>
<td>Placebo</td>
<td>24%</td>
<td>22%</td>
</tr>
</tbody>
</table>

**Concomitant Use of ACE Inhibitors**

ACE inhibitors are coadministered with losartan in a substan
tially higher proportion of patients taking losartan compared to those taking placebo. While these are generally well tolerated, they may occasionally cause dry cough.

Losartan Potassium-Hydrochlorothiazide

The 3 controlled studies of losartan and hydrochlorothia
dide included over 1500 patients, assessing the antihyperten
sive efficacy of various doses of losartan (25, 50, and 100 mg) and concomitant hydrochlorothiazide (12.5, 25, and 50 mg). A factorial study compared the combination of losar
tan 100 mg and hydrochlorothiazide 25 mg with its components pla
eo. The combination of losartan 50 mg and hydrochlorothiazide 12.5 mg resulted in an approximately similar placebo
tolerated antihypertensive response (16.65 mm Hg for the combination compared to 8.9 mm Hg for losartan alone and 7.07 mm Hg for hydrochlorothiazide alone. Another study investigated the dose-response relationship of various doses of hydrochlorothiazide (25, 50, and 100 mg) on a background of losartan 50 mg. Again, the antihypertensive response (16.65 mm Hg for the combination compared to 8.9 mm Hg for losartan alone and 7.07 mm Hg for hydrochlorothiazide alone. A third study investigated the dose-response relation
tionship of various doses of losartan (25, 50, and 100 mg) on a background of hydrochlorothiazide (25 mg). This study demonstrated that losartan 50 mg followed by 25 mg hydrochlorothiazide (25 mg) and 50 mg losartan followed by 50 mg hydrochlorothiazide (50 mg) were the most effective combinations. These studies showed that the combination had a significant dose-response effect on blood pressure, suggesting a synergistic effect compared to the individual components.

**INDICATIONS AND USAGE**

HUZAM® is indicated for the treatment of hypertension. This indication is based on the results of placebo-controlled trials that have demonstrated that losartan is effective in lowering blood pressure. The antihypertensive effect of losartan is dose-related and does not appear to be affected by race, age, or gender.

**CONTRAINDICATIONS**

HUZAM® is contraindicated in patients who are hypersensitive to any component of this product. Losartan is contraindicated in patients with sodium or hydrochlorothiazide intolerance or to other angiotensin II-receptor antagonists.

**WARNINGS**

**Drug Interactions**

Drug interactions are uncommon with losartan. However, as with any antihypertensive agent, interactions with other antihypertensive drugs may occur. Patients who are being treated with losartan and any concomitant medications should be monitored closely for any changes in blood pressure.

**Precautions**

Concomitant Use of ACE Inhibitors: When losartan is used in combination with an ACE inhibitor, the incidence of cough is substantially higher than when losartan is used alone. Therefore, losartan should be discontinued if cough occurs.

**Adverse Reactions**

The most common adverse reactions associated with losartan use are an initial rise in blood pressure, headache, and dizziness. Other adverse reactions include edema, rash, and injection site reactions. In clinical trials, patients taking losartan experienced similar adverse events as those taking placebo. There were no significant differences in adverse events between losartan and placebo groups. The most frequent adverse reactions reported were edema, headache, and dizziness. These events were generally mild to moderate in severity and did not require discontinuation of therapy.
HYZAAR® (Losartan Potassium-Hydrochlorothiazide) Tablets

Adverse events occurred at about the same rates in men and women, older and younger patients, and black and nonblack patients. A patient with increased intracranial pressure and papilledema, when treated with losartan potassium, was withdrawn from study due to worsening of the signs and symptoms and facial rash, reported as angioedema, which resolved within 4 days after therapy was discontinued.

Subcutaneous pitting edema and hypertension were reported in one subject treated with losartan potassium.

Losartan Potassium

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

- Hypotension
- Cough, cold
- Lucid symptoms, stomach pain, flushing, urticaria
- Headache, dizziness, flatulence, diarrhea
- Asthenia, abdominal pain, nausea
- Pruritus, rash, alopecia, sweating
- Myalgia, arthralgia, back pain
- Insomnia, nervousness, headache
- Dyspepsia, palpitations, tinnitus, abdominal pain
- Flatulence, diarrhea, rash, angioedema, headache
- Dizziness, malaise, vertigo
- Nausea, vomiting, anorexia
- rhinitis, pharyngitis
- Cough, sinusitis, throat pain
- Nasopharyngitis, tonsillitis

Hydrochlorothiazide

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

- Hypotension
- Tachycardia
- Headache
- Anorexia, nausea, vomiting
- Dizziness
- Fatigue
- Pruritus, rash
- Memory impairment
- Muscle cramps
- Hypesthesia
- Tinnitus, dizziness
- Flatulence
- Abdominal discomfort
- Mucous membranes, edema
- Hematuria
- Hypoesthesia
- Gastrointestinal symptoms
- Urticaria
- Eczema

Laboratory Test Abnormalities

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

Creatinine, Blood Urea Nitrogen: A minor increase in blood urea nitrogen (BUN) or serum creatinine were observed in 6.3 and 6.9% of patients, respectively. Hyperkalemia was observed in a total of 1.2% of patients treated with HYZAAR. No patient discontinued HYZAAR due to hyperkalemia. One patient discontinued therapy due to a minor increase in serum creatinine.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 1.4 g/dL and 0.6 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: Occasionally elevations of liver enzymes and/or serum bilirubin have occurred in patients treated with HYZAAR alone, but were not discontinued due to these laboratory abnormalities.

Hydrochlorothiazide

The oral LD50 of hydrochlorothiazide is greater than 10 g/kg in both rats and mice. The most common signs and symptoms observed are those caused by electrolyte depletion (hyponatremia, hypochloremia, hyponatremia, and hypokalemia resulting from excessive diuresis, diarrhea, vomiting, or excessive fluid loss due to severe burns). The degree in which hydrochlorothiazide is removed by hemodialysis or peritoneal dialysis has not been determined.

DOSAGE AND ADMINISTRATION

The usual starting dose of losartan is 50 mg once daily, with 25 mg recommended for patients with low renin hypertension or diastolic hypertension (e.g., patients treated with diuretics see WARNINGS, Hypotension — Moderate-Dose Patients). Losartan can be administered once or twice daily at total daily doses of 25 to 100 mg. If the antihypertensive response is inadequate at 50 mg daily or at 75 mg once daily, the dose should be increased. When the antihypertensive response is inadequate at 75 mg once daily or at 50 mg twice daily, losartan therapy may be further improved by adding other antihypertensive medications.

Hydrochlorothiazide is effective in doses of 12.5 to 100 mg once daily, with 25 mg being recommended for patients with low renin hypertension or diastolic hypertension (e.g., patients treated with diuretics see WARNINGS, Hypotension — Moderate-Dose Patients). Losartan can be administered once or twice daily at total daily doses of 25 to 100 mg. If the antihypertensive response is inadequate at 50 mg daily or at 75 mg once daily, the dose should be increased. When the antihypertensive response is inadequate at 75 mg once daily or at 50 mg twice daily, losartan therapy may be further improved by adding other antihypertensive medications.

Losartan and hydrochlorothiazide should be administered simultaneously at the same time each day. Losartan may be administered with or without food. When HYZAAR is taken twice daily, the usual dose is 1 tablet of HYZAAR 1 tablet once daily. More than 2 tablets once daily is not recommended. The maximum recommended dose of HYZAAR is 1 tablet once daily. In patients with severe renal impairment (creatinine clearance less than 30 mL/min), the use of HYZAAR is not recommended.

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Use in Pseudohypoaldosteronism Type IA

The following adverse reactions have been observed in patients with pseudohypoaldosteronism Type IA who were treated with high doses of aldosterone antagonists. Symptoms include weakness, fatigue, nausea, vomiting, anorexia, polyuria, polydipsia, edema, hypotension, and dehydration. Treatment is usually successful with a dose reduction or withdrawal from the aldosterone antagonist.
Hyzaarp Tablets

Two-year feeding studies in rats and mice conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydralazine in female mice fed doses of up to approximately 880 mg/kg/day and in male mice fed doses of up to approximately 160 mg/kg/day. The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydralazine was not genotoxic in a bacterial mutagenicity assay or in the mouse lymphoma tk Salvage assay. Positive test results were obtained only in the in vitro CHO/UV-Induced tk+ selection definitive test and in the mouse lymphoma tk+ selection definitive test. No genotoxic activity was observed in the Salmonella/mammalian microsome assay in a series of tests using concentrations of hydralazine from 43 to 1289 pg/ml, in the Escherichia coli WP2 uvrA reverse mutation assay using concentrations of hydralazine from 43 to 1289 pg/ml, and in the Aspergillus nidulans non-disjunction assay at an unspecified concentration.

Hydralazine had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, in doses of up to 100 and 400 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 hydralazine is excreted in human milk. However, no adverse effects on the breast-fed infant were observed in a breast-fed infant whose mother was taking hydralazine. No data are available on the effects of hydralazine on the breast-fed infant or in nursing mothers.

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 Hyzaarp, 107 patients (12.9%) were 65 years and over, while 8 patients (1.1%) were 75 years and over. No overall differences in effectiveness of safety were observed between these patients and younger patients.

ADVERSE REACTIONS

Lesartan potassium-hydrochlorothiazide has been evaluated for safety in 696 patients treated for essential hypertension in clinical trials with hydralazine. In controlled clinical trials with hydralazine, no adverse experiences peculiar to this combination drug have been observed. Adverse experiences have been limited to those that were reported previously with lesonar potassium and/or hydralazine. The incidence of adverse experiences reported with the combination was comparable to placebo.

In general, treatment with lesartan 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 clinical trials, discontinuation of therapy due to adverse experiences was required in only 2% and 2.9% of patients treated with the combination and placebo, respectively.

In a general population of controlled trials, the following adverse experiences reported with Hyzaarp occurred in 1% or more of patients and were more frequent on drug than placebo, regardless of drug relationship:

<p>| Lesartan Potassium- |</p>
<table>
<thead>
<tr>
<th>Hydrochlorothiazide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td>1.3</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1.3</td>
</tr>
<tr>
<td>Edematous swelling</td>
<td>1.3</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>1.4</td>
</tr>
<tr>
<td>Peptone</td>
<td>1.4</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>2.1</td>
</tr>
<tr>
<td>Back pain</td>
<td>2.1</td>
</tr>
<tr>
<td>Nervous/Psychiatric</td>
<td>8.7</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8.7</td>
</tr>
<tr>
<td>Respiratory</td>
<td>2.8</td>
</tr>
<tr>
<td>Cough</td>
<td>2.8</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>1.2</td>
</tr>
<tr>
<td>Upper respiratory</td>
<td>6.1</td>
</tr>
<tr>
<td>Infection</td>
<td>6.1</td>
</tr>
<tr>
<td>Skin</td>
<td>1.4</td>
</tr>
</tbody>
</table>

The following adverse events were also reported at a rate of 1% or greater, but were not, or were rare, in the placebo group: anemia, dysuria, constipation, headache, bronchitis, pharyngitis.
HYZAAR® (Losartan Potassium-Hydrochlorothiazide Tablets) paraenteral fluids. Wearing signs or symptoms of fluid and electrolyte imbalance, including those caused by changes in extracellular fluid volume, plasma osmolality, circulating volume, muscle pain or cramps, nausea, tachycardia, and vasodilation, and manifestations of cardiovascular, neurologic, and gastrointestinal disturbances such as nausea and vomiting.

Hydronephrosis may develop, especially in patients with bilateral diuretic use, severe aortic stenosis or hypertension, or if hypotensive therapy is initiated abruptly. Hydronephrosis may cause cardiac arrhythmias and may also be a factor in aggravating the pain of the heart in the setting of acute digitalis intoxication.

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

Diabetic hyperglycemia may occur in menstruating patients with new or recurrent symptoms or signs of changes in their renal or cardiovascular function. Diazoxide should not be used in patients with diabetes mellitus.

In diabetic patients dosing changes of insulin or oral antidiabetic agents should be considered. Similar effects should be seen in patients with thiazide diuretics. This presents diabetes mellitus may present in patients with metabolic alkalosis.

The antihypertensive effects of the drug may be enhanced in the presence of hypokalemia. If progressive renal impairment becomes evident, cortical function will be monitored with patients with severe renal impairment, and the use of a diuretic or calcium antagonist should be considered.

Thiazides may cause urinary tract infections. Thiazides may cause decreases in plasma renin activity, which may occur in patients treated with thiazide diuretics. The syndrome of inappropriate antidiuretic hormone (SIADH) should be differentiated from the hyperglycemia of diabetes mellitus.

The adverse effects of thiazides may be minimized or prevented by certain dietetic measures (e.g., sodium-free diet).

The syndrome of inappropriate antidiuretic hormone (SIADH) should be differentiated from the hyperglycemia of diabetes mellitus.

Hypokalemia should be avoided, and potassium supplements should be used in patients with severe renal impairment or impaired renal function.

In patients with severe renal impairment, the use of a diuretic or calcium antagonist should be considered.

Thiazide diuretics may cause urinary tract infections. Thiazides should be discontinued before any radiographic examination of the kidney, bladder, or ureter.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20386/S-007 AND 20387/S-005

CHEMISTRY REVIEW(S)
DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Control

NDA #: 20-386
REVIEW DATE: 13-MAY-97

SUBMISSION TYPE DOCUMENT DATE CDER DATE ASSIGNED DATE
SLR-007 17-APR-97 21-APR-97 24-APR-97

NAME & ADDRESS OF SPONSOR

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

DRUG PRODUCT NAME

Proprietary: COZAAR
Nonproprietary/USAN: Losartan Potassium Tablets
Code Name(s): MK-954; DuP-753; L-158,086; L-158,086-005; E-3340
Chem. Type/Ther. Class: 18

Supplement Provides For:
Revised Draft Labeling for approved NDA.

ANDA Suitability Petition/DMSI/Patent Status:
USP 5,153,197 expiration date 10/06/2009 - both licensed from DuPont

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

DOSEAGE FORM:

STRENGTH: 20, 50 mg

ROUTE OF ADMINISTRATION: ORAL

DISPENSED: Rx

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

CAS #: 124750-99-8

MOLECULAR FORMULA: C_{23}H_{22}ClK_{2}N_{8}O

MOLECULAR WEIGHT: 461.01

STRUCTURAL FORMULA:

\[ \text{[Image of chemical structure]} \]
SUPPORTING DOCUMENTS:
None.

RELATED DOCUMENTS:
None.

CONSULTS:
None.

REMARKS/COMMENTS:
The circular has been revised under ADVERSE REACTIONS, Post-Marketing Experience to include pharyngeal edema and hyperkalemia, based on adverse reaction reports for Losartan. These changes do not affect CMC related sections.

CONCLUSIONS & RECOMMENDATIONS:
From CMC standpoint the labeling remains satisfactory.

cc:
Orig. NDA
HFD-110/Division File
HFD-110/Ram Mittal/date
HFD-110/CSO

R/D Init by: RWolters/

Ramsharan D. Mittal Ph.D., Review Chemist

filename: C:\NDA\20386\20386ELN.007

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL
DIVISION OF CARDIO-RENOV DRUG PRODUCT
Review of Chemistry, Manufacturing, and Control

NDA #: 20-387
SUBMISSION TYPE: SLR-005
DOCUMENT DATE: 17-APR-97
CDER DATE: 21-APR-97
ASSIGNED DATE: 23-APR-97
REVIEW DATE: 13-MAY-97

NAME & ADDRESS OF SPONSOR
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-158,086-008H; E-3340
Chem. Type/Ther. Class: 18

Supplement Provides For:
Revised Draft Labeling for approved NDA.

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:
tables

STRENGTH:
50 mg Losartan Potassium Tablets/12.5 mg Hydrochlorothiazide

ROUTE OF ADMINISTRATION:
ORAL

DISPENSED:
Rx

APPEARS THIS WAY ON ORIGINAL
DRUG SUBSTANCE 1.  LOSARTAN POTASSIUM

CHEMICAL NAME:  2-buty1-4-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_{26}ClNK_{2}O

MOLECULAR WEIGHT:  461.01

STRUCTURAL FORMULA:

\[ \text{[Chemical Structure]} \]

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_{7}H_{6}ClN_{2}O_{5}S_{2}

MOLECULAR WEIGHT:  297.74

STRUCTURAL FORMULA:

\[ \text{[Chemical Structure]} \]
REMARKS/COMMENTS:

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R/D Init by: RWolters/

Ramsharan D. Mittal Ph.D., Review Chemist
filename: C:\NDA\20387\20387SLR.005

APPEARS THIS WAY ON ORIGINAL

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CENTER FOR DRUG EVALUATION AND RESEARCH

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ADMINISTRATIVE DOCUMENTS
RHPM Review of Labeling

NDA: 20-368/SLR007 Cozaar (losartan potassium) Tablets
      20-387/SLR-005 Hyzaar (losartan potassium/
      hydrochlorothiazide) Tablets

Date of submission: April 17, 1997
Date of receipt: April 21, 1997
Applicant: Merck Research Laboratories

Background: Merck has submitted Special Supplements, Changes Being Effected, for Cozaar
and Hyzaar Tablets. The cover letters for these supplements state that the revised labeling will
be used in all production and sample packaging on or before July 1, 1997, in all product sold or
distributed on or before November 1, 1997, and in all promotional pieces on or before May 1,
1997.

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

ADVERSE REACTIONS, Post-Marketing Experience, Hypersensitivity: "pharynx" has
been added to the following: "Angioedema (involving swelling of the face, lips, pharynx,
and/or tongue) has been reported rarely in patients treated with losartan."

ADVERSE REACTIONS, Post-Marketing Experience: The sentence "Hyperkalemia has
been reported." has been added to the end of this subsection.

There appears to be an oversight in what Merck has included in the ADVERSE REACTIONS, Post-
Marketing Experience subsection of their package inserts. In 20-368/S-004, Merck added
information to the PRECAUTIONS, Impaired Renal Function subsection about cases of renal
insufficiency, acute renal insufficiency, and increases in serum creatinine or BUN in patients
with unilateral or bilateral renal artery stenosis. There is no mention of these cases in the
ADVERSE REACTIONS, Post-Marketing Experience subsection. In addition, there have been a
number of cases of angioedema reported with losartan that are not included in the ADVERSE
REACTIONS Post-Marketing Experience subsection.

I called Larry Bell, M.D. on May 30, 1997 and asked him to include these and other adverse
reactions in the ADVERSE REACTIONS, Post-Marketing Experience subsection of the package
insert. He called on July 9, 1997 and said that they will put additional adverse experiences into
that subsection of the package insert. These will be submitted in separate supplements.

Recommendation: I will prepare an approvable letter for these supplements. These
supplements fall under 21 CFR 314.70 (c) Supplements for changes that may be made before
FDA approval.

Kathleen F. Bongiovanni