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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 20-386/S-015

Trade Name: Cozaar 25 and 50 mg Tablets

Generic Name: (losartan potassium)

Sponsor: Merck Research Laboratories

Approval Date: November 24, 1998

Indication: Provides for revised final printed label.
NDA 20-386/S-015
NDA 20-387/S-011

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

Dear Dr. White:

Please refer to your supplemental new drug applications dated October 14, 1998, received October 19, 1998, 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).

These supplemental new drug applications provide for final printed labeling revised as follows:

**NDA 20-386 and 20-387:**

**PRECAUTIONS, General:** "Hypersensitivity. See ADVERSE REACTIONS, Post-Marketing Experience." has been moved to the beginning of this subsection, and "Angioedema" has been added. It now reads, "Hypersensitivity: Angioedema. See ADVERSE REACTIONS, Post-Marketing Experience."

**ADVERSE REACTIONS, Post-Marketing Experience, Hypersensitivity:** This subsection has been revised to read, "Angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, an/or tongue has been reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors."

**HOW SUPPLIED:** The DuPont Pharma signature has been revised.

**NDA 20-386:**

**PRECAUTIONS, Information for Patients:** A new subsection has been added for consistency with the HYZAAR package insert, in which this change was made in supplement 010: "Potassium Supplements: A patient receiving COZAAR should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician (see PRECAUTIONS, Drug Interactions)."

**ADVERSE REACTIONS, Laboratory Test Findings, Creatinine, Blood Urea Nitrogen:** The cross-reference, "(see PRECAUTIONS, Impaired Renal Function)" has been added. This cross-reference was inadvertently deleted in supplement 014.
We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the submitted final printed labeling (package insert included in the October 14, 1998 submission). Accordingly, these 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:

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 NDAs 20-386, 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/11/9/98; 11/24/98

Initiated by: R Mittal/11/10/98
K Srinivasachar/11/12/98
A Proakis/11/16/98
C Resnick/11/17/98
K Knudsen/11/18/98
N Stockbridge/11/19/98
C Ganley/11/20/98
N Morgenstern/11/23/98

K Jv 11/24/98

Filename: 20386s015ap.doc

APPROVAL (AP)
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-386/S-015

FINAL PRINTED LABELING
COZAAR®
(LOSARTAN POTASSIUM TABLETS)

USE IN PREGNANCY

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

DESCRIPTION

COZAAR® (losartan potassium), the first of a new class of angiotensin II receptor (type AT1) antagonists, is a potassium-sparing diuretic, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-piperazinepentanoic acid. Its empirical formula is C_{18}H_{17}ClN_{2}O_{4}, and its structural formula is:

![Chemical structure of losartan potassium]

Losartan potassium is a white to off-white free-flowing crystalline powder with a molecular weight of 461.1. It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetone and methyl ethyl ketone. Oxidation of the 6-hydroxy group on the imidazole ring results in the active metabolite of losartan.

COZAAR is available for oral administration containing either 25 mg or 50 mg of losartan potassium and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, pregelatinized starch, magnesium stearate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, titanium dioxide, D&C yellow No. 10 aluminum lake and FD&C blue No. 2 aluminum lake. COZAAR 25 mg and 50 mg contain potassium in the following amounts: 2.12 mg (0.054 mEq) and 4.24 mg (0.108 mEq), respectively.

CLINICAL PHARMACOLOGY

Mechanism of Action

Angiotensin II (formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme [ACE, kininase II], a potent vasodepressor, is transformed into the vasoactive hormone of the renin-angiotensin system and an important regulator of the angiotensin system is 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 vasodepressor and other-agonist-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues, e.g., vascular smooth muscle, adrenal gland. There is also an AT2 receptor found in many tissues but it is not known to be associated with cardiovascular homeostasis. Both losartan and its principal active metabolite do not exhibit any antagonistic properties. Losartan and its active metabolite have much greater affinity (at least 1000-fold) for the AT1 receptor than for the AT2 receptor. Binding studies indicate that losartan is a reversible, competitive inhibitor of the AT1 receptor. The active metabolite is to 40 times more potent by weight than losartan and appears to be a reversible, non-competitive inhibitor of the AT1 receptor.

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

Pharmacokinetics

General

Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. It is converted, in part, to an active metabolite in the liver. The metabolites of losartan are responsible for most of the effect of the AT1 receptor antagonism that follows losartan treatment. The terminal half-life of losartan is about 2 hours and of the metabolite is about 6.5 hours. The pharmacokinetics of losartan and its active metabolites are linear with oral losartan doses up to 200 mg and do not change over time. Neither losartan nor its metabolites accumulate in plasma upon repeated once-daily dosing.

Following oral administration, losartan is well absorbed (based on a study of radiolabeled losartan) and undergoes substantial first-pass metabolism; the systemic bioavailability of losartan is approximately 33%. About 14% of an orally administered dose of losartan is converted to the active metabolite. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. While maximum plasma concentrations of losartan and its active metabolite are approximately equal, the AUC of losartan is about 4 times as great as that of losartan. A mean slow absorption of losartan and decreases its Tmax, but has no other effects on losartan. AUC or on the AUC of the metabolite (about 10%) decreased. Both losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2%, respectively. Plasma protein binding is concentration-dependent over the concentration range achieved with recommended doses. Studies in rats indicate that losartan crosses the blood-brain barrier poorly.

Losartan metabolites have been identified in human plasma and urine. In addition to the active carbonic acid metabolite, several inactive metabolites are formed. Following oral and intravenous administration of 14C-label of losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and its active metabolite. In vitro studies indicate that cytochrome P450 2C9 and 2C19 are involved in the transformation of losartan to its metabolites. Minimal conversion of losartan to the active metabolite (less than 1% of the dose compared to 14% of the dose in normal subjects) was seen in about one percent of individuals studied.

The volume of distribution of losartan is about 34 liters and of the active metabolite is about 12 liters. Total plasma clearance of losartan and the active metabolite is about 890 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 8% is excreted in urine as active metabolite. Dialysis contribution to the elimination of losartan and its metabolites. Following oral administration of 14C-label of losartan potassium, about 30% of radioactivity is recovered in the urine and about 60% in the feces. Following an intravenous dose of 14C-label of losartan potassium, about 40% of radioactivity is recovered in the urine and 50% in the feces.

Special Populations

Pediatric:

Losartan pharmacokinetics have not been investigated in pediatric patients. Losartan potassium is not recommended for use in children 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 and its active metabolite were similar in males and females. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).

Race:

Pharmacokinetic differences due to race have not been studied.

Renal Insufficiency:

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

Hepatic Insufficiency:

Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, lower, 3.5 times and about 1.7 times those observed 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 20%. No dosage adjustment for lower starting dose is recommended for patients with a history of hepatic impairment (see DOSAGE AND ADMINISTRATION).

Drug Interactions

Losartan, administered for 12 days, did not affect the pharmacokinetics or pharmacodynamics of a single dose of warfarin. Losartan did not affect the pharmacokinetics of doxazosin, a competitive inhibitor of the renin-angiotensin system.

Ahibbination of losartan and clinalhypertension led to an increase of about 19% in AUC of losartan but did not change the pharmacokinetics of its active metabolite. Administration of losartan and phenothiazine led to a reduction of about 20% in the AUC of losartan and of its active metabolite. Conversion of losartan to its active metabolite after intravenous administration is not affected by ketone- base, an inhibitor of P450 3A4. There is no pharmacokinetic interaction between losartan and hydrochlorothiazide.

Pharmacodynamics and Clinical Effects

Losartan inhibits the pressor effect of angiotensin II as well as angiotensin II infusions. A dose of 100 mg inhibits the pressor effect by about 85% at peak with 25-40% inhibition persisting...
COZAAR® (Losartan Potassium Tablets)

ing 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. Losartan does not affect the response to bradykinin, whereas ACE inhibitors increase the response to bradykinin. Aldosterone plasma concentrations fall following losartan administration. In spite of the effect of losartan on aldosterone secretion, very little effect on serum potassium was observed.

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

The antihypertensive effects of COZAAR were demonstrated principally in a 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) as once-daily or twice-daily regimens, comparisons of peak and trough effects, and comparisons of response by gender, age, and race. Three additional studies examined the antihypertensive effects of losartan and hydrochlorothiazide in combination.

The 4 studies of losartan monotherapy included a total of 1075 patients randomized to several doses of losartan and 334 to placebo. The 10 and 25 mg doses produced some effect at peak (6 hours after dosing) but small and inconsistent trough (24 hour) responses. Doses of 50, 100 and 150 mg once daily gave statistically significant systolic/diastolic mean decrease in blood pressure, compared to placebo in the range of greater effect than 50-100 mg. Twice-daily dosing at 50-100 mg/day gave consistently larger trough responses than once-uniformly, but moderately larger than trough effects, with the trough:peak ratio for systolic and diastolic responses 50-95% and 60-95%, respectively.

Addition of a low dose of hydrochlorothiazide (12.5 mg) to losartan 50 mg once daily resulted in placebo-adjusted blood pressure reductions of 10.5/7.2 mmHg.

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

The effect of losartan is substantially present within one week but in some studies the maximal effect occurred in 3-6 weeks. In long-term follow-up studies (without placebo control) the effect of losartan appeared to be maintained for up to 2 years. There is no apparent rebound effect after abrupt withdrawal of losartan. There was essentially no change in average heart rate in losartan-treated patients in controlled trials.

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

WARNINGS

Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases of renal failure 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 skeletal deformities, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios is associated with fetal lung abnormalities, craniofacial deformations, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug. These adverse effects do not appear to have resulted from maternal drug exposure alone.

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

Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mother's and fetal risks must be weighed against the potential hazards to the fetus, and 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. Oligohydramnios, a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not persist until after the fetus has sustained irreversible injury.

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

Losartan potassium has been shown to produce adverse effects in rat fetuses and neonates, including decreased body weight, decreased physical and behavioral development, morbidity and 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 are attributed to drug exposure in late gestation and during lactation. Significant levels of losartan and its active metabolite were shown to be present in rat fetal plasma during late gestation and in rat milk.

Hypotension — Volume-Depleted Patients

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

PRECAUTIONS

General

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

Impaired Hepatic Function

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

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been reported in susceptible individuals treated with COZAAR. In some patients, these changes in renal function were reversible upon discontinuation of therapy. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with COZAAR.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or BUN have been reported. Similar effects have been reported with 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 potential 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 intratubular drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

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

Drug Interactions

No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, diaspin, warfarin, ticlopidine, and placebo.

(Diuretics compare well with COZAAR in lowering BP.)

(See CLINICAL PHARMACOLOGY, Drug Interactions.) Potent inhibitors of cytochrome P450 3A4 and 2C9 have not been studied clinically but in vitro studies show significant inhibition of the formation of the active metabolite by inhibitors of P450 3A4 (ketocanozole, midazolam, tylopil, and ticlopidine) and P450 2C9 (flurbiprofen) and nearly complete inhibition by the combination of sulfaphenazole and ketocanozole. 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 3A4 have not been studied clinically. The pharmacodynamic consequences of concomitant use of losartan and inhibitors of P450 2C9 have not been examined.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Losartan potassium was not carcinogenic when administered at maximally tolerated dosages to rats and mice for 105 and 52 weeks, respectively. Female rats given the highest dose (270 mg/kg/day) had a slightly higher incidence of pancreatic acinar adenoma. The maximally tolerated dosages (270 mg/kg/day) in rats and mice provided systemic exposures for losartan and its metabolites that were approximately 15- to 30-times (rat) and 30- and 15-times (mouse) the exposure of a 50 kg human given 100 mg per day.

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

Fertility and reproductive performance were not affected in studies with male rats given oral doses of losartan potassium up to approximately 130 mg/kg/day. The administration of toxic dose levels in females (300/200 mg/kg/day) was associated with a significant (p < 0.05) decrease in the number of corpora lutea/female, implants/female, and live fetuses/female at C-section. At 100 mg/kg/day only a decrease in the number of corpora lutea/female was observed. The relationship between these findings to drug treatment is uncertain since there was no effect at these dose levels on gestation length, prepregnant female, percent post-implantation loss, or live animals/litter at parturition. In nonpregnant rats dosed at 135 mg/kg/day for 7 days, systemic exposures [AUC] for losartan and its active metabolite were approximately 48 and 25 times the exposure achieved in man at the maximum recommended human daily dosage (100 mg).

Pregnancy

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

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Use in the Elderly

The total number of patients receiving COZAAR in controlled clinical studies, 391 patients (19%) were 65 years of age or older, and 84 patients (4%) were 75 years and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

COZAAR has been evaluated for safety in more than 3300 patients treated for essential hypertension and 410 patients/subjects overall. Over 1200 patients were treated for over 6 months and more than 300 patients were treated for over 1 year. In general, treatment with COZAAR was well tolerated. The overall incidence of adverse experiences reported with COZAAR was similar to placebo.

In controlled clinical trials, discontinuation of therapy due to an adverse event occurred in 3% of patients treated with COZAAR and 1.3% of patients treated with placebo. The most frequent adverse events reported in these trials that were thought to be drug-related were headache (10.4% of patients treated with COZAAR compared to 3.7% of patients treated with placebo).

The following table shows adverse events reported on 6-12 week placebo controlled trials involving over 1000 patients on various doses (10-150 mg) of losartan and over 300 patients on various doses of losartan (50-300 mg) other than those listed above. The most frequent adverse events reported in patients treated with losartan and that were more frequent on losartan than placebo, were:

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<th>Placebo (n=334) Incidence</th>
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<tr>
<td>Nausea</td>
<td>1.3</td>
<td>1.2</td>
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<tr>
<td>Musculoskeletal</td>
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<tr>
<td>Cramer, ankle</td>
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<td>0.3</td>
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<tr>
<td>Myalgia</td>
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<td>Pain, back</td>
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<td>Sinusitis</td>
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The following adverse events were also reported at a rate of 1% or greater in patients treated with losartan, but were as, or more frequent, in the placebo group: asthenia, fatigue, edema/
COZAAR® (Losartan Potassium Tablets)

swelling, abdominal pain, chest pain, nausea, headache, pharyngitis.

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

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

Superficial palmar and plantar hemorhages were reported in two studies.

In addition to the adverse events above, potentially important events that occurred in at least two patients/subjects exposed to losartan or other adverse events that occurred in <1% of patients in clinical studies are listed below. It cannot be determined whether these events were causally related to losartan: Body as a Whole: accidental injury, fracture, tissue damage, urticaria, rash. Cardiovascular: Angina pectoris, second degree AV block, CVA, hypotension, myocaridal infection, arrhythmias, including atrial fibrillation, palpitation, sinus bradycardia, tachycardia, ventricular tachycardia, ventricular fibrillation; Digestive: anorexia, constipation, dental pain, dry mouth, flatulence, gastritis, vomiting. Hematologic: anemia; Metabolic: gout, Musculoskeletal: arm pain, hip pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthritis, arthralgia, fibromyalgia, muscle weakness; Nervous System/Psychiatric: anxiety, anxiety disorder, ataxia, confusion, depression, dream abnormalities, hyperventilation, decreased libido, memory impairment, migraine, nervousness, paresthesia, peripheral neuropathy, paresthesia, sleep disorder, somnolence, tremor, vertigo; Respiratory: dyspnea, bronchitis, pharyngeal discomfort, epistaxis, rhinitis, respiratory congestion; Skin: alopecia, dermatitis, dry skin, ecchymosis, erythema, flushing, photosensitivity, pruritus, rash, sweats, urticaria; Special Senses: blurred vision, tinnitus, ingesting in the eye, conjunctivitis, taste perversion, tinnitus, decrease in visual acuity; Urogenital: impotence, nocturia, urinary frequency, urinary tract infection. Persistent dry cough (with an incidence of a few percent) has been associated with ACE inhibitor use and in practice can be a cause of discontinuation of ACE inhibitor therapy. Two prospective, parallel group, double-blind, randomized, controlled trials were conducted to assess the effects of losartan on the incidence of cough in hypertensive patients who had experienced cough while receiving ACE inhibitor therapy. Patients who had typical ACE inhibitor cough when challenged with lisinopril, whose cough disappeared on placebo, were randomized to losartan 50 mg, lisinopril 20 mg, or either placebo (taste study, n=33/1) or 25 mg hydrochlorothiazide (n=123). 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>HCTZ</th>
<th>Losartan</th>
<th>Lisinopril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>25%</td>
<td>17%</td>
<td>69%</td>
</tr>
<tr>
<td>Study 2</td>
<td>Placebo</td>
<td>Losartan</td>
<td>Lisinopril</td>
</tr>
<tr>
<td>Cough</td>
<td>35%</td>
<td>29%</td>
<td>62%</td>
</tr>
</tbody>
</table>

1 Demographics = 89% Caucasian, 6% females
2 Demographics = 96% Caucasian, 5% females

These studies demonstrate that the incidence of cough associated with losartan therapy, in a population that all had cough associated with ACE inhibitor therapy, is similar to that associated with hydrochlorothiazide or placebo therapy. Cases of cough, including positive re-challenges, have been reported with the use of losartan in post-marketing experience.

Post-Marketing Experience
The following additional adverse reactions have been reported in post-marketing experience:
Hypersensitivity: Angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue has been reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors.
Dysphonia (reported rarely).
Respiratory: Dry cough (see above).
Hyperkalemia has been reported.
Laboratory Test Findings
In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of COZAAR.
Creatinine, Blood Urea Nitrogen: Minor increase in blood urea nitrogen (BUN) or serum creatinine were observed in less than 0.1% patients of patients with essential hypertension treated with COZAAR alone (see PRECAUTIONS, Impaired Renal Function).
Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.15 grams percent and 0.06 volume percent, respectively) occurred frequently in patients treated with COZAAR alone, but were rarely of clinical importance. No patients were discontinued due to anemia.
Liver Function Tests: Occasional elevations of liver enzymes and/or serum bilirubin have occurred; in patients with essential hypertension treated with COZAAR alone, one patient (0.1%) was discontinued due to these laboratory adverse experiences.

OVERDOSAGE
Significant lethality was observed in mice and rats after oral administration of 1000 mg/kg and 2000 mg/kg, respectively, about 44 and 170 times the maximum recommended human dose on a mg/m² basis.
Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur when large quantities are ingested. If symptomatic hypotension should occur, supportive treatment should be instituted.
Neither losartan nor its active metabolite can be removed by hemodialysis.

DOSEAGE AND ADMINISTRATION
The usual starting dose of COZAAR is 50 mg once daily, with 25 mg used in patients with possible depletion of intravascular volume e.g., patients treated with diuretics (see WARNINGS, Hypotension — Volume-Depressed Patients, and patients with a history of hemocritural hypertension (see PRECAUTIONS, Geriatric). COZAAR can be administered once or twice daily with total daily doses ranging from 25 mg to 100 mg.
If the antihypertensive effect measured at trough using once-a-day dosing is inadequate, a twice-a-day regimen at the same total daily dose or an increase in dose may give a more satisfactory response.
If blood pressure is not controlled by COZAAR alone, a low dose of a diuretic may be added. Hydrochlorothiazide has been shown to have an additive effect see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects.
No initial dosage adjustment is necessary for elderly patients or for patients with renal impairment, including patients on dialysis.
COZAAR may be administered with other antihypertensive agents.
COZAAR may be administered with or without food.

HOW SUPPLIED
36/12 — Tablets COZAAR, 25 mg, are light green, tear-drop shaped, film-coated tablets with code MRK on one side and 951 on the other. They are supplied as follows:
500 (05-01-414406, 25 mg/90's)
NDC 0006-0590-10, 25 mg/100's
NDC 0006-0614-010, 25 mg/100's
NDC 0006-0614-020, 25 mg/100's
NDC 0006-0614-016, 25 mg individually sealed 100's.
NDC 0006-0614-021, Tablets COZAAR, 50 mg, are green, tear-drop shaped, film-coated tablets with code MRK 952 on one side and COZAAR on the other. They are supplied as follows:
NDC 0006-0595-31, 21 units of use bottles of 50
NDC 0006-0595-16, 50 mg/50's
NDC 0006-0605-74, 54 unit of use bottles of 90
NDC 0006-0614-020, 50 mg/100's
NDC 0006-0614-020, 50 mg/100's
NDC 0006-0614-030, 50 mg individually sealed 100's.
NDC 0006-0614-016, 50 mg/100's
NDC 0006-0614-016, 50 mg individually sealed 100's
NDC 0006-0595-82, bottles of 1,000.
Storage
Store at controlled room temperature, 15-30°C (59-86°F).
Keep container tightly closed. Protect from light.

MERCK & CO., INC., West Point, PA 19488, USA
by:
DuPont Pharma
Wilmington, DE 19880, USA
Issued August 1989
Printed in USA
RHPM Review of Labeling

NDA:
20-386/SLR-015 Cozaar (losartan potassium) Tablets
20-387/SLR-011 Hyzaar (losartan potassium/hydrochlorothiazide) Tablets

Date of submissions: October 14, 1998
Date of receipt: October 19, 1998
Applicant: Merck Research Laboratories

Background: Merck has submitted Changes Being Effected supplements for their losartan-containing products to provide for changes to the PRECAUTIONS and ADVERSE REACTIONS sections of the labeling.

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

NDA 20-386 and 20-387:
PRECAUTIONS, General: “Hypersensitivity. See ADVERSE REACTIONS, Post-Marketing Experience.” has been moved to the beginning of this subsection, and “Angioedema” has been added. It now reads, “Hypersensitivity: Angioedema. See ADVERSE REACTIONS, Post-Marketing Experience.”

ADVERSE REACTIONS, Post-Marketing Experience, Hypersensitivity: this subsection has been revised to read, “Angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, an/or tongue has been reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors.”

HOW SUPPLIED: the DuPont Pharma signature has been revised.

NDA 20-386:
PRECAUTIONS, Information for Patients: a new subsection has been added for consistency with the HYZAAR package insert, in which this change was made in supplement 010:
“Potassium Supplements: A patient receiving COZAAR should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician (see PRECAUTIONS, Drug Interactions).”

ADVERSE REACTIONS, Laboratory Test Findings, Creatinine, Blood Urea Nitrogen: the cross-reference, “(see PRECAUTIONS, Impaired Renal Function)” has been added. This cross-reference was inadvertently deleted in supplement 014.

Recommendation: I will prepare an approval letter for these supplements for Dr. Lipicky’s signature. These supplements fall under 21 CFR 314.70 (c), Supplements for changes that may be made before FDA approval.
cc:   NDA 20-386/S-015
      NDA 20-387/S-011
      HFD-110 (both)
      HF-2/MedWatch
      HFD-110/KBongiovanni
      HFD-110/SBenton

kb/10/30/98.