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

CENTER FOR DRUG EVALUATION AND RESEARCH

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

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
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Chemistry Review(s)	X			
EA/FONSI				X
Pharmacology Review(s)				X
Statistical Review(s)				X
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)				X
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CENTER FOR DRUG EVALUATION AND RESEARCH

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

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-386/S-007
20-387/S-005

JUL 7 1997

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.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

NDA

If you have any questions, please contact:

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

Sincerely yours,

11/7/97

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-613/OGD (with labeling)
HFD-735/DPE (with labeling)
DISTRICT OFFICE
HFD-810/ONDC Division Director
HFI-20/Press Office (with labeling)
HFD-110/KBonglovanni
sb/10/27/97;11/6/97
R/D: KKnudsen/10/28/97
NStockbridge/10/28/97
CGanley/10/29/97
RMittal/10/29/97
RWolters/10/29/97
AProakis/10/29/97
CResnick/10/29/97
NMorgenstern/11/5/97

K Bonglovanni 11-6-97

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

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

COZAAR®
(LOSARTAN POTASSIUM TABLETS)

USE IN PREGNANCY

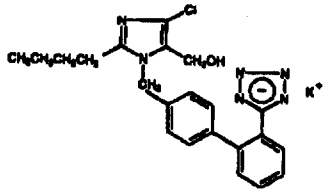
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, COZAAR should be discontinued as soon as possible. See WARNINGS: *Fetal/Neonatal Morbidity and Mortality*.

DESCRIPTION

COZAAR* (losartan potassium), the first of a new class of antihypertensives, is an angiotensin II receptor (type AT_1) antagonist.

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

Its empirical formula is $C_{22}H_{22}ClKN_6O$, and its structural formula is:



Losartan potassium is a white to off-white free-flowing crystalline powder with a molecular weight of 461.01. It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone. Oxidation of the 5-hydroxymethyl group on the imidazole ring results in the active metabolite of losartan.

COZAAR is available for oral administration containing either 25 mg or 50 mg of losartan potassium and the following inactive ingredients: microcrystalline cellulose, lactose hydrous, 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), is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland). There is also an AT_2 receptor found in many tissues but it is not known to be associated with cardiovascular homeostasis. Both losartan and its principal active metabolite do not exhibit any partial agonist activity at the AT_1 receptor and have much greater affinity (about 1000-fold) for the AT_1 receptor than for the AT_2 receptor. *In vitro* binding studies indicate that losartan is a reversible, competitive inhibitor of the AT_1 receptor. The active metabolite is 10 to 40 times more potent by weight than losartan and appears to be a reversible, non-competitive inhibitor of the AT_1 receptor.

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

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 carboxylic acid metabolite that is responsible for most of the angiotensin II receptor antagonism that follows losartan treatment. The terminal half-life of losartan is about 2 hours and of the metabolite is about 6-9 hours. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan doses up to 200 mg and do not change over time. Neither losartan nor its metabolite accumulate in plasma upon repeated once-daily dosing.

Following oral administration, losartan is well absorbed (based on absorption of radiolabeled losartan) and undergoes substantial first-pass metabolism; the systemic bioavailability of losartan is approximately 33%. About 14% of an orally-administered dose of losartan is converted to the active metabolite. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. While maximum plasma concentrations of losartan and its active metabolite are approximately equal, the AUC of the metabolite is about 4 times as great as that of losartan. A meal slows absorption of losartan and decreases its C_{max} but has only minor effects on losartan AUC or on the AUC of the metabolite (about 10% decreased).

Both losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2% respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed. Following oral and intravenous administration of ^{14}C-labeled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and its active metabolite. *In vitro* studies indicate that cytochrome P450 2C9 and 3A4 are involved in the biotransformation of losartan to its metabolites. Minimal conversion of losartan to the active metabolite (less than 1% of the dose compared to 14% of the dose in normal subjects) was seen in about one percent of individuals studied.

The volume of distribution of losartan is about 34 liters and of the active metabolite is about 12 liters. Total plasma clearance of losartan and the active metabolite is about 600 mL/min and 50 mL/min, respectively, with renal clearance of about 75 mL/min and 25 mL/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% is excreted in urine as active metabolite. Biliary excretion contributes to the elimination of losartan and its metabolites. Following oral ^{14}C-labeled losartan, about 35% of radioactivity is recovered in the urine and about 60% in the feces. Following an intravenous dose of ^{14}C-labeled losartan, about 45% of radioactivity is recovered in the urine and 50% in the feces.

Special Populations

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

Geriatric and Gender: Losartan pharmacokinetics have been investigated in the elderly (65-75 years) and in both genders. Plasma concentrations of losartan and its active metabolite are similar in elderly and young hypertensives. Plasma concentrations of losartan were about twice as high in female hypertensives as male hypertensives, but concentrations of the active metabolite were similar in males and females. 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 for 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, 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 80% lower and the oral bioavailability was about 2-times higher. A 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 oral or intravenous digoxin. Coadministration of losartan and cimetidine led to an increase of about 18% in AUC of losartan but did not affect the pharmacokinetics of its active metabolite. Coadministration of losartan and phenobarbital led to a reduction of about 20% in the AUC of losartan and that of its active metabolite. 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 I) infusions. A dose of 100 mg inhibits the pressor effect by about 85% at peak with 25-40% inhibition persisting for 24 hours. Removal of the negative feedback of angiotensin II causes a 2-3 fold rise in plasma renin activity and consequent rise in angiotensin II plasma concentration in hypertensive patients. Losartan does not affect the response to bradykinin, whereas ACE inhibitors increase the response to bradykinin. Aldosterone plasma concentrations fall follow-

ing 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 4 placebo-controlled 6-12 week trials of dosages from 10 to 150 mg per day in patients with baseline diastolic blood pressures of 95-115. The studies allowed comparisons of two doses (50-100 mg/day) as once-daily or twice-daily regimens, comparisons of peak and trough effects, and comparisons of response by gender, age, and race. Three additional studies examined the antihypertensive effects of losartan and hydrochlorothiazide in combination.

The 4 studies of losartan monotherapy included a total of 1075 patients randomized to several doses of losartan and 334 to placebo. The 10 and 25 mg doses produced some effect at peak (6 hours after dosing) but small and inconsistent trough (24 hour) responses. Doses of 50, 100 and 150 mg once daily gave statistically significant systolic/diastolic mean decreases in blood pressure, compared to placebo in the range of 5.5-10.5/3.5-7.5 mmHg, with the 150 mg dose giving no greater effect than 50-100 mg. Twice-daily dosing at 50-100 mg/day gave consistently larger trough responses than once-daily dosing at the same total dose. Peak (6 hour) effects were uniformly, but moderately, larger than trough effects, with the trough-to-peak ratio for systolic and diastolic responses 50-95% and 60-90%, respectively.

Addition of a low dose of hydrochlorothiazide (12.5 mg) to losartan 50 mg once daily resulted in placebo-adjusted blood pressure reductions of 15.5/9.3 mmHg.

Analysis of age, gender, and race subgroups of patients showed that men and women, and patients over and under 65, had generally similar responses. Black patients, however, had notably smaller responses to losartan monotherapy.

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

Persistent dry cough (with an incidence of a few percent) has been associated with ACE inhibitor use and in practice can be a cause of discontinuation of ACE inhibitor therapy. Two prospective, parallel-group, double-blind, randomized, controlled trials were conducted to assess the effects of losartan on the incidence of cough in hypertensive patients who had experienced cough while receiving ACE inhibitor therapy. Patients who had typical ACE inhibitor cough when challenged with lisinopril, whose cough disappeared on placebo, were randomized to losartan 50 mg, lisinopril 20 mg, or either placebo (one study, n=97) or 25 mg hydrochlorothiazide (n=135). The double-blind treatment period lasted up to 8 weeks. The incidence of cough is shown below.

Study 1†	HCTZ	Losartan	Lisinopril
Cough	25%	17%	69%
Study 2††	**Placebo**	**Losartan**	**Lisinopril**
Cough	36%	29%	62%

†Demographics = (88% caucasian, 64% female)
††Demographics = (80% caucasian, 51% female)

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

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 notably less in black patients than in non-blacks, a finding similar to the small effect of angiotensin converting enzyme inhibitors in blacks.

CONTRAINDICATIONS

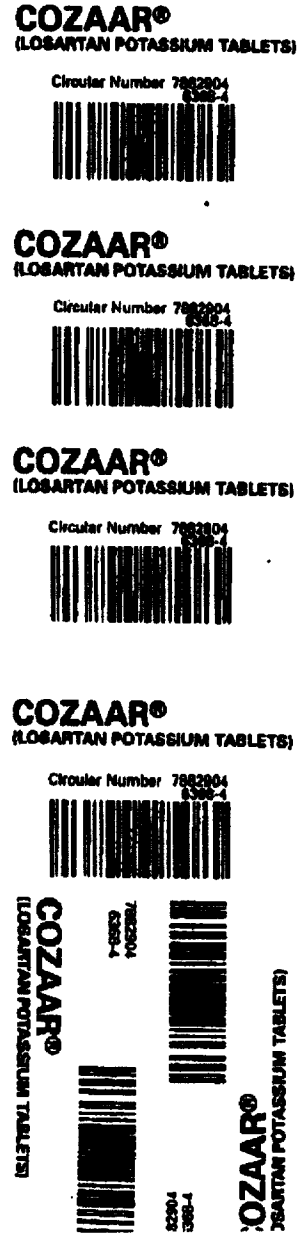
COZAAR is contraindicated in patients who are hypersensitive to any component of this product.

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 dozen cases 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 skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has



COZAAR® (Losartan Potassium Tablets)

also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester.

Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of 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 mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, COZAAR should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

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

Losartan potassium has been shown to produce adverse effects in rat fetuses and neonates, including decreased body weight, delayed physical and behavioral development, mortality and renal toxicity. 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/m^2 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

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

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

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 consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions

No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, cimetidine and phenobarbital. (See CLINICAL PHARMACOLOGY, *Drug Interactions.*) Potent inhibitors of cytochrome P450 3A4 and 2C9 have not been studied clinically but *in vitro* studies show significant inhibition of the formation of the active metabolite by inhibitors of P450 3A4 (ketoconazole, troleandomycin, gestodene), or P450 2C9 (sulfaphenazole) and nearly complete inhibition by the combination of sulfaphenazole and ketoconazole. The pharmacodynamic consequences of concomitant use of losartan and these inhibitors have not been examined.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Losartan potassium was not carcinogenic when administered at maximally tolerated dosages to rats and mice for 105 and 93 weeks, respectively. Female rats given the highest dose (270 mg/kg/day) had a slightly higher incidence of pancreatic acinar adenoma. The maximally tolerated dosages (270 mg/kg/day in rats, 200 mg/kg/day in mice) provided systemic exposures for losartan and its pharmacologically active metabolite that were approximately 160- and 90-times (rats) and 30- and 15-times (mice) the exposure of a 50 kg human given 100 mg per day.

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

Fertility and reproductive performance were not affected in studies with male rats given oral doses of losartan potassium up to approximately 188 mg/kg/day. The administration of toxic dosage levels in females (300/200 mg/kg/day) was associated with a significant ($p<0.05$) decrease in the number of corpora lutea/female, implants/female, and live fetuses/female at C-section. At 100 mg/kg/day only a decrease in the number of corpora lutea/female was observed. The relationship of these findings to drug-treatment is uncertain since there was no effect at these dosage levels on implants/pregnant female, percent post-implantation loss, or live animals/litter at parturition. In nonpregnant rats dosed at 135 mg/kg/day for 7 days, systemic exposure (AUCs) for losartan and its active metabolite were approximately 65 and 26 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 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. 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 receiving COZAAR in controlled clinical studies, 991 patients (19%) were 65 years and over, while 37 patients (2%) 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 4059 patients/subjects overall. Over 1200 patients were treated for over 6 months and more than 800 for over one 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 clinical adverse experiences was required in 2.3 percent of patients treated with COZAAR and 3.7 percent of patients given placebo.

The following table of adverse events is based on four 6-12 week placebo controlled trials involving over 1000 patients on various doses (10-150 mg) of losartan and over 300 patients given placebo. All doses 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 attributed to the treatment, occurring in at least 1% of patients treated with losartan and that were more frequent on losartan than placebo.

	Losartan (n=1076) Incidence	Placebo (n=334) Incidence
Digestive		
Diarrhea	2.4	2.1
Dyspepsia	1.3	1.2
Musculoskeletal		
Cramp, muscle	1.1	0.3
Myalgia	1.0	0.9
Pain, back	1.8	1.2
Pain, leg	1.0	0.0
Nervous System/Psychiatric		
Dizziness	3.5	2.1
Insomnia	1.4	0.6
Respiratory		
Congestion, nasal	2.0	1.2
Cough	3.4	3.3
Infection, upper respiratory	7.9	6.9
Sinus disorder	1.5	1.2
Sinusitis	1.0	0.3

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

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

A patient with known hypersensitivity to aspirin and penicillin, when treated with 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 peeling of palms and hemolysis was reported in one subject.

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:* facial edema, fever, orthostatic effects, syncope; *Cardiovascular:* angina pectoris, second degree AV block, CVA, hypotension, myocardial infarction, 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, arthralgia, arthritis, fibromyalgia, muscle weakness; *Nervous System/Psychiatric:* anxiety, anxiety disorder, ataxia, confusion, depression, dream abnormality, hypesthesia, decreased libido, memory impairment, migraine, nervousness, paresthesia, peripheral neuropathy, panic disorder, 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, sweating, urticaria; *Special Senses:* blurred vision, burning/stinging in the eye, conjunctivitis, taste perversion, tinnitus, decrease in visual acuity; *Urogenital:* impotence, nocturia, urinary frequency, urinary tract infection.

Post-Marketing Experience

The following 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.

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 increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 0.1 percent of patients with essential hypertension treated with COZAAR alone. No patient discontinued taking COZAAR alone due to increased BUN or serum creatinine. (See PRECAUTIONS, *Impaired Renal Function.*)

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.11 grams percent and 0.33 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 176 times the maximum recommended human dose on a mg/m² basis.

Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan nor its active metabolite can be removed by hemodialysis.

DOSAGE 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-Depleted Patients*) and patients with a history of hepatic impairment (see PRECAUTIONS, *General*). 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.

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COZAAR® (Losartan Potassium Tablets)

COZAAR may be administered with other antihypertensive agents.

COZAAR may be administered with or without food.

HOW SUPPLIED

No. 3612 — Tablets COZAAR, 25 mg, are light green, tear drop-shaped, film-coated tablets with code MRK on one side and 961 on the other. They are supplied as follows:
NDC 0006-0961-54 unit of use bottles of 90
(6505-01-414-4064, 25 mg 90's)
NDC 0006-0961-58 unit of use bottles of 100
(6505-01-414-4068, 25 mg 100's)
NDC 0006-0961-28 unit dose packages of 100
(6505-01-414-4063, 25 mg individually sealed 100's).

No. 3613 — Tablets COZAAR, 50 mg, are green, teardrop shaped, film-coated tablets with code MRK 962 on one side and COZAAR on the other. They are supplied as follows:
NDC 0006-0962-31 unit of use bottles of 30
(6505-01-414-4062, 50 mg 30's)
NDC 0006-0962-54 unit of use bottles of 90
(6505-01-414-4060, 50 mg 90's)
NDC 0006-0962-58 unit of use bottles of 100
(6505-01-414-4065, 50 mg 100's)
NDC 0006-0962-28 unit dose packages of 100
(6505-01-414-4061, 50 mg individually sealed 100's)
NDC 0006-0962-82 bottles of 1,000.

Storage

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

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

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

HYZAAR®

(LOSARTAN POTASSIUM-HYDROCHLOROTHIAZIDE TABLETS)

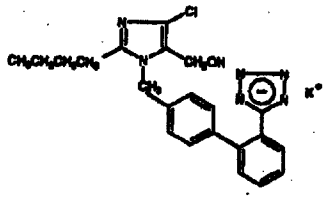
USE IN PREGNANCY

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/Neonatal Morbidity and Mortality*.

DESCRIPTION

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

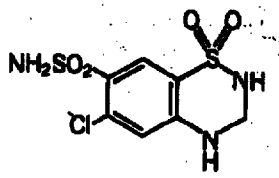
Losartan potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt. Its empirical formula is $C_{22}H_{22}ClKN_6O$, and its structural formula is:



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

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

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$, and its structural formula is:



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

HYZAAR is available for oral administration containing 50 mg of losartan potassium, 12.5 mg of hydrochlorothiazide and the following inactive ingredients: microcrystalline cellulose, lactose hydrous, pregelatinized starch, magnesium stearate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, titanium dioxide and D&C yellow No. 10 aluminum lake.

HYZAAR contains 4.24 mg (0.108 mEq) of potassium.

CLINICAL PHARMACOLOGY

Mechanism of Action

Angiotensin II (formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II)), is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland). There is also an AT_2 receptor found in many tissues but it is not known to be associated with cardiovascular homeostasis. Both losartan and its principal active metabolite do not exhibit any partial agonist activity at the AT_1 receptor and have much greater affinity (about 1000-fold) for the AT_1 receptor than for the AT_2 receptor. *In vitro* binding studies indicate that losartan is a reversible, competitive inhibitor of the AT_1 receptor. The active metabolite is 10 to 40 times more potent by weight than losartan and appears to be a reversible, non-competitive inhibitor of the AT_1 receptor.

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

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

The mechanism of the antihypertensive effect of thiazides is unknown.

Pharmacokinetics

General

Losartan Potassium

Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. It is converted, in part, to an active carboxylic acid metabolite that is responsible for most of the angiotensin II receptor antagonism that follows losartan treatment. The terminal half-life of losartan is about 2 hours and of the metabolite is about 6-9 hours. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan doses up to 200 mg and do not change over time. Neither losartan nor its metabolite accumulate in plasma upon repeated once-daily dosing.

Following oral administration, losartan is well absorbed (based on absorption of radiolabeled losartan) and undergoes substantial first-pass metabolism; the systemic bioavailability of losartan is approximately 33%. About 14% of an orally-administered dose of losartan is converted to the active metabolite. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. While maximum plasma concentrations of losartan and its active metabolite are approximately equal, the AUC of the metabolite is about 4 times as great as that of losartan. A meal slows absorption of losartan and decreases its C_{max} but has only minor effects on losartan AUC or on the AUC of the metabolite (about 10% decreased).

Both losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2% respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed. Following oral and intravenous administration of ^{14}C-labeled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and its active metabolite. *In vitro* studies indicate that cytochrome P450 2C9 and 3A4 are involved in the biotransformation of losartan to its metabolites. Minimal conversion of losartan to the active metabolite (less than 1% of the dose compared to 14% of the dose in normal subjects) was seen in about one person of individuals studied.

The volume of distribution of losartan is about 34 liters and of the active metabolite is about 12 liters. Total plasma clearance of losartan and the active metabolite is about 600 mL/min and 50 mL/min, respectively, with renal clearance of about 75 mL/min and 25 mL/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% is excreted in urine as active metabolite. Biliary excretion contributes to the elimination of losartan and its metabolites. Following oral ^{14}C-labeled losartan, about 35% of radioactivity is recovered in the urine and about 60% in the feces. Following an intravenous dose of ^{14}C-labeled losartan, about 43% of radioactivity is recovered in the urine and 50% in the feces.

Special Populations

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

Geriatric and Gender: Losartan pharmacokinetics have been investigated in the elderly (65-75 years) and in both genders. Plasma concentrations of losartan and its active metabolite are similar in elderly and young hypertensives. Plasma concentrations of losartan were about twice as high in female hypertensives as male hypertensives, but concentrations of the active metabolite were similar in males and females.

Race: Pharmacokinetic differences due to race have not been studied.

Renal Insufficiency: Plasma concentrations of losartan are not altered in patients with creatinine clearance above 20 mL/min. In patients with lower creatinine clearance, AUCs are about 80% greater and are doubled in hemodialysis patients. Plasma concentrations of the active metabolite are not significantly altered in patients with renal impairment or in hemodialysis patients. Neither losartan nor its active metabolite can be removed by hemodialysis.

Hepatic Insufficiency: Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5 times and about 1.7 times those in young male volunteers. Compared to normal subjects the total plasma clearance of losartan in patients with hepatic insufficiency was about 50% lower and the oral bioavailability was about 2-times higher. The lower starting dose of losartan recommended for use in patients with hepatic impairment cannot be given using HYZAAR. Its use in such patients as a means of losartan titration is, therefore, not recommended (see DOSAGE AND ADMINISTRATION).

Drug Interactions

Losartan Potassium

Losartan, administered for 12 days, did not affect the pharmacokinetics or pharmacodynamics of a single dose of warfarin. Losartan did not affect the pharmacokinetics of oral or intravenous digoxin. Coadministration of losartan and cimetidine led to an increase of about 18% in AUC of losartan but did not affect the pharmacokinetics of its active metabolite. Coadministration of losartan and phenobarbital led to a reduction of about 20% in the AUC of losartan and that of its active metabolite. There is no pharmacokinetic interaction between losartan and hydrochlorothiazide.

Hydrochlorothiazide

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

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Pharmacodynamics and Clinical Effects

Losartan Potassium

Losartan inhibits the pressor effect of angiotensin II (as well as angiotensin 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, whereas ACE inhibitors increase the response to bradykinin. Aldosterone plasma concentrations fall following losartan administration. In spite of the effect of losartan on aldosterone secretion, very little effect on serum potassium was observed.

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

The antihypertensive effects of losartan were demonstrated principally in 4 placebo-controlled 6-12 week trials of dosages from 10 to 150 mg per day in patients with baseline diastolic blood pressures of 95-115. The studies allowed comparisons of two doses (50-100 mg/day) as once-daily or twice-daily regimens, comparisons of peak and trough effects, and comparisons of response by gender, age, and race. Three additional studies examined the antihypertensive effects of losartan and hydrochlorothiazide in combination.

The 4 studies of losartan monotherapy included a total of 1075 patients randomized to several doses of losartan and 334 to placebo. The 10 and 25 mg doses produced some effect at peak (6 hours after dosing) but small and inconsistent trough (24 hour) responses. Doses of 50, 100, and 150 mg once daily gave statistically significant systolic/diastolic mean decreases in blood pressure, compared to placebo in the range of 5.5-10.5/3.5-7.5 mmHg, with the 150 mg dose giving no greater effect than 50-100 mg. Twice-daily dosing at 50-100 mg/day gave consistently larger trough responses than once daily dosing at the same total dose. Peak (6 hour) effects were uniformly, but moderately larger than trough effects, with the trough to peak ratio for systolic and diastolic responses 50-85% and 80-60% 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

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placebo (one study, n=87) or 25 mg hydrochlorothiazide (n=139). The double-blind treatment period lasted up to 8 weeks. The incidence of cough is shown below.

Study 1[†]	HCTZ	Losartan	Lisinopril
Cough	28%	17%	68%

Study 2[††]	Placebo	Losartan	Lisinopril
Cough	36%	29%	62%

[†]Demographics = (68% caucasian, 84% female)
[††]Demographics = (86% caucasian, 81% female)

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

Losartan Potassium-Hydrochlorothiazide

The 3 controlled studies of losartan and hydrochlorothiazide included over 1300 patients assessing the antihypertensive efficacy of various doses of losartan (25, 50 and 100 mg) and concomitant hydrochlorothiazide (6.25, 12.5 and 25 mg). A factorial study compared the combination of losartan/hydrochlorothiazide 50/12.5 mg with its components and placebo. The combination of losartan/hydrochlorothiazide 50/12.5 mg resulted in an approximately additive placebo-adjusted systolic/diastolic response (16.5/8.0 mmHg for the combination compared to 8.5/6.0 mmHg for losartan alone and 7.0/3.0 mmHg for hydrochlorothiazide alone). Another study investigated the dose-response relationship of various doses of hydrochlorothiazide (6.25, 12.5 and 25 mg) or placebo on a background of losartan (50 mg) in patients not adequately controlled (SiDBP 93-120 mmHg) on losartan (50 mg) alone. The third study investigated the dose-response relationship of various doses of losartan (25, 50 and 100 mg) or placebo on a background of hydrochlorothiazide (25 mg) in patients not adequately controlled (SiDBP 93-120 mmHg) on hydrochlorothiazide (25 mg) alone. These studies showed an added antihypertensive response at trough (24 hours post-dosing) of hydrochlorothiazide 12.5 or 25 mg added to losartan 50 mg of 5.5/5.5 and 10.0/6.0 mmHg, respectively. Similarly, there was an added antihypertensive response at trough when losartan 50 or 100 mg was added to hydrochlorothiazide 25 mg of 9.0/5.5 and 12.5/6.5 mmHg, respectively. There was no significant effect on heart rate.

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

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

INDICATIONS AND USAGE

HYZAAR is indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

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

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

WARNINGS

Fetal/Neonatal Morbidity and Mortality

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

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester.

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

Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, HYZAAR should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

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

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

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

Hypotension — Volume-Depleted Patients

In patients who are intravascularly volume-depleted (e.g., those treated with diuretics), symptomatic hypotension may occur after initiation of therapy with HYZAAR. This condition should be corrected prior to administration of HYZAAR (see DOSAGE AND ADMINISTRATION).

Impaired Hepatic Function

Losartan Potassium-Hydrochlorothiazide

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

Hydrochlorothiazide

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

Hypersensitivity Reaction

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

Systemic Lupus Erythematosus

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

Lithium Interaction

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

PRECAUTIONS

General

Losartan Potassium-Hydrochlorothiazide

In double-blind clinical trials of various doses of losartan potassium and hydrochlorothiazide, the incidence of hypertensive patients who developed hypokalemia (serum potassium <3.5 mEq/L) was 0.7% versus 3.8% for placebo; the incidence of hyperkalemia (serum potassium >5.7 mEq/L) was 0.4%. No patient discontinued due to increases or decreases in serum potassium. The mean decrease in serum potassium in patients treated with various doses of losartan and hydrochlorothiazide was 0.123 mEq/L. In patients treated with various doses of losartan and hydrochlorothiazide, there was also a dose-related decrease in the hypokalemic response to hydrochlorothiazide as the dose of losartan was increased, as well as a dose-related decrease in serum uric acid with increasing doses of losartan.

Hydrochlorothiazide

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

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving

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

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

Superficial peeling of palms and hemolysis were reported in one subject treated with losartan potassium.

Losartan Potassium

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

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

Hydrochlorothiazide

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

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

Post-Marketing Experience

The following 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.

Hyperkalemia has been reported with losartan.

Laboratory Test Findings

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

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

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.14 grams percent and 0.72 volume percent, respectively) occurred frequently in patients treated with HYZAAR alone, but were rarely of clinical importance. No patients were discontinued due to anemia.

Liver Function Tests: Occasional elevations of liver enzymes and/or serum bilirubin have occurred. In patients with essential hypertension treated with HYZAAR alone, no patients were discontinued due to these laboratory adverse experiences.

Serum Electrolytes: See PRECAUTIONS.

OVERDOSAGE

Losartan Potassium

Significant lethality was observed in mice and rats after oral administration of 1000 mg/kg and 2000 mg/kg, respectively, about 44 and 170 times the maximum recommended human dose on a mg/m² basis.

Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan nor its active metabolite can be removed by hemodialysis.

Hydrochlorothiazide

The oral LD_{50} of hydrochlorothiazide is greater than 10 g/kg in both mice and rats. The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

DOSAGE AND ADMINISTRATION

The usual starting dose of losartan is 50 mg once daily, with 25 mg recommended for patients with intravascular volume depletion (e.g., patients treated with diuretics) (see WARNINGS, *Hypotension — Volume-Depleted Patients*) and patients with a history of hepatic impairment (see WARNINGS, *Impaired Hepatic Function*). Losartan can be administered once or twice daily at total daily doses of 25 to 100 mg. If the antihypertensive effect measured at trough using once-a-day dosing is inadequate, a twice-a-day regimen at the same total daily dose or an increase in dose may give a more satisfactory response.

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

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

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

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

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

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

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

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

HYZAAR may be administered with other antihypertensive agents.

HYZAAR may be administered with or without food.

HOW SUPPLIED

No. 2802 — Tablets HYZAAR, 50-12.5 are yellow, teardrop shaped, film-coated tablets, coded MRK 717 on one side and HYZAAR on the other. Each tablet contains 50 mg of losartan potassium and 12.5 mg of hydrochlorothiazide. They are supplied as follows:

NDC 0006-0717-31 unit of use bottles of 30
NDC 0006-0717-54 unit of use bottles of 90
NDC 0006-0717-58 unit of use bottles of 100
(0606-61-416-4330, 50-12.5 100's)
NDC 0006-0717-38 unit dose packages of 100.

Storage

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

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

by:
DU PONT PHARMA Wilmington, DE 19880 USA

Issued February 1997
Printed in USA

exposure achieved in man at the maximum recommended human daily dosage (100 mg).

Hydrochlorothiazide

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

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

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

Pregnancy

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

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Use in the Elderly

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

ADVERSE REACTIONS

Losartan potassium-hydrochlorothiazide has been evaluated for safety in 858 patients treated for essential hypertension. In clinical trials with losartan potassium-hydrochlorothiazide, no adverse experiences peculiar to this combination 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 therapy. In controlled clinical trials, discontinuation of therapy due to clinical adverse experiences was required in only 2.8% and 2.3% of patients treated with the combination and placebo, respectively.

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

	Losartan Potassium-Hydrochlorothiazide (n=858)	Placebo (n=173)
Body as a Whole		
Abdominal pain	1.2	0.6
Edema/swelling	1.3	1.2
Cardiovascular		
Palpitation	1.4	0.0
Musculoskeletal		
Back pain	2.1	0.6
Nervous/Psychiatric		
Dizziness	5.7	2.9
Respiratory		
Cough	2.8	2.3
Sinusitis	1.2	0.6
Upper respiratory infection	6.1	4.6
Skin		
Rash	1.4	0.0

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

parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

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

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

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

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

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

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

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

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

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

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

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

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

Impaired Renal Function

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

In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with losartan.

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

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

Information for Patients

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

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

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

Potassium Supplements: A patient receiving HYZAAR should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician.

Drug Interactions

Losartan Potassium

No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, cimetidine and phenobarbital. (See CLINICAL PHARMACOLOGY, *Drug Interactions*.) Potent inhibitors of cytochrome P450 2A4 and 2C9 have not been studied clinically but *in vitro* studies show significant inhibition of the formation of the active metabolite by inhibitors of P450 3A4 (ketoconazole, troleandomycin, gestodene), or P450 2C9 (sulfaphenazole) and nearly complete inhibition by the combination of sulfaphenazole and ketoconazole. The pharmacodynamic consequences of concomitant use of losartan and these inhibitors have not been examined.

Hydrochlorothiazide

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

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

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

Other antihypertensive drugs — additive effect or potentiation.

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

Corticosteroids, ACTH — intensified electrolyte depletion, particularly hypokalemia.

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

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

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Losartan Potassium-Hydrochlorothiazide

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

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

Losartan potassium, coadministered with hydrochlorothiazide, had no effect on the fertility or mating behavior of male rats at dosages up to 135 mg/kg/day of losartan and 33.75 mg/kg/day of hydrochlorothiazide. These dosages have been shown to provide respective systemic exposures (AUCs) for losartan, its active metabolite and hydrochlorothiazide that are approximately 80, 60 and 30 times greater than those achieved in humans with 100 mg of losartan potassium in combination with 25 mg of hydrochlorothiazide. In female rats, however, the coadministration of doses as low as 10 mg/kg/day of losartan and 2.5 mg/kg/day of hydrochlorothiazide was associated with slight but statistically significant decreases in fecundity and fertility indices. AUC values for losartan, its active metabolite and hydrochlorothiazide, extrapolated from data obtained with losartan administered to rats at a dose of 60 mg/kg/day in combination with 12.5 mg/kg/day of hydrochlorothiazide, were approximately 6, 2, and 2 times greater than those achieved in humans with 100 mg of losartan in combination with 25 mg of hydrochlorothiazide.

Losartan Potassium

Losartan potassium was not carcinogenic when administered at maximally tolerated dosages to rats and mice for 105 and 92 weeks, respectively. Female rats given the highest dose (270 mg/kg/day) had a slightly higher incidence of pancreatic acinar adenoma. The maximally tolerated dosages (270 mg/kg/day in rats, 200 mg/kg/day in mice) provided systemic exposures for losartan and its pharmacologically active metabolite that were approximately 160 and 90 times (rats) and 30 and 15 times (mice) the exposure of a 50 kg human given 100 mg per day.

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

Fertility and reproductive performance were not affected in studies with male rats given oral doses of losartan potassium up to approximately 180 mg/kg/day. The administration of toxic dosage levels in females (360/280 mg/kg/day) was associated with a significant ($p \leq 0.05$) decrease in the number of corpora lutea/female, implants/female, and live fetuses/female at C-section. At 100 mg/kg/day only a decrease in the number of corpora lutea/female was observed. The relationship of these findings to drug-treatment is uncertain since there was no effect at these dosage levels on implants/pregnant female, percent post-implantation loss, or live animals/litter at parturition. In nonpregnant rats dosed at 135 mg/kg/day for 7 days, systemic exposure (AUCs) for losartan and its active metabolite were approximately 66 and 26 times the

CENTER FOR DRUG EVALUATION AND RESEARCH

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

CHEMISTRY REVIEW(S)

MAY 13 1997

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/#:	MK-954; DuP-753; 1-158,086; L-158,086-005H;E-3340
Chem.Type/Ther.Class:	1s

Supplement Provides For:

Revised Draft Labeling for approved NDA.

ANDA Suitability Petition/DESI/Patent Status:

U.S. Patent 5,138,069 expiration date - 8/11/2009;
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.

DOSAGE FORM: tablets

STRENGTH: 20, 50 mg

ROUTE OF ADMINISTRATION: ORAL

DISPENSED: Rx

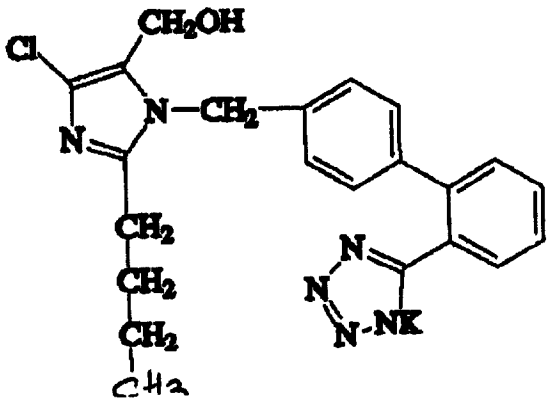
CHEMICAL NAME: 2-butyl-4-chloro-1[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]-methyl]-1H-imidazole-5-methanol, monopotassium salt.

CAS #: 124750-99-8

MOLECULAR FORMULA: $C_{22}H_{22}ClKN_6O$

MOLECULAR WEIGHT: 461.01

STRUCTURAL FORMULA:



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 effect 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/

5/13/97

Ramsharan D. Mittal Ph.D., Review Chemist
filename: C:\NDA\20386\20386MLR.007

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APPEARS THIS WAY
ON ORIGINAL

MAY 13 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCT
Review of Chemistry, Manufacturing, and Control

NDA #: 20-387 **REVIEW DATE:** 13-MAY-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SLR-005	17-APR-97	21-APR-97	23-APR-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-158,086-005H;E-3340
Chem.Type/Ther.Class:	1S

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: tablets

STRENGTH: 50 mg Losartan Potassium Tablets/12.5 mg Hydrochlorothiazide

ROUTE OF ADMINISTRATION: ORAL

DISPENSED: Rx

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

DRUG SUBSTANCE 1. LOSARTAN POTASSIUM

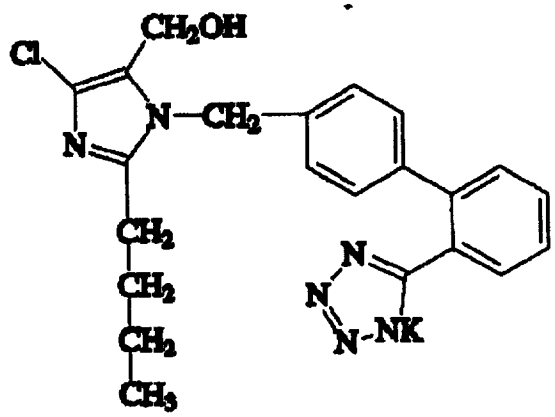
CHEMICAL NAME: 2-butyl-4-chloro-1[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]-methyl]-1H-imidazole-5-methanol, monopotassium salt.

CAS #: 124750-99-8

MOLECULAR FORMULA: $C_{22}H_{22}ClKN_6O$

MOLECULAR WEIGHT: 461.01

STRUCTURAL FORMULA:



DRUG SUBSTANCE 2. HYDROCHLOROTHIAZIDE

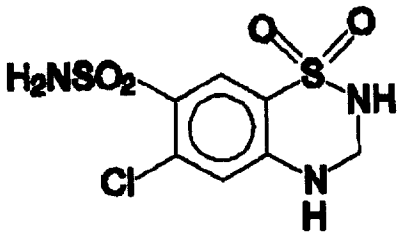
CHEMICAL NAME: 6-chloro-3, 4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

CAS #: 58-93-5

MOLECULAR FORMULA: $C_7H_8ClN_3O_4S_2$

MOLECULAR WEIGHT: 297.74

STRUCTURAL FORMULA:



REMARKS/COMMENTS:

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 effect 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/

RDMittal

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

5/13/97

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APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

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

ADMINISTRATIVE DOCUMENTS

JUL 10 1997

RHPM Review of Labeling

NDA: 20-386/SLR-007 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 20-386/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.

7-10-97
Kathleen F. Bonglovanni