

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

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## COZAAR® (LOSARTAN POTASSIUM TABLETS)

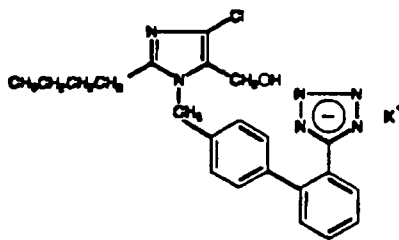
### USE IN PREGNANCY

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) is an angiotensin II receptor (type AT<sub>1</sub>) antagonist. Losartan potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-yl)phenyl]benzyl]imidazole-5-methanol monopotassium salt.

Its empirical formula is C<sub>22</sub>H<sub>22</sub>ClKN<sub>6</sub>O, 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 as tablets for oral administration containing either 25 mg, 50 mg or 100 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, 50 mg and 100 mg tablets contain potassium in the following amounts: 2.12 mg (0.054 mEq), 4.24 mg (0.108 mEq) and 8.48 mg (0.216 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<sub>1</sub> receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland). There is also an AT<sub>2</sub> 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<sub>1</sub> receptor and have much greater affinity (about 1000-fold) for the AT<sub>1</sub> receptor than for the AT<sub>2</sub> receptor. *In vitro* binding studies indicate that losartan is a reversible, competitive inhibitor of the AT<sub>1</sub> 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<sub>1</sub> 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 50% 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. Conversion of losartan to its active metabolite after intravenous administration is not affected by ketoconazole, an inhibitor of P450 3A4. There is no pharmacokinetic interaction between losartan and hydrochlorothiazide.

#### *Pharmacodynamics and Clinical Effects*

**Hypertension:** Losartan inhibits the pressor effect of angiotensin II (as well as angiotensin I) infusions. A dose of 100 mg inhibits the pressor effect by about 85% at peak with 25-40% inhibition persisting for 24 hours. Removal of the negative feedback of angiotensin II causes a 2-3 fold rise in plasma renin activity and consequent rise in angiotensin II plasma concentration in hypertensive patients. Losartan does not affect the response to bradykinin, whereas ACE inhibitors increase the response to bradykinin. Aldosterone plasma concentrations fall following losartan administration. In spite of the effect of losartan on aldosterone secretion, very little effect on serum potassium was observed.

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

The antihypertensive effects of 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 15.5/9.2 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. COZAAR was effective in reducing blood pressure regardless of race, although the effect was somewhat less in black patients (usually a low-renin population).

The effect of losartan is substantially present within one week but in some studies the maximal effect occurred in 3-6 weeks. In long-term follow-up studies (without placebo control) the effect of losartan appeared to be maintained for up to 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.

**Nephropathy in Type 2 Diabetic Patients:** The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study was a randomized, placebo-controlled, double-blind, multicenter study conducted worldwide in 1513 patients with type 2 diabetes with nephropathy (defined as serum creatinine 1.3 to 3.0 mg/dl in females or males  $\leq$ 60 kg and 1.5 to 3.0 mg/dl in males >60 kg and proteinuria [urinary albumin to creatinine ratio  $\geq$ 300 mg/g]).

Patients were randomized to receive COZAAR 50 mg once daily or placebo on a background of conventional antihypertensive therapy excluding ACE inhibitors and angiotensin II antagonists. After one month, investigators were instructed to titrate study drug to 100 mg once daily if the trough blood pressure goal (140/90 mmHg) was not achieved. Overall, 72% of patients received the 100 mg daily dose more than 50% of the time they were on study drug. Because the study was designed to achieve equal blood pressure control in both groups, other antihypertensive agents (diuretics, calcium-channel blockers, alpha- or beta-blockers, and centrally acting agents) could be added as needed in both groups. Patients were followed for a mean duration of 3.4 years.

The study population was diverse with regard to race (Asian 16.7%, Black 15.2%, Hispanic 18.3%, White 48.6%). Overall, 63.2% of the patients were men, and 66.4% were under the age of 65 years. Almost all of the patients (96.6%) had a history of hypertension, and the patients entered the trial with a mean serum creatinine of 1.9 mg/dl and mean proteinuria (urinary albumin/creatinine) of 1808 mg/g at baseline.

The primary endpoint of the study was the time to first occurrence of any one of the following events: doubling of serum creatinine, end-stage renal disease (need for dialysis or transplantation), or death. Treatment with COZAAR

resulted in a 16% risk reduction in this endpoint (see Figure 1 and Table 1). Treatment with COZAAR also reduced the occurrence of sustained doubling of serum creatinine by 25% and ESRD by 29% as separate endpoints, but had no effect on overall mortality (see Table 1).

The mean baseline blood pressures were 152/82 mmHg for COZAAR plus conventional antihypertensive therapy and 153/82 mmHg for placebo plus conventional antihypertensive therapy. At the end of the study, the mean blood pressures were 143/76 mmHg for the group treated with COZAAR and 146/77 mmHg for the group treated with placebo.

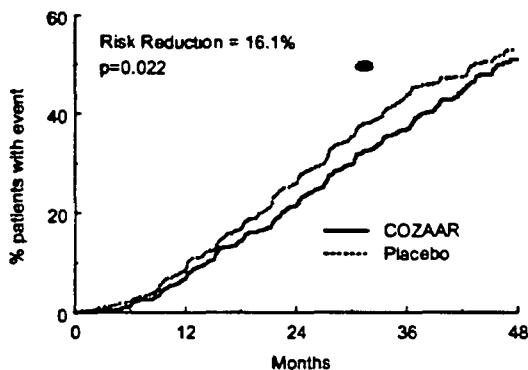


FIGURE 1: Kaplan-Meier curve for the primary composite endpoint of doubling of serum creatinine, end stage renal disease (need for dialysis or transplantation) or death.

Table 1 Incidence of Primary Endpoint Events

	Incidence		Risk Reduction	95% C.I	p-Value
	Losartan	Placebo			
Primary Composite Endpoint	43.5%	47.1%	16.1%	2.3% to 27.9%	0.022
Doubling of Serum Creatinine, ESRD and Death Occurring as a First Event					
Doubling of Serum Creatinine	21.6%	26.0%			
ESRD	8.5%	8.5%			
Death	13.4%	12.6%			
Overall Incidence of Doubling of Serum Creatinine, ESRD and Death					
Doubling of Serum Creatinine	21.6%	26.0%	25.3%	7.8% to 39.4%	0.006
ESRD	19.6%	25.5%	28.6%	11.5% to 42.4%	0.002
Death	21.0%	20.3%	-1.7%	-26.9% to 18.6%	0.884

The secondary endpoints of the study were change in proteinuria, change in the rate of progression of renal disease, and the composite of morbidity and mortality from cardiovascular causes (hospitalization for heart failure, myocardial infarction, revascularization, stroke, hospitalization for unstable angina, or cardiovascular death). Compared with placebo, COZAAR significantly reduced proteinuria by an average of 34%, an effect that was evident within 3 months of starting therapy, and significantly reduced the rate of decline in glomerular filtration rate during the study by 13%, as measured by the reciprocal of the serum creatinine concentration. There was no significant difference in the incidence of the composite endpoint of cardiovascular morbidity and mortality.

The favorable effects of COZAAR were seen in patients also taking other anti-hypertensive medications (angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors were not allowed), oral hypoglycemic agents and lipid-lowering agents.

For the primary endpoint and ESRD, the effects of COZAAR in patient subgroups defined by age, gender and race are shown in Table 2 below. Subgroup analyses can be difficult to interpret and it is not known whether these represent true differences or chance effects.

Table 2 Efficacy Outcomes within Demographic Subgroups

	No. of Patients	Primary Composite Endpoint			ESRD		
		COZAAR Event Rate %	Placebo Event Rate %	Hazard Ratio (95% CI)	COZAAR Event Rate %	Placebo Event Rate %	Hazard Ratio (95% CI)
Overall Results	1513	43.5	47.1	0.839 (0.721, 0.977)	19.6	25.5	0.714 (0.576, 0.885)
Age							
<65 years	1005	44.1	49.0	0.784 (0.653, 0.941)	21.1	28.5	0.670 (0.521, 0.863)
≥65 years	508	42.3	43.5	0.978 (0.749, 1.277)	16.5	19.6	0.847 (0.560, 1.281)
Gender							
Female	557	47.8	54.1	0.762 (0.603, 0.962)	22.8	32.8	0.601 (0.436, 0.828)
Male	956	40.9	43.3	0.892 (0.733, 1.085)	17.5	21.5	0.809 (0.605, 1.081)
Race							
Asian	252	41.9	54.8	0.655 (0.453, 0.947)	18.8	27.4	0.625 (0.367, 1.066)
Black	230	40.0	39.0	0.983 (0.647, 1.495)	17.6	21.0	0.831 (0.456, 1.516)
Hispanic	277	55.0	54.0	1.003 (0.728, 1.380)	30.0	28.5	1.024 (0.661, 1.586)
White	735	40.5	43.2	0.809 (0.645, 1.013)	16.2	23.9	0.596 (0.427, 0.831)

## INDICATIONS AND USAGE

### *Hypertension*

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

### *Nephropathy in Type 2 Diabetic Patients*

COZAAR is indicated for the treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria (urinary albumin to creatinine ratio ≥300 mg/g) in patients with type 2 diabetes and a history of hypertension. In this population, COZAAR reduces the rate of progression of nephropathy as measured by the occurrence of doubling of serum creatinine or end stage renal disease (need for dialysis or renal transplantation) (see CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects*).

## 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 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<sup>2</sup> basis). These findings are attributed to drug exposure in late gestation and during lactation. Significant levels of losartan and its active metabolite were shown to be present in rat fetal plasma during late gestation and in rat milk.

#### *Hypotension — Volume-Depleted Patients*

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

## **PRECAUTIONS**

### *General*

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

### *Impaired Hepatic Function*

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

### *Impaired Renal Function*

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

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

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

### *Electrolyte Imbalance*

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with proteinuria, the incidence of hyperkalemia was higher in the group treated with COZAAR as compared to the placebo group; however, few patients discontinued therapy due to hyperkalemia (see ADVERSE REACTIONS).

### *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.

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

### *Drug Interactions*

No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, cimetidine and phenobarbital. (See CLINICAL PHARMACOLOGY, *Drug Interactions*.) Potent inhibitors of cytochrome P450 3A4 and 2C9 have not been studied clinically but *in vitro* studies show significant inhibition of the formation of the active metabolite by inhibitors of P450 3A4 (ketoconazole, troleandomycin, gestodene), or P450 2C9 (sulfaphenazole) and nearly complete inhibition by the combination of sulfaphenazole and ketoconazole. In humans, ketoconazole, an inhibitor of P450 3A4, did not affect the conversion of losartan to the active metabolite after intravenous administration of losartan. Inhibitors of cytochrome P450 2C9

have not been studied clinically. The pharmacodynamic consequences of concomitant use of losartan and inhibitors of P450 2C9 have not been examined.

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

As with other antihypertensive agents, the antihypertensive effect of losartan may be blunted by the non-steroidal anti-inflammatory drug indomethacin.

#### *Carcinogenesis, Mutagenesis, Impairment of Fertility*

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

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

Fertility and reproductive performance were not affected in studies with male rats given oral doses of losartan potassium up to approximately 150 mg/kg/day. The administration of toxic dosage levels in females (300/200 mg/kg/day) was associated with a significant ( $p < 0.05$ ) decrease in the number of corpora lutea/female, implants/female, and live fetuses/female at C-section. At 100 mg/kg/day only a decrease in the number of corpora lutea/female was observed. The relationship of these findings to drug-treatment is uncertain since there was no effect at these dosage levels on implants/pregnant female, percent post-implantation loss, or live animals/litter at parturition. In nonpregnant rats dosed at 135 mg/kg/day for 7 days, systemic exposure (AUCs) for losartan and its active metabolite were approximately 66 and 26 times the exposure achieved in man at the maximum recommended human daily dosage (100 mg).

#### *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 for hypertension, 391 patients (19%) were 65 years and over, while 37 patients (2%) were 75 years and over. In a controlled clinical study for renal protection in type 2 diabetic patients with proteinuria, 248 patients (33%) were 65 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**

### *Hypertension*

COZAAR has been evaluated for safety in more than 3300 patients treated for essential hypertension and 4058 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 adverse experiences reported in  $\geq 1\%$  of patients treated with COZAAR and more commonly than placebo are shown in the table below.



	Losartan (n=1075) Incidence %	Placebo (n=334) Incidence %
<i>Musculoskeletal</i>		
Cramp, muscle	1	0
Pain, back	2	1
Pain, leg	1	0
<i>Nervous System/Psychiatric</i>		
Dizziness	3	2
<i>Respiratory</i>		
Congestion, nasal	2	1
Infection, upper respiratory	8	7
Sinusitis	1	0

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, diarrhea, dyspepsia, myalgia, insomnia, cough, sinus disorder.

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.

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	35%	29%	62%

† Demographics = (89% caucasian, 64% female)

†† Demographics = (90% caucasian, 51% female)

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

Cases of cough, including positive re-challenges, have been reported with the use of losartan in post-marketing experience.

#### *Nephropathy in Type 2 Diabetic Patients*

In the RENAAL study involving 1513 patients treated with COZAAR or placebo, the overall incidences of reported adverse experiences were similar for the two groups. COZAAR was generally well tolerated as evidenced by a similar incidence of discontinuations due to side effects compared to placebo (19% for COZAAR, 24% for placebo). The adverse experiences regardless of drug relationship, reported with an incidence of  $\geq 4\%$  of patients treated with COZAAR and occurring more commonly than placebo, on a background of conventional antihypertensive therapy are shown in the table below.

	Losartan and Conventional Antihypertensive Therapy Incidence % (n=751)	Placebo and Conventional Antihypertensive Therapy Incidence % (n=762)
<i>Body as a Whole</i>		
Asthenia/Fatigue	14	10
Chest Pain	12	8
Fever	4	3
Infection	5	4
Influenza-like disease	10	9
Trauma	4	3
<i>Cardiovascular</i>		
Hypotension	7	3
Orthostatic hypotension	4	1
<i>Digestive</i>		
Diarrhea	15	10
Dyspepsia	4	3
Gastritis	5	4
<i>Endocrine</i>		
Diabetic neuropathy	4	3
Diabetic vascular disease	10	9
<i>Eyes, Ears, Nose and Throat</i>		
Cataract	7	5
Sinusitis	6	5
<i>Hemic</i>		
Anemia	14	11
<i>Metabolic and Nutrition</i>		
Hyperkalemia	7	3
Hypoglycemia	14	10
Weight gain	4	3
<i>Musculoskeletal</i>		
Back pain	12	10
Leg pain	5	4
Knee pain	5	4
Muscular weakness	7	4
<i>Nervous System</i>		
Hypesthesia	5	4
<i>Respiratory</i>		
Bronchitis	10	9
Cough	11	10
<i>Skin</i>		
Cellulitis	7	6
<i>Urogenital</i>		
Urinary tract infection	16	13

#### *Post-Marketing Experience*

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

**Hypersensitivity:** Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue has been reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Vasculitis, including Henoch-Schönlein purpura, has been reported. Anaphylactic reactions have been reported.

**Digestive:** Hepatitis (reported rarely).

**Respiratory:** Dry cough (see above).

Hyperkalemia and hyponatremia have 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 (see PRECAUTIONS, *Impaired Renal Function*).

**Hemoglobin and Hematocrit:** Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.11 grams percent and 0.09 volume percent, respectively) occurred frequently in patients treated with COZAAR alone, but were rarely of clinical importance. No patients were discontinued due to anemia.

**Liver Function Tests:** Occasional elevations of liver enzymes and/or serum bilirubin have occurred. In patients with essential hypertension treated with COZAAR alone, one patient (<0.1%) was discontinued due to these laboratory adverse experiences.

## OVERDOSAGE

Significant lethality was observed in mice and rats after oral administration of 1000 mg/kg and 2000 mg/kg, respectively, about 44 and 170 times the maximum recommended human dose on a mg/m<sup>2</sup> 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

COZAAR may be administered with other antihypertensive agents, and with or without food.

### *Hypertension*

Dosing must be individualized. 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. The effect of losartan is substantially present within one week but in some studies the maximal effect occurred in 3-6 weeks (see CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects*).

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.

### *Nephropathy in Type 2 Diabetic Patients*

The usual starting dose is 50 mg once daily. The dose should be increased to 100 mg once daily based on blood pressure response (see CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects*). COZAAR may be administered with insulin and other commonly used hypoglycemic agents (e.g., sulfonylureas, glitazones and glucosidase inhibitors).

## HOW SUPPLIED

No. 3612 — Tablets COZAAR, 25 mg, are light green, teardrop-shaped, film-coated tablets with code MRK on one side and 951 on the other. They are supplied as follows:

NDC 0006-0951-54 unit of use bottles of 90

NDC 0006-0951-58 unit of use bottles of 100

NDC 0006-0951-28 unit dose packages of 100.

No. 3613 — Tablets COZAAR, 50 mg, are green, teardrop-shaped, film-coated tablets with code MRK 952 on one side and COZAAR on the other. They are supplied as follows:

NDC 0006-0952-31 unit of use bottles of 30

NDC 0006-0952-54 unit of use bottles of 90

NDC 0006-0952-58 unit of use bottles of 100

NDC 0006-0952-28 unit dose packages of 100

NDC 0006-0952-82 bottles of 1,000.

No. 6536 — Tablets COZAAR, 100 mg, are dark green, teardrop-shaped, film-coated tablets with code 960 on one side and MRK on the other. They are supplied as follows:


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NDC 0006-0960-31 unit of use bottles of 30  
NDC 0006-0960-58 unit of use bottles of 100  
NDC 0006-0960-28 unit dose packages of 100.

*Storage*

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

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