PRODUCT CIRCULAR

PAK-CZR-T-082009

Tablets
COZAAR®†
(losartan potassium)

I. THERAPEUTIC CLASS

COZAAR (losartan potassium), the first of a new class of agents for the treatment of hypertension, is an angiotensin II receptor (type AT_1) antagonist. COZAAR also provides a reduction in the combined risk of cardiovascular death, stroke, and myocardial infarction in hypertensive patients with left ventricular hypertrophy and renal protection for type 2 diabetic patients with proteinuria.

II. INDICATIONS

Hypertension
COZAAR is indicated for the treatment of hypertension.

Reduction in the Risk of Cardiovascular Morbidity and Mortality in Hypertensive Patients with Left Ventricular Hypertrophy
COZAAR is indicated to reduce the risk of cardiovascular morbidity and mortality as measured by the combined incidence of cardiovascular death, stroke, and myocardial infarction in hypertensive patients with left ventricular hypertrophy (see RACE).

Renal Protection in Type 2 Diabetic Patients with Proteinuria
COZAAR is indicated to delay the progression of renal disease as measured by a reduction in the combined incidence of doubling of serum creatinine, end stage renal disease (need for dialysis or renal transplantation) or death; and to reduce proteinuria.

III. DOSAGE AND ADMINISTRATION

COZAAR may be administered with or without food.

COZAAR may be administered with other antihypertensive agents.

Hypertension
The usual starting and maintenance dose is 50 mg once daily for most patients. The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy. Some patients may receive an additional benefit by increasing the dose to 100 mg once daily.

For patients with intravascular volume-depletion (e.g., those treated with high-dose diuretics), a starting dose of 25 mg once daily should be considered (see PRECAUTIONS).

No initial dosage adjustment is necessary for elderly patients or for patients with renal impairment, including patients on dialysis. A lower dose should be considered for patients with a history of hepatic impairment (see PRECAUTIONS).

Reduction in the Risk of Cardiovascular Morbidity and Mortality in Hypertensive Patients with Left Ventricular Hypertrophy
The usual starting dose is 50 mg of COZAAR once daily. A low dose of hydrochlorothiazide should be added and/or the dose of COZAAR should be increased to 100 mg once daily based on blood pressure response.

Renal Protection in Type 2 Diabetic Patients with Proteinuria
The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily based on blood pressure response. COZAAR may be administered with other antihypertensive agents (e.g., diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycemic agents (e.g., sulfonylureas, glitazones and glucosidase inhibitors).

IV. CONTRAINDICATIONS

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

V. PRECAUTIONS

Hypersensitivity: Angioedema. See SIDE EFFECTS.

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

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 SIDE EFFECTS and Laboratory Test Findings).

Liver Function Impairment
Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with a history of hepatic impairment (see DOSAGE AND ADMINISTRATION)

Renal Function Impairment
As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported in susceptible individuals; these changes in renal function may be reversible upon discontinuation of therapy.

Other drugs that affect the renin-angiotensin system may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. Similar effects have been reported with COZAAR; these changes in renal function may be reversible upon discontinuation of therapy.

VI. 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 in the developing fetus. When pregnancy is detected, COZAAR should be discontinued as soon as possible.

Although there is no experience with the use of COZAAR in pregnant women, animal studies with losartan potassium have demonstrated fetal and neonatal injury and death, the mechanism of which is believed to be pharmacologically mediated through effects on the renin-angiotensin system. In humans, fetal renal perfusion, which is dependent upon the development of the renin angiotensin system, begins in the second trimester; thus, risk to the fetus increases if COZAAR is administered during the second or third trimesters of pregnancy.

VII. NURSING MOTHERS

It is not known whether losartan is excreted in human milk. Because many drugs are excreted in human milk and 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.

VIII. PEDIATRIC USE

Antihypertensive effects of COZAAR have been established in hypertensive pediatric patients aged > 1 month to 16 years. Use of COZAAR in these age groups is supported by evidence from adequate and well-controlled studies of COZAAR in pediatric and adult patients as well as by literature in pediatric patients.

The pharmacokinetics of losartan have been investigated in 50 hypertensive pediatric patients >1 month to <16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/kg of losartan (mean doses). The active metabolite is formed from losartan in all age groups. Pharmacokinetics of losartan and its active metabolite are generally similar across the studied age groups and consistent with pharmacokinetic historic data in adults.

In a clinical study involving 177 hypertensive pediatric patients 6 to 16 years of age, patients who weighed ≥20 kg to <50 kg received either 2.5, 25 or 50 mg of losartan daily and patients who weighed ≥50 kg received either 5, 50 or 100 mg of losartan daily. Losartan administration once daily lowered trough blood pressure in a dose-dependent manner. The dose response to losartan was observed across all subgroups (e.g., age, Tanner stage, gender, race). However, the lowest doses studied, 2.5 mg and 5 mg, corresponding to an average daily dose of 0.07 mg/kg, did not appear to offer consistent antihypertensive efficacy. In this study, COZAAR was generally well tolerated.

For patients who can swallow tablets, the recommended dose is 25 mg once daily in patients ≥20 to <50 kg. The dose can be increased to a maximum of 50 mg once daily. In patients ≥50 kg, the starting dose is 50 mg once daily. The dose can be increased to a maximum of 100 mg once daily.

In pediatric patients who are intravascularly volume depleted, these conditions should be corrected prior to administration of COZAAR.

The adverse experience profile for pediatric patients appears to be similar to that seen in adult patients.

COZAAR is not recommended in pediatric patients with glomerular filtration rate <30 mL/min/1.73 m^2, in pediatric patients with hepatic impairment, or in neonates as no data are available.

IX. USE IN THE ELDERLY

In clinical studies there was no age-related difference in the efficacy or safety profile of losartan.

X. RACE

Based on the LIFE (Losartan Intervention For Endpoint reduction in hypertension) study, the benefits of COZAAR on cardiovascular morbidity and mortality compared to atenolol do not apply to Black patients with hypertension and left ventricular hypertrophy although both treatment regimens effectively lowered blood pressure in Black patients. In the overall LIFE study population (n=9193), treatment with COZAAR resulted in a 13.0% risk reduction (p=0.021) as compared to atenolol for patients reaching the primary composite endpoint of the combined incidence of cardiovascular death, stroke, and myocardial infarction. In this study, COZAAR decreased the risk of cardiovascular morbidity and mortality compared to atenolol in non-Black, hypertensive patients with left ventricular hypertrophy (n=8660) as measured by the primary endpoint of the combined incidence of cardiovascular death, stroke, and myocardial infarction (p=0.003). In this study, however, Black patients treated with atenolol were at lower risk of experiencing the primary composite endpoint compared with Black patients treated with COZAAR (p=0.03). In the subgroup of Black patients (n=533; 6% of the LIFE study patients), there were 29 primary endpoints among 263 patients on atenolol (11%, 25.9 per 1000 patient-years) and 46 primary endpoints among 270 patients (17%, 41.8 per 1000 patient-years) on COZAAR.

XI. DRUG INTERACTION

In clinical pharmacokinetic trials, no drug interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbital, ketoconazole, and erythromycin. Rifampin and fluconazole have been reported to reduce levels of active metabolite. The clinical consequences of these interactions have not been evaluated.

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 drugs which affect the excretion of sodium, lithium excretion may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be co-administered with angiotensin II receptor antagonists.

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of diuretics and other antihypertensive drugs. Therefore, the antihypertensive effect of angiotensin II receptor antagonists or ACE inhibitors may be attenuated by NSAIDs including selective COX-2 inhibitors.

In some patients with compromised renal function (e.g., elderly patients or patients who are volume-depleted, including those on diuretic therapy) who are being treated with non-steroidal anti-inflammatory drugs, including selective cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists or ACE inhibitors may result in a further deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Therefore, the combination should be administered with caution in patients with compromised renal function.

XII. SIDE EFFECTS

COZAAR has been found to be generally well tolerated in controlled clinical trials for hypertension; side effects have usually been mild and transient in nature and have not required discontinuation of therapy. The overall incidence of side effects reported with COZAAR was comparable to placebo.

In controlled clinical trials for essential hypertension, dizziness was the only side effect reported as drug related that occurred with an incidence greater than placebo in one percent or more of patients treated with COZAAR. In addition, dose-related orthostatic effects were seen in less than one percent of patients. Rarely, rash was reported, although the incidence in controlled clinical trials was less than placebo.

In these double-blind controlled clinical trials for essential hypertension, the following adverse experiences reported with COZAAR occurred in ≥1 percent of patients, regardless of drug relationship:

	COZAAR (n=2085)	**Placebo (n=535)**
Body as a Whole		
Abdominal pain	1.7	1.7
Asthenia/fatigue	3.8	3.9
Chest pain	1.1	2.6
Edema/swelling	1.7	1.9
Cardiovascular		
Palpitation	1.0	0.4
Tachycardia	1.0	1.7
Digestive		
Diarrhea	1.9	1.9
Dyspepsia	1.1	1.5
Nausea	1.8	2.8
Musculoskeletal		
Back pain	1.6	1.1
Muscle cramps	1.0	1.1
Nervous/Psychiatric		
Dizziness	4.1	2.4
Headache	14.1	17.2
Insomnia	1.1	0.7
Respiratory		
Cough	3.1	2.6
Nasal congestion	1.3	1.1
Pharyngitis	1.5	2.6
Sinus disorder	1.0	1.3
Upper respiratory Infection	6.5	5.6

COZAAR was generally well tolerated in a controlled clinical trial in hypertensive patients with left ventricular hypertrophy. The most common drug-related side effects were dizziness, asthenia/fatigue, and vertigo.

In the LIFE study, among patients without diabetes at baseline, there was a lower incidence of new onset diabetes mellitus with COZAAR as compared to atenolol (242 patients versus 320 patients, respectively, $p<0.001$). Because there was no placebo group included in the study, it is not known if this represents a beneficial effect of COZAAR or an adverse effect of atenolol.

COZAAR was generally well tolerated in a controlled clinical trial in type 2 diabetic patients with proteinuria. The most common drug-related side effects were asthenia/fatigue, dizziness, hypotension and hyperkalemia (see PRECAUTIONS, Hypotension and Electrolyte/Fluid Imbalance).

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

Hypersensitivity: Anaphylactic reactions, 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-Schoenlein purpura, has been reported rarely.
Gastrointestinal: Hepatitis (reported rarely), liver function abnormalities, vomiting.
General disorders and administration site conditions: Malaise.
Hematologic: Anemia, thrombocytopenia (reported rarely).
Musculoskeletal: Myalgia, arthralgia.
Nervous System/Psychiatric: Migraine, dysgeusia.
Reproductive system and breast disorders: Erectile dysfunction/impotence.
Respiratory: Cough.
Skin: Urticaria, pruritus, erythroderma, photosensitivity..

XIIa. Laboratory Test Findings

In controlled clinical trials for essential hypertension, clinically important changes in standard laboratory parameters were rarely associated with administration of COZAAR. Hyperkalemia (serum potassium >5.5 mEq/L) occurred in 1.5% of patients in the hypertension clinical trials. In a clinical study conducted in type 2 diabetic patients with proteinuria, 9.9% of patients treated with COZAAR and 3.4% of patients treated with placebo developed hyperkalemia (see PRECAUTIONS, Hypotension and Electrolyte/Fluid Imbalance). Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy.

XIII. OVERDOSAGE

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 the active metabolite can be removed by hemodialysis.

XIV. AVAILABILITY

Cozaar® Tablets (losartan potassium, MSD) is available as:

- 50 mg in blister pack of 2 x 14’s.
- 100 mg in blister pack of 2 x 14’s.