

LOZAR

Tablets

Composition

Each tablet contains Losartan potassium 50 mg.

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 AT₁ receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland). There is also an AT₂ receptor found in many tissues but it unknown to be associated with cardiovascular homeostasis. Both Losartan and its principal active metabolite do not exhibit any partial agonist activity at the AT₁ receptor and have much greater affinity (about 1000-fold) for the AT₁ receptor than for the AT₂ receptor.

In vitro binding studies indicate that Losartan is a reversible, competitive inhibitor of the AT₁ 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 AT₁ 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

Absorption

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. There was no clinically significant effect on the plasma concentration profile of losartan when the medicine was administered with a standardized meal.

Distribution

Both losartan and its active metabolite are >99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 liters. Losartan crosses the blood-brain barrier poorly, if at all.

Metabolism

About 14% of an administered dose of losartan is converted to its active metabolite. In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N-2 tetrazole glucuronide.

Elimination

Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.

Following oral administration, plasma concentrations of losartan, and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6-9 hours, respectively. During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.

Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose losartan in man, about 35% is recovered in the urine and 58% in the faeces.

Special Populations

Pediatric

Losartan Pharmacokinetics have not been investigated in patients <18 years of age.

Geriatric and Gender

Losartan pharmacokinetics has been investigated in the elderly (65-75 years) and in both genders. Plasma concentrations of Losartan and its active 1 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.

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. 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 in-sufficiency 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.

Indications

Hypertension

Lozar is indicated for the treatment of hypertension.

Reduction in the Risk of Cardiovascular Morbidity and Mortality in Hypertensive Patients with Left Ventricular Hypertrophy

Lozar 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.

Heart Failure

Lozar is indicated for the treatment of heart failure in patients who cannot tolerate an ACE inhibitor. Switching patients with heart failure who are stable on an ACE inhibitor to Lozar is not recommended.

Renal Protection in Type 2 Diabetic Patients with Proteinuria

Lozar 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.

Contraindications

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

Warnings

Pregnancy

Category C (If used in 2nd & 3rd trimester, it is Category D)

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, Losartan should be discontinued as soon as possible.

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 Losartan. These conditions should be corrected prior to administration of Losartan, or a lower starting dose should be used.

Adverse Reactions

The following 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. Occurring in at least 1% of patients treated with Losartan and that were more frequent on Losartan than placebo.

Digestive

Diarrhea, Dyspepsia

Musculoskeletal

Muscle cramp, Myalgia, Back pain, Leg Pain

Nervous System/Psychiatric

Dizziness, Insomnia

Respiratory

Nasal congestion, Cough, Upper respiratory infections, Sinus disorder, Sinusitis

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, head-ache, pharyngitis.

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

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. It cannot be determined whether these events were causally related to Losartan

Body as a whole

Facial edema, fever, or thostatic 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, decrease lipido, 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.

Precautions

General

Hypersensitivity: Angioedema.

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.

Impaired Renal Function

Because 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 up on 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.

Potassium Supplements

A patient receiving Losartan should be told *not* to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician

Nursing Mothers

It is not known whether Losartan is excreted 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.

Elderly Use

No overall differences in effectiveness or safety were observed between the elderly and younger patients but greater sensitivity of some older individuals cannot be ruled out.

Drug Interactions

No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, cimetidine, and phenobarbital. 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, troleanomycin, gestodene), or P450 2C9 (sulfaphenazole) and nearly complete inhibition by the combination of sulfaphenazole and ketoconazole. 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, and amiloride), potassium supplements, or salt substitutes containing potassium may lead to Increases In serum potassium.

Dosage and Administration

Lozar may be administered with or without food.
Lozar 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.

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.

Reduction in the Risk of Cardiovascular Morbidity and Mortality in Hypertensive Patients with Left Ventricular Hypertrophy

The usual starting dose is 50 mg of Lozar once daily. A low dose of hydrochlorothiazide should be added and/or the dose of Lozar should be increased to 100 mg once daily based on blood pressure response.

Heart Failure

The initial dose of Lozar in patients with heart failure is 12.5 mg once daily. The dose should generally be titrated at weekly intervals (i.e., 12.5 mg daily, 25 mg daily, and 50 mg daily) to the usual maintenance dose of 50 mg once daily, as tolerated by the patient.

Lozar is usually given in combination with diuretics and digitalis.

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. Lozar 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).

Over Dosage

Limited data are available concerning over dosage in humans. The most likely manifestation of over dosage 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.

Presentation

Box of 30 tablets.