24 mm

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory.

Presartan-50 mg Film-Coated Tablet

Losartan Potassium Tablets

Presartan-100 mg Film-Coated Tablet

Losartan Potassium Tablets

PRODUCT DESCRIPTION

Presartan-50 mg Film-Coated tablet: White to off white, oval, biconvex, film coated tablets with "50" debossing on one side and "BL" on other side.

Presartan-100 mg Film-Coated tablet: White to off white, almond shaped, biconvex, film coated tablets with "100" debossing on one side and "BL" on other side.

THERAPEUTIC CLASS

Losartan potassium, the first of a new class of agents for the treatment of hypertension, is an angiotensin II receptor (type AT_1) antagonist. Losartan potassium also provides renal protection for type 2 diabetic patients with proteinuria.

COMPOSITION

Presartan-50 mg Film-Coated Tablet
Each film-coated tablet contains:
Losartan Potassium 50mg
Presartan-100 mg Film-Coated Tablet
Each film-coated tablet contains:
Losartan Potassium 100mg

CLINICAL PHARMACOLOGY

Pharmacodynamics

Angiotensin II is the primary vasoactive hormone of the renin-angiotensin system. It is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II)]. It is a potent vasoconstrictor and is an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Losartan and its principal active metabolite block the 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). 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, noncompetitive inhibitor of the AT_1receptor.

Neither losartan nor its active metabolite inhibits ACE nor do they bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Despite the significant decrease in blood pressure, administration of losartan had no clinically significant effect on heart rate. 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 of losartan.

Pharmacokinetics

Following oral administration, losartan is well absorbed. The systemic bioavailability of losartan is approximately 33%. It undergoes substantial first-pass metabolism by cytochrome P450 enzymes. It is converted, in part, to an active carboxylic acid metabolite E-3174 that is responsible for most of the angiotensin II receptor antagonism that follows losartan treatment. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed. 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). The terminal half-life of losartan is about 2 hours and of the metabolite is about 6-9 hours. Both losartan and its active metabolite are highly bound to plasma proteins ($\geq$99%). Losartan crosses the blood-brain barrier poorly, if at all. 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.

INDICATIONS

Losartan potassium is indicated:

- In the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents, including diuretics.
- To reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy
- 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, losartan 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).

CONTRAINDICATIONS

Losartan potassium is contraindicated in patients who are hypersensitive to losartan or to any component of this product.

Losartan potassium should not be administered with aliskiren in patients with diabetes (see DRUG INTERACTIONS).

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. 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.

PRECAUTIONS

Hypersensitivity - Angioedema.

Impaired hepatic function – Based on pharmacokinetic data, which demonstrate significantly increased plasma concentrations of losartan potassium in cirrhotic patients, a lower dose should be considered for patients with impaired liver function.

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 potassium; 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 potassium.

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

Caution is required in patients with significant renal disease and renal transplant recipients as there have been reports of anaemia developing in such patients treated with losartan potassium .

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 losartan potassium as compared to the placebo group; however, few patients discontinued therapy due to hyperkalemia.

Since hyperkalemia may occur, serum potassium concentrations should be monitored, especially in the elderly and patients with renal impairment, and the concomitant use of potassium sparing diuretics should generally be avoided.

Interactions with Other Medicaments

No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, cimetidine and phenobarbital.

Rifampicin decreased the concentrations of losartan and its active metabolite.

In humans, ketoconazole, an inhibitor of P450 3A4, did not affect the conversion of losartan to the active metabolite after intravenous administration of losartan and erythromycin had no clinically significant effect after oral administration.

Fluconazole, an inhibitor of P450 2C9, decreased active metabolite concentration and increased losartan concentration.

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 antiinflammatory drug indomethacin.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Closely monitor blood pressure, renal function, and electrolytes in patients on losartan potassium and other agents that affect the RAAS. Do not co-administer aliskiren with losartan potassium in patients with diabetes. Avoid use of aliskiren with losartan potassium in patients with renal impairment (GFR <60 ml/min).

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Size: 240x150 mm

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Pregnancy and Lactation
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.
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 of adverse effects on the nursing infant, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

SIDE EFFECTS
For essential hypertension, hypertensive patients with left ventricular hypertrophy, chronic heart failure as well as for hypertension and type 2 diabetes mellitus with renal disease, the most common adverse event was dizziness.
Hypertension
For essential hypertension with losartan potassium the following adverse events were reported.
Nervous system disorders - *Common:* dizziness, vertigo; *Uncommon:* somnolence, headache, sleep disorders.
Cardiac disorder - *Uncommon:* palpitations, angina pectoris.
Vascular disorders - *Uncommon:* symptomatic hypotension (especially in patients with intravascular volume depletion, e.g. patients with severe heart failure or under treatment with high dose diuretics), dose-related orthostatic effects, rash.
Gastrointestinal disorders - *Uncommon:* abdominal pain, obstipation.
General disorders and administration site conditions - *Uncommon:* asthenia, fatigue, oedema.
Hypertensive patients with left ventricular hypertrophy
In hypertensive patients with left ventricular hypertrophy the following adverse events were reported:
Nervous system disorders - *Common:* dizziness.
Ear and labyrinth disorders - *Common:* vertigo.
General disorders and administration site conditions - *Common:* asthenia/fatigue.
Chronic heart failure
In patients with cardiac insufficiency the following adverse events were reported:
Nervous system disorders - *Uncommon:* dizziness, headache; *Rare:* paraesthesia.
Cardiac disorders - *Rare:* syncope, artrial fibrillation, cerebrovascular accident.
Vascular disorders - *Uncommon:* hypotension, including orthostatic hypotension.
Respiratory, thoracic and mediastinal disorders - *Uncommon:* dyspnoea.
Gastrointestinal disorders - *Uncommon:* diarrhoea, nausea, vomiting.
Skin and subcutanous tissue disorders - *Uncommon:* urticaria, pruritus, rash.
General disorders and administration site conditions - *Uncommon:* asthenia/fatigue.
Hypertension and type 2 diabetes with renal disease
In a controlled clinical trial in type 2 diabetic patients with proteinuria the most common drug-related adverse events which were reported for losartan potassium are as follows:
Nervous system disorders - *Common:* dizziness.
Vascular disorders - *Common:* hypotension.
General disorders and administration site conditions - *Common:* asthenia/fatigue.
Investigations - *Common:* hypoglycaemia, hyperkalaemia.
The following adverse events occurred more often in patients receiving losartan potassium than placebo:
Blood and lymphatic system disorders - *Not known:* anaemia.
Cardiac disorders - *Not known:* syncope, palpitations.
Vascular disorders - *Not known:* orthostatic hypotension.
Gastrointestinal disorders - *Not known:* diarrhoea.
Musculoskeletal and connective tissue disorders - *Not known:* back pain.
Renal and urinary disorders - *Not known:* urinary tract infections.
General disorders and administration site conditions - *Not known:* flu-like symptoms.
Post-marketing experience
The following adverse events have been reported in post-marketing experience:
Blood and lymphatic system disorders - *Not known:* Anaemia, thrombocytopenia.
Immune system disorders - *Rare:* hypersensitivity: anaphylactic reactions, angiooedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue; in some of these patients angiooedema had been reported in the past in connection with the administration of other medicines, including ACE inhibitors; vasculitis, including Henoch-Schonlein purpura.
Nervous system disorders - *Not known:* migraine.
Respiratory, thoracic and mediastinal disorders - *Not known:* cough.
Gastrointestinal disorders - *Not known:* diarrhoea.
Hepatobiliary disorders - *Rare:* hepatitis; *Not known:* liver function abnormalities.
Skin and subcutaneous tissue disorders - *Not known:* urticaria, pruritus, rash.
Musculoskeletal and connective tissue disorders - *Not known*: myalgia, arthralgia.
Renal disorders
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function including renal failure have been reported in patients at risk; these changes in renal function may be reversible upon discontinuation of therapy

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^2 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
Losartan potassium may be administered with or without food.
Losartan potassium may be administered with other antihypertensive agents.
Hypertension
The usual starting and maintenance dose is 50 mg once daily for most patients. The maximal anti-hypertensive 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 25mg 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 (see PRECAUTIONS).
Hypertensive Patients with Left Ventricular Hypertrophy
The usual starting dose is 50 mg of Presartan once daily. A low dose of hydrochlorothiazide should be added and/or the dose of Presartan should be increased to 100 mg once daily based on blood pressure response.
Renal Protection in Type 2 Diabetic Patients with Proteinuria and Hypertension
This usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily based on blood pressure response. Presartan 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 glycosidase inhibitors).

ROUTE OF ADMINISTRATION: Oral

STORAGE
Store below 30ºC in a dry place, away from light
KEEP OUT OF REACH OF CHILDREN

PRESENTATION
Presartan-50 mg Film-Coated tablet: Blister strip of 14 tablets [Box of 2 x 14's (28's) tablets]
Presartan-100 mg Film-Coated tablet: Blister strip of 14 tablets [Box of 2 x 14's (28's) tablets]

DATE OF REVISION
January 2016

Product Registration Holder:
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