

Losanta

(Losartan potassium)

لوسانتا

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, Losanta should be discontinued as soon as possible.

DESCRIPTION

Losanta (losartan potassium) is an angiotensin II receptor (type AT₁) antagonist.

COMPOSITION

Each **Losanta** 25 mg tablet contains 25 mg of losartan potassium.

Each **Losanta** 50 mg tablet contains 50 mg of losartan potassium.

MECHANISM OF ACTION

Angiotensin II [formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kinase 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). 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 (kinase 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.

PHARMACOKINETIC

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 drug was administered with a standardised meal.

Distribution: Both losartan and its active metabolite are 99% bound to plasma proteins, primarily albumin. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Bioretransformation: About 14% of orally-administered dose of losartan is converted to its active metabolite. Following oral administration of ¹⁴C-labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. In addition to the active metabolite, inactive metabolites are formed.

Elimination: Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose of ¹⁴C-labelled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the faeces. During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.

Characteristics in patients

Hepatic Insufficiency: A lower starting dose is recommended for patients with a history of hepatic impairment.

Renal Insufficiency: No dosage adjustment is necessary for patients with renal impairment unless they are volume-depleted.

Geriatric and Gender: Losartan pharmacokinetics have been investigated in the elderly (65-75 years) and in both genders. No dosage adjustment is necessary.

Paediatric patients: The pharmacokinetics of losartan have been investigated in 50 hypertensive paediatric 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 results showed that the active metabolite is formed from losartan in all age groups. Pharmacokinetics of losartan and its active metabolite were generally similar across the studied age groups and consistent with pharmacokinetic historic data in adults.

INDICATIONS

Hypertension: Losanta is indicated for the treatment of hypertension.

Hypertensive patients with left ventricular hypertrophy: In hypertensive patients with left ventricular hypertrophy a reduced risk of stroke was demonstrated.

Renal protection in type 2 diabetic patients with nephropathy (macroalbuminuria): Losanta 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.

DOSAGE AND ADMINISTRATION

Losanta may be administered with or without food.

Losanta may be administered with other antihypertensive agents. The concomitant use of **Losanta** and ACE inhibitors has not been adequately studied.

Hypertension: The 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.

Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy: The usual starting dose is 50 mg of **Losanta** once daily. A low dose of hydrochlorothiazide may be added and/or the dose of **Losanta** may be increased to 100 mg once daily based on blood pressure.

Renal protection in type 2 diabetic patients with nephropathy: The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily according to blood pressure response from one month after initiation of therapy onwards. **Losanta** 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 hypoglycaemic agents (e.g., sulfonylureas, glitazones and glucosidase inhibitors).

Losanta was not studied in type 2 diabetic patients with severe renal impairment.

Use in patients with intravascular volume depletion: For the very small proportion of patients who have intravascular volume depletion (e.g. those treated with high-dose diuretics), a starting dose of 25 mg once daily is recommended.

Use in renal impairment: No initial dosage adjustment is necessary in patients with mild renal impairment (i.e. creatinine clearance 20-50 ml/min). For patients with moderate to severe renal impairment (i.e. creatinine clearance <20 ml/min) or patients on dialysis, a lower starting dose of 25 mg once daily is recommended.

Use in hepatic impairment: A lower dose should be considered for patients with a history of hepatic impairment.

Patients over 75 years: Presently there is limited clinical experience in this group; a lower starting dose of 25 mg once daily is recommended.

Use in children and adolescents: There are limited data on the efficacy and safety of losartan in children and adolescents aged 6-16 years old for the treatment of hypertension.

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 adjusted to a maximum of 100 mg once daily.

Losartan is not recommended in neonates and in children with glomerular filtration rate < 30 ml/min/1.73 m², as no data are available.

Losartan is also not recommended in children with hepatic impairment.

UNDESIRABLE EFFECTS

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 **Losanta** 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 1% or more of patients treated with **Losanta**. In addition, dose-related orthostatic effects were seen in less than 1% of patients.

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

Losanta 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.

Losanta was generally well tolerated in a controlled clinical trial in type 2 diabetic patients with nephropathy. The most common drug-related side effects were asthenia/fatigue, dizziness, hypotension and hyperkalaemia. In this study, few patients discontinued due to hyperkalaemia.

The following 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 have 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 rarely.

Gastro-intestinal: Hepatitis (reported rarely), diarrhoea, liver function abnormalities.

Haematologic: Anaemia, thrombocytopenia (reported rarely).

Musculoskeletal: Myalgia, arthralgia.

Nervous system/Psychiatric: Migraine.

Respiratory: Cough.

Skin: Urticaria, pruritus, rash.

Laboratory test findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of **Losanta**. Hyperkalaemia (serum potassium > 5.5 mmol/l) occurred in 1.5% of patients in hypertension clinical trials. In a clinical study conducted in type 2 diabetic patients with nephropathy, 9.9% of patients treated with **Losanta** and 3.4% of patients treated with placebo developed hyperkalaemia. Serum potassium should be monitored, particularly in the elderly and patients with renal impairment. Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy.

DRUG INTERACTIONS

- In clinical pharmacokinetic trials, no drug interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, ketoconazole, erythromycin and phenobarbital (phenobarbitone). Rifampicin 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 other drugs which retain potassium or may increase potassium levels (e.g. potassium-sparing diuretics, potassium supplements or salt substitutes containing potassium) may lead to increases in serum potassium. Co-medication is not advisable.
- When Angiotensin II antagonists are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. selective COX-2 inhibitors, acetylsalicylic acid > 3 g / day) and non-selective NSAIDs, attenuation of the antihypertensive effect may occur.
- As with ACE inhibitors, concomitant use of Angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.
- Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme (ACE) inhibitors. Very rare cases have also been reported with angiotensin II receptor antagonists. Co-administration of lithium and losartan should be undertaken with caution. If this combination proves essential, serum lithium level monitoring is recommended during concomitant use.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

- Hypersensitivity: Angioedema.
- The use of **Losanta** in patients with haemodynamically significant obstructive valvular disease or cardiomyopathy has not been adequately studied.
- 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 **Losanta**, or a lower starting dose should be used.
- 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 nephropathy, the incidence of hyperkalaemia was higher in the group treated with **Losanta** as compared to the placebo group.

- 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.
- As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function including renal failure have been reported (in particular, in patients whose renal function is dependent on the renin-angiotensin system such as those with severe cardiac insufficiency or pre-existing renal dysfunction).
- As with other drugs that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be 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 **Losanta**.

PREGNANCY AND LACTATION

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin-aldosterone system can cause injury and even death in the developing fetus. **Losanta** should not be used in pregnancy, and if pregnancy is detected **Losanta** should be discontinued as soon as possible.

It is not known whether losartan is excreted in human milk. However, significant levels of losartan and the 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 breast-feeding or discontinue the drug, taking into account the importance of the drug to the mother.

OVERDOSE

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.

CONTRAINDICATIONS

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

PRESENTATION

Losanta 25mg tablet: 2 x 10's/pack.

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Issued : 10/2011

Detailed prescribing information is available on request.

خوراک:

ڈاکٹر کی ہدایت کے مطابق۔

ہدایات:

دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

دھوپ اور نمی سے بچائیں۔

بچوں کی پہنچ سے دور رکھیں۔



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