

Losanta DIU

(Losartan potassium + Hydrochlorothiazide)

لوسانتا ڈیو

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 DIU should be discontinued as soon as possible.

DESCRIPTION

Losanta DIU (losartan potassium + hydrochlorothiazide) is a combination of an angiotensin II receptor (type AT1) antagonist and a diuretic, hydrochlorothiazide.

COMPOSITION

Each **Losanta DIU** tablet contains 50 mg of losartan potassium, and 12.5 mg of hydrochlorothiazide.

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 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 (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. Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increase in plasma renin activity, increase in aldosterone secretion, increase in urinary potassium loss, and decrease in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

The mechanism of the antihypertensive effect of thiazides is unknown.

PHARMACOKINETICS

Absorption

Losartan: 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.

Hydrochlorothiazide: Oral absorption of hydrochlorothiazide is relatively rapid. The bioavailability of hydrochlorothiazide varies between 60 and 80%. The time to peak plasma concentration (Tmax) varies between 1.5 and 5 hours, with a mean of about 4 hours.

Distribution

Losartan: 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.

Hydrochlorothiazide: Protein binding is approximately 40%. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. Hydrochlorothiazide crosses the placenta but not the blood-brain barrier and is excreted in breast milk.

Biotransformation

Losartan: About 14% of an orally 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.

Hydrochlorothiazide: Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney.

Elimination

Losartan: 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.

Hydrochlorothiazide: Hydrochlorothiazide is eliminated unchanged rapidly by the kidney. At least 61% of the oral dose is eliminated unchanged within 24 hours.

Characteristics in Patients

Losartan and hydrochlorothiazide combination tablet: The plasma concentrations of losartan and its active metabolite and the absorption of hydrochlorothiazide in elderly hypertensives are not significantly different from those in young hypertensives.

Losartan: 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-fold and 1.7-fold greater than those seen in young male volunteers. Neither losartan nor the active metabolite can be removed by haemodialysis.

INDICATIONS

Hypertension

Losanta DIU is indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy of hypertension, except when the hypertension is severe enough that the value of achieving prompt blood pressure control exceeds the risk of initiating combination therapy in these patients.

Hypertensive Patients with Left Ventricular Hypertrophy

Losanta DIU is indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy.

DOSAGE AND ADMINISTRATION

Losanta DIU may be administered with or without food.

Hypertension

When clinically appropriate direct change from monotherapy to the fixed combinations may be considered in patients whose blood pressure is not adequately controlled.

The usual starting and maintenance dose is 1 tablet once daily for most patients. For patients who do not respond adequately, the dosage may be increased to 2 tablets once daily. The maximum dose is 2 tablets once daily. In general, the antihypertensive effect is attained within three weeks after initiation of therapy.

Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy

The usual starting dose is 50 mg of losartan once daily. If goal blood pressure is not reached with losartan 50 mg, therapy should be titrated using a combination of losartan and a low dose of hydrochlorothiazide (12.5 mg) and, if necessary, the dose should be increased to losartan 100 mg/ hydrochlorothiazide 25 mg daily.

Patients over 75 years: Presently there is limited clinical experience in this group. Any therapy involving the angiotensin II antagonist, losartan, should be initiated with 25 mg losartan in these patients.

Use in renal impairment: No initial dosage adjustment is necessary in patients with mild renal impairment (i.e. creatinine clearance 20-50 ml/min). **Losanta DIU** is not recommended for patients with moderate to severe renal impairment (i.e. creatinine clearance <20 ml/min) or patients on dialysis.

Use in patients with intravascular volume depletion: **Losanta DIU** should not be initiated in patients who are intravascularly volume depleted (e.g. those treated with high-dose diuretics).

Use in hepatic impairment: **Losanta DIU** is not recommended for patients with hepatic impairment.

Concomitant therapy: **Losanta DIU** may be administered with other antihypertensive agents.

Use in children: Safety and efficacy in children have not been established.

UNDESIRABLE EFFECTS

In clinical trials with the combination tablet of losartan and hydrochlorothiazide, no adverse experiences peculiar to this combination drug have been observed. Adverse experiences have been limited to those that were reported previously with losartan potassium and/or hydrochlorothiazide. The overall incidence of adverse experiences reported with the combination was comparable to placebo. The percentage of discontinuations of therapy was also comparable to placebo. For the most part, adverse experiences have been mild and transient in nature and have not required discontinuation of therapy.

In controlled clinical trials for essential hypertension, dizziness was the only adverse experience reported as drug related that occurred with an incidence greater than placebo in 1% or more of patients treated with losartan potassium-hydrochlorothiazide. In a controlled trial in hypertensive patients with left ventricular hypertrophy, losartan used usually with hydrochlorothiazide was generally well tolerated. The most common drug-related side effects were dizziness, asthenia/fatigue, and vertigo. 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 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-Schonlein purpura, has been reported rarely with losartan.

Gastro-intestinal: Hepatitis has been reported rarely in patients treated with losartan, diarrhoea.

Respiratory: Cough has been reported with losartan.

Skin: Urticaria

Additional side effects that have been seen with one of the individual components and may be potential side effects with **Losanta DIU** are the following:

Losartan

Dose-related orthostatic effects, liver function abnormalities, myalgia, migraine, rash, anaemia, pruritus.

Hydrochlorothiazide

Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhoea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialoadenitis, vertigo, paraesthesia, headache, xanthopsia, leucopenia, agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, purpura, photosensitivity, fever, necrotising angitis, respiratory distress (including pneumonitis and pulmonary oedema), anaphylactic reactions, toxic epidermal necrolysis, hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance (including

hyponatraemia and hypokalaemia), renal dysfunction, interstitial nephritis, renal failure, muscle spasm, weakness, restlessness, transient blurred vision.

Laboratory test findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of losartan potassium-hydrochlorothiazide. Hyperkalaemia (serum potassium > 5.5 mmol/l) occurred in 0.7% of patients, but in these trials discontinuation of losartan potassium-hydrochlorothiazide due to hyperkalaemia was not necessary. 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

Losartan Potassium

- No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, cimetidine and phenobarbital. Rifampin, an inducer of drug metabolism, decreased the concentrations of losartan and its active metabolite. In humans, two inhibitors of P450 3A4 have been studied. Ketoconazole 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. Subjects who do not metabolize losartan to active metabolite have been shown to have a specific, rare defect in cytochrome P450 2C9. These data suggest that the conversion of losartan to its active metabolite is mediated primarily by P450 2C9 and not P450 3A4.
- 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 increase in serum potassium.
- Lithium: 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 Agents including Selective Cyclooxygenase-2 Inhibitors: In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs (NSAIDs) including those that selectively inhibit cyclooxygenase-2 inhibitors (COX-2 inhibitors), the co-administration of angiotensin II receptor antagonists including losartan, may result in a further deterioration of renal function. These effects are usually reversible.
- Reports suggest that NSAIDs including selective COX-2 inhibitors may diminish the antihypertensive effect of angiotensin II receptor antagonists, including losartan. This interaction should be given consideration in patients taking NSAIDs including selective COX-2 inhibitors concomitantly with angiotensin II receptor antagonists.

Hydrochlorothiazide

- Alcohol, barbiturates, or narcotics - potentiation of orthostatic hypotension may occur.
- Antidiabetic drugs (oral agents and insulin) - dosage adjustment of the antidiabetic drug may be required.
- Other antihypertensive drugs - additive effect or potentiation.
- Cholestyramine and colestipol resins - Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.
- Corticosteroids, ACTH - intensified electrolyte depletion, particularly hypokalemia.
- Pressor amines (e.g., norepinephrine) - possible decreased response to pressor amines but not sufficient to preclude their use.
- Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine) - possible increased responsiveness to the muscle relaxant.
- Lithium - should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with **Losanta DIU**.
- Non-steroidal Anti-inflammatory Drugs including Selective Cyclooxygenase-2 Inhibitors - In some patients, the administration of a non-steroidal anti-inflammatory agent including a selective cyclooxygenase-2 inhibitor can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when **Losanta DIU** and non-steroidal anti-inflammatory agents including selective cyclooxygenase-2 inhibitors are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Losartan and hydrochlorothiazide combination tablet

- Hypersensitivity: Angioedema.
- Hepatic and renal impairment: **Losanta DIU** is not recommended for patients with hepatic impairment or moderate to severe renal impairment (creatinine clearance < 20 ml/min).

Losartan

- Renal function 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-aldosterone system, such as those with severe cardiac insufficiency or pre-existing renal dysfunction).
- As with other drugs that affect the renin-angiotensin-aldosterone system, increase 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 losartan potassium.
- The use of losartan potassium in patients with haemodynamically significant obstructive valvular disease and cardiomyopathy has not been adequately studied.

Hydrochlorothiazide

- Hypotension and electrolyte/fluid imbalance: As with all antihypertensive therapy, symptomatic hypotension may occur in some patients. This was rarely seen in uncomplicated hypertensive patients, but was more likely in the presence of fluid depletion or electrolyte imbalance. Periodic determination of serum electrolytes should be performed at appropriate intervals, as in any patients receiving diuretics.
- Metabolic and endocrine effects: Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required.
- Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.
- Increase in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.
- Thiazide therapy may precipitate hyperuricaemia and/or gout in certain patients. Because losartan decreases uric acid, losartan in combination with hydrochlorothiazide attenuates the diuretic-induced hyperuricaemia.
- Other: In patients receiving thiazides, hypersensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

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, **Losanta DIU** should be discontinued as soon as possible. It is not known whether losartan is excreted in human milk. Significant levels of losartan and the active metabolite were shown to be present in rat milk. Thiazides appear in human milk. Because of the potential for adverse effects on the breast-feeding 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

Losartan Potassium

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.

Hydrochlorothiazide

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

CONTRAINDICATIONS

Losanta DIU is contraindicated in patients who are hypersensitive to any component of this product. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

PRESENTATION

Losanta DIU 50/12.5 mg tablet : 2 x 10's/ pack

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Detailed prescribing information is available on request.

خوراک :

ڈاکٹر کی ہدایت کے مطابق۔

ہدایات :

دوا کو سرد گری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

دھوپ اور نمی سے بچائیں۔

بچوں کی پہنچ سے دور رکھیں۔



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