

LOTAN-H®

(Losartan Potassium & Hydrochlorothiazide)

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Losartan potassium is an angiotensin II receptor (type AT1) antagonist. Oxidation of the 5-hydroxymethyl group on the imidazole ring results in the active metabolite of losartan. Hydrochlorothiazide is a thiazide diuretic.

QUALITATIVE & QUANTITATIVE COMPOSITION:

LOTAN-H is available for oral administration as;

LOTAN-H Tablets: Each film-coated tablet contains Losartan Potassium 50 mg + Hydrochlorothiazide 12.5 mg.

CLINICAL PHARMACOLOGY

Mechanism of Action:

Losartan:

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 is not known 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.

Hydrochlorothiazide:

It is thiazide diuretic. It blocks the Na/Cl transporter in the distal convoluted tubule, resulting in decreased NaCl reabsorption and eventual reduced blood volume, reduced venous pressure & reduced preload. Thiazides enhance Ca reabsorption in the distal convoluted tubule, perhaps by Na/Ca exchange. 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 angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

Pharmacokinetics:

Losartan:

General Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. It is converted, in part, to an active carboxylic acid metabolite that is responsible for most of the angiotensin II receptor antagonism that follows losartan treatment. Losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed. In vitro studies indicate that cytochrome P450 2C9 and 3A4 are involved in the biotransformation of losartan to its metabolites. The terminal half-life of losartan is about 2 hours and of the metabolite is about 6-9 hours.

Following oral administration, losartan is well absorbed (based on absorption of radio-labeled losartan) and undergoes substantial first-pass metabolism; the systemic bioavailability of losartan is approximately 33%. About 14% of an orally-administered dose of losartan is converted to the active metabolite. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively.

A 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).

Total plasma clearance of losartan and the active metabolite is about 600 mL/min and 50 mL/min, respectively, with renal clearance of about 75 mL/min and 25 mL/min, respectively. After single doses of losartan 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.

Both losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2%, respectively. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

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 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: Following oral administration, plasma concentrations and AUCs of losartan and its active metabolite are increased by 50-90% in patients with mild (creatinine clearance of 50 to 74 mL/min) or moderate (creatinine clearance 30 to 49 mL/min) renal insufficiency. In this study, renal clearance was reduced by 55-85% for both losartan and its active metabolite in patients with mild or moderate renal insufficiency. 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 insufficiency 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.

Hydrochlorothiazide:

It is variably absorbed from GI tract. HCTZ half-life is 5.6 to 14.8 hrs. Excretion is normally renal. Onset of action is within 6 – 12 hrs.

DRUG INTERACTIONS:

Losartan:

- Losartan, administered for 12 days, did not affect the pharmacokinetics or pharmacodynamics of a single dose of warfarin.
- Losartan did not affect the pharmacokinetics of oral or intravenous digoxin.
- There is no pharmacokinetic interaction between losartan and hydrochlorothiazide.
- Co-administration of losartan and cimetidine led to an increase of about 18% in AUC of losartan but did not affect the pharmacokinetics of its active metabolite.
- Co-administration of losartan and phenobarbital led to a reduction of about 20% in the AUC of losartan and that of its active metabolite.
- A somewhat greater interaction (approximately 40% reduction in the AUC of active metabolite and approximately 30% reduction in the AUC of losartan) has been reported with rifampin.
- Fluconazole, an inhibitor of cytochrome P450 2C9, decreased the AUC of the active metabolite by approximately 40%, but increased the AUC of losartan by approximately 70% following multiple doses.
- Conversion of losartan to its active metabolite after intravenous administration is not affected by ketoconazole, an inhibitor of P450 3A4.
- The AUC of active metabolite following oral losartan was not affected by erythromycin, another inhibitor of P450 3A4, but the AUC of losartan was increased by 30%.
- ARBs may increase blood levels of potassium. Therefore, the use of potassium supplements, salt substitutes (which often contain potassium), or other drugs that increase potassium may result in excessive blood potassium levels.
- ARBs may also increase the blood concentration of lithium and lead to an increase in side effects from lithium.

Hydrochlorothiazide:

When given concurrently the following drugs may interact with thiazide diuretics:

- 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 - Cholestyramine and colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.
- Corticosteroid, 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 - generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and greatly increase the risk of lithium toxicity.
- Non-steroidal anti-inflammatory drugs - In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics.

INDICATIONS AND USAGE

LOTAN-H is indicated for the treatment of hypertension in patients not adequately controlled with Losartan alone. This fixed dose combination is not indicated for the initial therapy. It is now indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy (LVH).

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. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, LOTAN 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 LOTAN (Losartan Potassium). These conditions should be corrected prior to administration of LOTAN, or a lower starting dose should be used.

PRECAUTIONS

- **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:** 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.
- 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 Potassium; in some patients, these effects were reversible upon discontinuation of therapy.
- **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.

DOSAGE AND ADMINISTRATION

- One tablet of LOTAN -H once daily with or without food.
- If blood pressure remains uncontrolled after three weeks of therapy, the dose may be increased to two tablets once daily. More than two tablets once daily is not recommended.

SIDE EFFECTS:

Losartan:

ARBs are well-tolerated by most individuals. Compared to ACE inhibitors, cough occurs less often with ARBs.

The most common side effects are Cough, Elevated potassium

levels, Low blood pressure, Dizziness, Headache, Drowsiness, Diarrhea, Abnormal taste sensation (metallic or salty taste), and rash. The most serious, but rare, side effects are Kidney failure, Liver failure, Allergic reactions, A decrease in white blood cells, and Swelling of tissues (angioedema).

Hydrochlorothiazide:

Common side effects include; weakness, low blood pressure, light sensitivity, blurred vision, impotence, nausea, abdominal or stomach pain, constipation, electrolyte disturbances, pancreatitis, yellow skin or eyes (jaundice), severe allergic reaction (anaphylaxis), and rashes.

CONTRAINDICATION:

Losartan:

Pregnant patients: Losartan Potassium is not prescribed for pregnant patients because it may cause birth defects. 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.

Nursing mothers: Nursing mothers should avoid taking Losartan Potassium.

Kidney & Liver problem patients: It is not prescribed for those individuals with severe problems. Reduction in dose by 50% is suggested in patients with impaired liver function.

Hypersensitivity: It is not prescribed to those patients who have had a severe reaction to ARBs.

Children: Losartan's safety and efficacy in children has not been established.

Hydrochlorothiazide:

Hydrochlorothiazide should not be given to patients receiving other potassium-sparing agents such as spironolactone, amiloride. Concomitant potassium-containing salt substitutes should also not be used.

Potassium supplementation should not be used with hydrochlorothiazide except in severe cases of hypokalemia. Such concomitant therapy can be associated with rapid increases in serum potassium levels. If potassium supplementation is used, careful monitoring of the serum potassium level is necessary.

Impaired Renal Function: Hydrochlorothiazide is contraindicated in patients with anuria, acute and chronic renal insufficiency or significant renal impairment.

Hypersensitivity: Hypersensitivity to either drug in the preparation or to other sulfonamide-derived drugs is a contraindication.

Hyperkalemia: Hydrochlorothiazide should not be used in patients with preexisting elevated serum potassium.

DOSAGE FORMS & STRENGTHS:

LOTAN-H Tablets are available as:

- Losartan 50mg + Hydrochlorothiazide 12.5 mg (Film Coated Tablets)

Packaging: 10 Tablets x 10 Blisters

ID: 01 pi LHT 20

Manufactured by:

Deurali-Janta Pharmaceuticals Pvt. Ltd.



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