LOTAN®

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(Losartan Potassium)

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.

QUALITATIVE & QUANTITATIVE COMPOSITION:

LOTAN is available for oral administration as:

LOTAN-25: Each film coated tablet contains Losartan potassium 25 mg.

LOTAN-50: Each film coated tablet contains Losartan potassium 50 mg.

CLINICAL PHARMACOLOGY

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). 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.

Pharmacokinetics:

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 Cmax 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.

DRUG INTERACTIONS:

- 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.

INDICATIONS AND USAGE

Hypertension: LOTAN is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents, including diuretics. In hypertensive Patients with Left Ventricular Hypertrophy LOTAN is indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy, but there is evidence that this benefit does not apply to Black patients.

Nephropathy in Type 2 Diabetic Patients: LOTAN is indicated 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, LOTAN 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).

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

Adult Hypertension: The usual starting dose of LOTAN is 50 mg once daily. The dosage can be increased to a maximum dose of 100 mg once daily as needed to control blood pressure. A starting dose of 25 mg is recommended for patients with possible intravascular depletion (e.g., on diuretictherapy).

Pediatric Hypertension: The usual recommended starting dose is 0.7 mg per kg once daily (up to 50 mg total) administered as a tablet or a suspension. Dosage should be adjusted according to blood pressure response. Doses above 1.4 mg per kg (or in excess of 100 mg) daily have not been studied in pediatric patients.
LOTAN is not recommended in pediatric patients less than 6 years of age or in pediatric patients with estimated glomerular filtration rate less than 30 mL/min/1.73 m^2.

Hypertensive Patients with Left Ventricular Hypertrophy: The usual starting dose is 50 mg of LOTAN once daily. Hydrochlorothiazide 12.5 mg daily should be added and/or the dose of LOTAN should be increased to 100 mg once daily followed by an increase in hydrochlorothiazide to 25 mg once daily based on blood pressure response.
Nephropathy in Type 2 Diabetic Patients: The usual starting dose is 50 mg once daily. The dose should be increased to 100 mg once daily based on blood pressure response.

Dosage Modifications in Patients with Hepatic Impairment: In patients with mild-to-moderate hepatic impairment the recommended starting dose of LOTAN is 25 mg once daily. LOTAN has not been studied in patients with severe hepatic impairment.

SIDE EFFECTS:

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).

CONTRAINDICATIOIN:

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 withsevere 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.

DOSAGE FORMS & STRENGTHS:

LOTAN is available as:

- 25 mg FCT (Film Coated Tablets)
  Packaging: 30 Tablets x 5 Blisters
- 50 mg FCT (Film Coated Tablets)
  Packaging: 30 Tablets x 5 Blisters

ID: 01 pi LOT 20

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