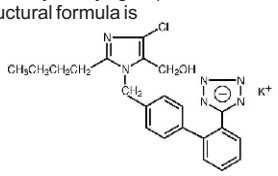
Losascot
Tablets

WARNING: FETAL TOXICITY
When pregnancy is detected, discontinue LOSASCOT PLUS as soon as possible. Drugs that act directly on the renin-angiotensin system (RAS) can cause injury and death to the developing fetus.

COMPOSITION:
Each tablet contains:
LOSARTAN Potassioum BP/USP /Hydrochlorothiazide BP/USP…….....……50/12.5 mg.

DESCRIPTION
LOSASCOT PLUS tablets combine an angiotensin II receptor blocker acting on the AT 1 receptor subtype, losartan potassium and a diuretic, hydrochlorothiazide.

Losartan Potassium:
Losartan potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[p-(o-1H tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt. Its empirical formula is C22H22ClKN6O. It is a white to off-white free-flowing crystalline powder with a molecular weight of 461.01. It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents. Oxidation of the 5-hydroxymethyl group on the imidazole ring results in the active metabolite of losartan and its structural formula is



Hydrochlorothiazide:
Hydrochlorothiazide is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide. Its empirical formula is C 7H8ClN3O4S2. It is a white, or practically white, crystalline powder with a molecular weight of 297.74, which is slightly soluble in water, but freely soluble in sodium hydroxide solution and its structural formula is:

CLINICAL PHARMACOLOGY
Mechanism of Action:
Losartan Potassium: Angiotensin 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).
Hydrochlorothiazide: 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 increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium.
Pharmacodynamics:

Losartan Potassium: Losartan inhibits the pressor effect of angiotensin II (as well as angiotensin I) infusions. A dose of 100 mg inhibits the pressor effect by about 85% at peak with 25-40% inhibition persisting for 24 hours. Removal of the negative feedback of angiotensin II causes a doubling to tripling in plasma renin activity and consequent rise in angiotensin II plasma concentration in hypertensive patients. Aldosterone plasma concentrations fall following losartan administration and it has a very little effect on serum potassium.
Hydrochlorothiazide: After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours, and lasts about 6 to 12 hours.
Pharmacokinetics:

Losartan Potassium:
Absorption: Following oral administration, losartan is well absorbed and undergoes substantial first-pass metabolism. The systemic bioavailability of losartan is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively.
Distribution: The volume of distribution of losartan and the active metabolite is about 34 liters and 12 liters, respectively. 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. Plasma protein binding is constant over the concentration range achieved with recommended doses.
Metabolism: 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. About 14% of an orally-administered dose of losartan is converted to the active metabolite. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed.
Elimination: 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. The terminal half-life of losartan is about 2 hours and of the metabolite is about 6-9 hours. 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.
Hydrochlorothiazide:

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. 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. At least 61 percent of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

INDICATIONS AND USAGE
Hypertension: LOSASCOT PLUS is indicated for the treatment of hypertension, to lower blood pressure AND may be administered with other antihypertensive agents.
Hypertensive Patients with Left Ventricular Hypertrophy: LOSASCOT PLUS is indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy.

CONTRAINDICATIONS
LOSASCOT PLUS is contraindicated:
- In patients who are hypersensitive to any component of this product.
- In patients with anuria.
- For coadministration with aliskiren in patients with diabetes.

ADVERSE REACTIONS
The following adverse reactions have been reported with losartan potassium/hydrochlorothiazide therapy:

- Blood and the lymphatic system disorders: Anemia, aplastic anemia, hemolytic anemia, leukopenia, agranulocytosis.
- Metabolism and nutrition disorders: Anorexia, hyperglycemia, hyperuricemia, electrolyte imbalance including hyponatremia and hypokalemia.
- Nervous system disorders: Insomnia, restlessness, dysgeusia, headache, migraine, paraesthesias.
- Eye disorders: Xanthopsia, transient blurred vision.
- Cardiovascular disorders: Palpitation, tachycardia, dose-related orthostatic effects, necrotizing angiitis (vasculitis, cutaneous vasculitis).
- Respiratory, thoracic and mediastinal disorders: Cough, nasal congestion, pharyngitis, sinus disorder, respiratory distress (including pneumonitis and pulmonary edema).
- Gastrointestinal disorders: Dyspepsia, abdominal pain, gastric irritation, cramping, diarrhea, constipation, nausea, vomiting, pancreatitis, sialoadenitis
- Hepato-biliary disorders: Jaundice (intrahepatic cholestatic jaundice).
- Skin and subcutaneous tissue disorders: Rash, pruritus, purpura, toxic epidermal necrolysis, urticaria, photosensitivity, cutaneous lupus erythematosus.

- Musculoskeletal and connective tissue disorders: Muscle cramps, muscle spasm, myalgia, arthralgia.
- Renal and urinary disorders: Glycosuria, renal dysfunction, interstitial nephritis, renal failure.
- Reproductive system disorders: Erectile dysfunction/impotence.
- General disorders: Chest pain, edema/swelling, malaise, fever, weakness.
- Investigations: Liver function abnormalities.

DRUG INTERACTIONS

Agents Increasing Serum Potassium: Coadministration of losartan with other drugs that raise serum potassium levels may result in hyperkalemia.

Lithium: Increases in serum lithium concentrations and lithium toxicity have been reported with concomitant use of angiotensin II receptor antagonists or thiazide diuretics.

Non-Steroidal Anti-Inflammatory Agents Including Selective Cyclooxygenase-2 Inhibitors:

Losartan Potassium: In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, coadministration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists (including losartan) may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.The antihypertensive effect of angiotensin II receptor antagonists, including losartan, may be attenuated by NSAIDs, including selective COX-2 inhibitors.

Hydrochlorothiazide: The administration of a non-steroidal anti-inflammatory agent including a selective COX-2 inhibitor can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. In patients receiving diuretic therapy, coadministration of NSAIDs with angiotensin receptor blockers, including losartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.

Dual Blockade of the Renin-Angiotensin System (RAS): Dual blockade of the RAS 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. Do not coadminister aliskiren with LOSACOT PLUS in patients with diabetes. Avoid use of aliskiren with LOSACOT PLUS in patients with renal impairment (GFR <60 mL/min).

The Use of Hydrochlorothiazide with Other Drugs: When administered concurrently, the following drugs may interact with thiazide diuretics:

Antidiabetic drugs (oral agents and insulin) — dosage adjustment of the antidiabetic drug may be required.

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. Stagger the dosage of hydrochlorothiazide and the resin such that hydrochlorothiazide is administered at least 4 hours before or 4 to 6 hours after the administration of the resin.

USE IN SPECIFIC POPULATION

Pregnancy: Pregnancy Category D. Use of drugs that act on RAS system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. When pregnancy is detected, discontinue losartan as soon as possible. Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Nursing Mothers: It is not known whether losartan is excreted in human milk. Thiazides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: No overall differences in effectiveness appears between elderly and younger patients. Adverse events appear somewhat more frequent in the elderly compared to non-elderly patients.

Hepatic Impairment: Initiation of losartan potassium/hydrochlorothiazide therapy is not recommended for patients with hepatic impairment because the appropriate starting dose of losartan, 25 mg, is not available.

Renal Impairment: Changes in renal function have been reported in susceptible individuals. Safety and effectiveness in patients with severe renal impairment (creatinine clearance <30 mL/min) have not been established.

WARNINGS AND PRECAUTIONS

Fetal Toxicity: Use of drugs that act on RAS during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. When pregnancy is detected, discontinue LOSASCOT PLUS as soon as possible. Thiazides cross the placental barrier and appear in cord blood. Adverse reactions include fetal or neonatal jaundice, thrombocytopenia.

Hypotension in Volume- or Salt-Depleted Patients: In patients with an activated RAS, such as volume- or salt- depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of treatment with LOSASCOT PLUS. Correct volume or salt depletion prior to administration of LOSASCOT PLUS. Do not use LOSASCOT PLUS as initial therapy in patients with intravascular volume depletion.

Impaired Renal Function: Changes in renal function including acute renal failure can be caused by drugs that inhibit RAS and by diuretics. Patients whose renal function may depend in part on the activity of the renin-angiotensin system (e.g., patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) may be at particular risk of developing acute renal failure on LOSASCOT PLUS. Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on LOSASCOT PLUS.

Hypersensitivity: Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

Electrolyte and Metabolic Effects: LOSASCOT PLUS contains hydrochlorothiazide which can cause hypokalemia, hyponatremia and hypomagnesemia. Hypomagnesemia can result in hypokalemia which may be difficult to treat despite potassium repletion. LOSASCOT PLUS also contains losartan which can cause hyperkalemia. Monitor serum electrolytes periodically. Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides. Hyperuricemia may occur or frank gout may be precipitated in patients receiving thiazide therapy. Because losartan decreases uric acid, losartan in combination with hydrochlorothiazide attenuates the diuretic-induced hyperuricemia. Hydrochlorothiazide decreases urinary calcium excretion and may cause elevations of serum calcium. Monitor calcium levels.

Acute Myopia and Secondary Angle-Closure Glaucoma: Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle- closure glaucoma. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Systemic Lupus Erythematosus: Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

Postsympathectomy Patients: The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

DOSAGE AND ADMINISTRATION

Hypertension:

The usual starting dose of LOSASCOT PLUS is 50/12.5 (losartan 50 mg/hydrochlorothiazide 12.5 mg) once daily. The dosage can be increased after 3 weeks of therapy to a maximum of 100/25 (losartan 100 mg/hydrochlorothiazide 25 mg) once daily as needed to control blood pressure. Initiate a patient whose blood pressure is not adequately controlled with losartan 50 mg monotherapy with LOSASCOT PLUS 50/12.5 once daily. If blood pressure remains uncontrolled after about 3 weeks of therapy, the dosage may be increased to two tablets of LOSASCOT PLUS 50/12.5 once daily or one tablet of LOSASCOT PLUS 100/25 once daily. Initiate a patient whose blood pressure is not adequately controlled with losartan 100 mg monotherapy with LOSASCOT PLUS 100/12.5 (losartan 100 mg/hydrochlorothiazide 12.5 mg) once daily. If blood pressure remains uncontrolled after about 3 weeks of therapy, increase the dose to two tablets of LOSASCOT PLUS 50/12.5 once daily or one tablet of LOSASCOT PLUS 100/25 once daily. Initiate a patient whose blood pressure is inadequately controlled with hydrochlorothiazide 25 mg once daily, or is controlled but who experiences hypokalemia with this regimen, on LOSASCOT PLUS 50/12.5 once daily, reducing the dose of hydrochlorothiazide without reducing the overall expected antihypertensive response. Evaluate the clinical response to LOSASCOT PLUS 50/12.5 and, if blood pressure remains uncontrolled after about 3 weeks of therapy, increase the dose to two tablets of LOSASCOT PLUS 50/12.5 once daily or one tablet of LOSASCOT PLUS 100/25 once daily.

Hypertensive Patients with Left Ventricular Hypertrophy:

In patients whose blood pressure is not adequately controlled on 50 mg losartan potassium, initiate treatment with LOSASCOT PLUS 50/12.5. If additional blood pressure reduction is needed, increase the dose to LOSASCOT PLUS 100/12.5, followed by LOSASCOT PLUS 100/25. For further blood pressure reduction add other antihypertensives.

OVERDOSAGE

Losartan Potassium: Limited data is available in regard to overdosagE. 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.

STORAGE/PRECAUTIONS. Store in a cool, dry and dark place between 15 - 30 °C. Keep all medicines out of the reach of children. To be used on the prescription of Registered Medical Practitioners.

PRESENTATION

LOSASCOT PLUS Tablets are available in packing containing 10 tablets.