For the use of only a Registered Medical Practitioner or a Hospital or a Laboratory

Not to be sold by retail without the prescription of a Registered Medical Practitioner

Prescribing Information

1. Generic Name

Losartan Potassium and Hydrochlorothiazide Tablets IP
(Brand Name: LOSTAT®-H Tablets)

2. Qualitative and Quantitative Composition

Each film-coated tablet contains:
Losartan Potassium IP …… 50 mg.
Hydrochlorothiazide IP…… 12.5 mg.
Excipients …… q.s.
Colours: Lake of Sunset Yellow and Titanium Dioxide IP.

3. Dosage Form and Strength

Dosage Form: Tablets.
Dosage Strength: Losartan potassium 50 mg and hydrochlorothiazide 12.5 mg per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

LOSTAT-H Tablets are indicated for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled by losartan or hydrochlorothiazide monotherapy. Lowering blood pressure reduces the risk of fatal and non-fatal cardiovascular events, primarily stroke and myocardial infarction.
LOSTAT-H Tablets are also indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy.

4.2Posology and Method of Administration

For oral administration in adults.

Hypertension

Usual starting dose is one tablet of LOSTAT-H to be administered once daily.
If blood pressure is not adequately controlled within 3 weeks of therapy, the dosage can be increased to a maximum of 2 tablets once daily.

Hypertensive Patients with Left Ventricular Hypertrophy

Usual starting dose is one tablet of LOSTAT-H to be administered once daily.

If additional blood pressure reduction is needed, increase the dose to 2 tablets once daily.

Losartan is effective in doses between 25 mg to maximum of 100 mg once daily.
Hydrochlorothiazide is effective in doses between 12.5 mg to 50 mg once daily.
LOSTAT-H Tablets may be administered with or without food.
Or, as directed by the physician.

4.3Contraindications

LOSTAT-H Tablets are contraindicated in the following:

- Hypersensitivity to losartan or to hydrochlorothiazide or to any component of the formulation.
- During 2nd and 3rd trimester of pregnancy.
- Refractory hyponatraemia.
- Symptomatic hyperuricaemia/gout.
- Severe hepatic impairment, cholestasis, and biliary obstructive disorders.
- Severe renal impairment.
- In patients with anuria.
- The concomitant use of losartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73m^2).

4.4Special Warnings and Precautions for Use

Fetal Toxicity: Use of drugs that act on the renin-angiotensin aldosterone system (RAAS) during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformity. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue losartan therapy as soon as possible.

Hypotension in Volume- or Salt-Depleted Patients: In patients with an activated RAAS, 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 LOSTAT-H Tablets. Do not use LOSTAT-H Tablets as initial therapy in patients with intravascular volume depletion. Correct volume or salt depletion prior to drug therapy.

Impaired Renal Function: Changes in renal function including acute renal failure can be caused by drugs that inhibit the RAAS and by diuretics. Patients whose renal function depends on the activity of the RAAS (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 with LOSTAT-H Tablets. Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function with LOSTAT-H Tablets.

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

1. **Effect on Potassium, Sodium, and Magnesium:** LOSTAT-H Tablet contains hydrochlorothiazide which can cause hypokalemia, hyponatremia and hypomagnesemia. Hypomagnesemia can result in hypokalemia which may be difficult to treat despite potassium repletion. LOSTAT-H Tablet also contains losartan which can cause hyperkalemia. Monitor serum electrolytes periodically. Hydrochlorothiazide-induced hypokalemia has been reported to be less prevalent in clinical studies when hydrochlorothiazide is combined with agent that works on RAAS.

   In double-blind clinical trials of various doses of losartan potassium and hydrochlorothiazide, the incidence of hypertensive patients who developed hypokalemia (serum potassium < 3.5 meq/l) was 6.7% versus 3.5% for placebo; the incidence of hyperkalemia (serum potassium > 5.7 meq/l) was 0.4% versus 0% for placebo.
2. **Effect on Lipids:** Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides.
3. **Effect on Uric Acid:** 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.
4. **Effect on Calcium:** 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. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Seek immediate medical attention if patients experience any symptoms. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. 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.

Symptomatic Hypotension: Advise patients that light-headedness can occur, especially during the initial days of therapy, and to report this symptom to a healthcare provider. Inform patients that dehydration from inadequate fluid intake, excessive perspiration, vomiting, or diarrhea may lead to an excessive fall in blood pressure. If syncope occurs advise patients to contact their healthcare provider.

Potassium Supplements: As this product contains potassium salt of losartan, patients are advised not to use potassium supplements or salt substitutes containing potassium without consulting their healthcare provider.

4.5Drug Interactions

Losartan

Agents Increasing Serum Potassium: Co-administration of losartan with other drugs that raise serum potassium levels may result in hyperkalemia. Monitor serum potassium in such patients.

Lithium: Increase in serum lithium concentration and lithium toxicity has been reported during concomitant administration of lithium with angiotensin II receptor antagonists (e.g., losartan). Monitor serum lithium levels during concomitant use.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration 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. Monitor renal function periodically in patients receiving losartan and NSAID therapy. The antihypertensive effect of angiotensin II receptor antagonists, including losartan, may be attenuated by NSAIDs, including selective COX-2 inhibitors.

Dual Blockade of the Renin-Angiotensin Aldosterone System (RAAS): Dual blockade of the RAAS with angiotensin receptor blockers (ARBs), angiotensin converting enzyme (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.

In most patients no benefit has been associated with using two RAAS inhibitors concomitantly. In general, avoid combined use of RAAS inhibitors. Closely monitor blood pressure, renal function, and electrolytes in patients on losartan and other agents that affect the RAAS.

Aliskiren: Do not co-administer aliskiren with losartan in patients with diabetes. Avoid use of aliskiren with losartan in patients with renal impairment (GFR <60 ml/min).

Hydrochlorothiazide

When administered 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 antihypertensive effect may occur, thus, reduction in dosage is 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 hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 %, respectively.

Corticosteroids, Adrenocorticotropic Hormone (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 (e.g., Tubocurarine): Possible increased responsiveness to the muscle relaxants such as curare derivatives.

NSAIDs: In some patients, administration of NSAID can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics.

Digoxin: Thiazide-induced hypokalemia or hypomagnesemia may predispose the patient to digoxin toxicity.

Lithium: Lithium generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and greatly increase the risk of lithium toxicity.

Laboratory Test Interactions: Thiazides should be discontinued before carrying out tests for parathyroid function.

4.6Use in Special Populations

Pregnant Women

Losartan potassium: Pregnancy Category D; Hydrochlorothiazide: Pregnancy Category B. When used in pregnancy during the 2nd and 3rd trimesters, drugs that act directly on the renin-angiotensin aldosterone system - RAAS (e.g., losartan) can cause injury and even death in the developing fetus. Also, the routine use of diuretics exposes mother and fetus to unnecessary hazard. Thus, when pregnancy is detected or planned, LOSTAT-H Tablets should be discontinued as soon as possible.

Lactating Women

It is not known whether losartan is excreted in human milk, but a significant amount of losartan and its active metabolite has been reported to be present in rat milk. Thiazides appear in human milk. Because many drugs are excreted in human milk and have potential for causing 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.

Paediatric Patients

Safety and effectiveness of LOSTAT-H Tablets in paediatric patients have not been established. Thus, LOSTAT-H Tablets are not indicated for use in children.

Geriatric Patients

With losartan, no overall differences in efficacy or safety have been observed between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. A greater blood pressure reduction and an increase in side effects have been reported in the elderly (>65 years) patients treated with hydrochlorothiazide. Elderly patients also have decreased clearance of

hydrochlorothiazide. Thus, in elderly patients, dose selection should be cautious and usually a lower initial dose is recommended.

Renal Impairment Patients

Patients with renal insufficiency have elevated plasma concentrations of losartan and its active metabolite compared to subjects with normal renal function. However, no dose adjustment of losartan is necessary in patients with renal impairment unless a patient is also volume-depleted. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function. Thus, LOSTAT-H Tablets should be used with caution in patient with mild-to-moderate renal impairment. LOSTAT-H Tablets are contraindicated in patients with severe renal impairment.

Hepatic Impairment Patients

In patients with mild-to-moderate hepatic impairment, plasma concentrations of losartan and its active metabolite have been 5-times and 1.7-times higher than those seen in healthy volunteers. Thiazides should be used with caution in patients with impaired hepatic function. Thus, in patients with mild-to-moderate hepatic impairment, caution should be exercised and lower initial dose should be used. LOSTAT-H Tablet contains 50 mg of losartan while initial dosage requirement of losartan is 25 mg in hepatic impairment patients. Thus, Initiation of therapy with LOSTAT-H Tablets is not recommended in these patients. Both, losartan and hydrochlorothiazide have not been studied in patients with severe hepatic impairment. Therefore, LOSTAT-H Tablets must not be administered in patients with severe hepatic impairment.

4.7Effect on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed with losartan potassium and hydrochlorothiazide combination therapy. However, hydrochlorothiazide can have minor or moderate influence on the ability to drive and use machines, particularly at the initiation of the therapy. Thus, caution is recommended during driving a vehicle or operating machinery especially at the start of treatment.

4.8Undesirable Effects

Losartan

Clinical Trials Experience

The adverse events that occurred in ≥2% of patients treated with losartan and more commonly than placebo were dizziness, upper respiratory infection, nasal congestion, and back pain.

The following adverse reactions have been reported less frequently:

Blood and Lymphatic System: Anemia.

Psychiatric: Depression.

Nervous System: Somnolence, headache, sleep disorders, paresthesia, migraine.

Ear and Labyrinth: Vertigo, tinnitus.

Cardiac: Palpitations, syncope, atrial fibrillation, cerebrovascular accidents.
Respiratory, Thoracic and Mediastinal: Dyspnea.
Gastrointestinal: Abdominal pain, constipation, nausea, vomiting.
Skin and Subcutaneous Tissue: Urticaria, pruritus, rash, photosensitivity.
Musculoskeletal and Connective Tissue: Myalgia, arthralgia.
Reproductive System: Impotence.
General Disorders and Administration Site Conditions: Edema.

Post-Marketing Experience
Digestive: Hepatitis.
General Disorders and Administration Site Conditions: Malaise.
Hematologic: Thrombocytopenia.
Hypersensitivity: 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.
Metabolic and Nutrition: Hyponatremia.
Musculoskeletal: Rhabdomyolysis, muscle spasm.
Nervous System: Dysgeusia.
Skin: Erythroderma.

Hydrochlorothiazide
Adverse events that have been reported with hydrochlorothiazide, without regard to causality, are listed below:
Body as a Whole: Weakness.
Digestive: Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation.
Hematologic: Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia.
Hypersensitivity: Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions.
Metabolic: Electrolyte imbalance, hyperglycemia, glycosuria, hyperuricemia.
Musculoskeletal: Muscle spasm.
Nervous System/Psychiatric: Restlessness.
Renal: Renal dysfunction, interstitial nephritis, renal failure.
Skin: Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis.
Special Senses: Transient blurred vision, xanthopsia.
Urogenital: Impotence.

4.9Overdose

Losartan

Limited data is available with regard to overdose of losartan in humans. The most likely manifestation of overdose 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.

In the event of overdose, symptomatic and supportive measures should be employed. Emesis should be induced or gastric lavage performed. Correct dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures. If required, give oxygen or artificial respiration for respiratory impairment. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

5. Pharmacological Properties

5.1 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 aldosterone 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).

Both, losartan and its active metabolite, 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 than losartan and appears to be a reversible, non-competitive inhibitor of the AT1 receptor.

Hydrochlorothiazide

Hydrochlorothiazide (HCTZ) is a thiazide class of diuretic drugs which blocks the reabsorption of sodium (Na^+) and chloride (Cl^-) ions, and it thereby increases the quantity of sodium traversing the distal tubule of nephron. By this mechanism, hydrochlorothiazide increases excretion of water (diuretic effect), reduces blood volume, and thereby decreases cardiac output. These effects help to reduce increased blood pressure. As hydrochlorothiazide has weak antihypertensive effect, it is usually combined with other antihypertensive drugs.

A portion of the additional sodium presented to the distal tubule of nephron is exchanged there for potassium (K^+) and hydrogen (H^+) ions. With continued use of hydrochlorothiazide and depletion of sodium, compensatory mechanisms tend to increase this exchange and may produce excessive loss of potassium, hydrogen, and chloride ions (electrolyte imbalance). Hydrochlorothiazide also decreases the excretion of calcium (Ca^{++}) and uric acid, may increase the excretion of iodide and may reduce glomerular filtration rate.

5.2Pharmacodynamic Properties

Losartan

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 to 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. In spite of the effect of losartan on aldosterone secretion, very little effect on serum potassium was observed.
The effect of losartan is substantially present within one week but in some studies the maximal effect occurred in 3 to 6 weeks. In long-term follow-up studies (without placebo control) the effect of losartan appeared to be maintained for up to a year. There is no apparent rebound effect after abrupt withdrawal of losartan. There was essentially no change in average heart rate in losartan-treated patients in controlled trials

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide class of diuretic agent. Hydrochlorothiazide is widely used to treat hypertension and edema. Acute antihypertensive effects of thiazides are thought to result from a reduction in blood volume and cardiac output, secondary to a natriuretic effect, although a direct vasodilatory mechanism has also been proposed. With chronic administration, plasma volume returns toward normal, but peripheral vascular resistance is decreased.
Thiazides do not affect normal blood pressure. Peak effect of hydrochlorothiazide is observed at about 4 hours of dosing and activity persists for up to 24 hours.

5.3Pharmacokinetic Properties

Losartan

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 to 4 hours, respectively. While maximum plasma concentrations of losartan and its active metabolite are approximately equal, the AUC (area under the curve) of the metabolite is about 4 times as high as that of losartan. 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 (~10% decrease). The pharmacokinetics

of losartan and its active metabolite are linear with oral losartan doses up to 200 mg and do not change over time.

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 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. 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. *In vitro* studies indicate that cytochrome P450 2C9 and 3A4 are involved in the biotransformation of losartan to its metabolites.

Excretion: 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 that of the metabolite is about 6 to 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 the active metabolite. Biliary excretion contributes to the elimination of losartan and its metabolites. Following oral 14C-labeled losartan, about 35% of the radioactivity is recovered in the urine and about 60% in the feces. Neither losartan nor its metabolite accumulates in plasma upon repeated once-daily dosing.

Hydrochlorothiazide

Absorption: Hydrochlorothiazide is well absorbed (65% to 75%) following oral administration. Absorption of hydrochlorothiazide is reduced in patients with congestive heart failure. Peak plasma concentrations are observed within 1 to 5 hours of dosing, and range from 70 to 490 ng/ml following oral doses of 12.5 to 100 mg.

Distribution: Plasma concentrations are linearly related to the administered dose. Concentrations of hydrochlorothiazide are 1.6 to 1.8 times higher in whole blood than in plasma. Plasma protein binding is approximately 40% to 68%.

Metabolism and Excretion: The plasma elimination half-life is 6 to 15 hours. Hydrochlorothiazide is eliminated primarily by renal pathways. Following oral doses of 12.5 to 100 mg, 55% to 77% of the administered dose appears in urine and greater than 95% of the absorbed dose is excreted in urine as unchanged drug. In patients with renal disease, plasma concentration of hydrochlorothiazide is increased and the elimination half-life is prolonged.

6. Nonclinical Properties

6.1 Animal Toxicology

Losartan

Carcinogenesis: Losartan potassium was not carcinogenic when administered at maximally tolerated dosages to rats and mice for 105 and 92 weeks, respectively. Female rats given the highest

dose (270 mg/kg/day) had a slightly higher incidence of pancreatic acinar adenoma. The maximally tolerated dosages (270 mg/kg/day in rats, 200 mg/kg/day in mice) provided systemic exposures for losartan and its pharmacologically active metabolite that were approximately 160 and 90 times (rats) and 30 and 15 times (mice) the exposure of a 50 kg human given 100 mg per day.

Mutagenesis: Losartan potassium was negative in the microbial mutagenesis and V-79 mammalian cell mutagenesis assays and in the *in vitro* alkaline elution and *in vitro* and *in vivo* chromosomal aberration assays. In addition, the active metabolite showed no evidence of genotoxicity in the microbial mutagenesis, *in vitro* alkaline elution, and *in vitro* chromosomal aberration assays.

Impairment of Fertility: Fertility and reproductive performance were not affected in studies with male rats given oral doses of losartan potassium up to approximately 150 mg/kg/day. The administration of toxic dosage levels in females (300/200 mg/kg/day) was associated with a significant decrease in the number of corpora lutea/female, implants/female, and live fetuses/female at C-section. At 100 mg/kg/day only a decrease in the number of corpora lutea/female was observed. The relationship of these findings to drug treatment is uncertain since there was no effect at these dosage levels on implants/pregnant female, percent post-implantation loss, or live animals/litter at parturition. In non-pregnant rats dosed at 135 mg/kg/day for 7 days, systemic exposure (AUCs) for losartan and its active metabolite were approximately 66 and 26 times the exposure achieved in man at the maximum recommended human daily dosage (100 mg).

Teratogenicity: Losartan potassium has been shown to produce adverse effects in rat fetuses and neonates, including decreased body weight, delayed physical and behavioral development, mortality and renal toxicity. With the exception of neonatal weight gain (which was affected at doses as low as 10 mg/kg/day), doses associated with these effects exceeded 25 mg/kg/day (approximately three times the maximum recommended human dose of 100 mg on a mg/m2 basis). These findings are attributed to drug exposure in late gestation and during lactation. Significant levels of losartan and its active metabolite were shown to be present in rat fetal plasma during late gestation and in rat milk.

Hydrochlorothiazide

Carcinogenesis: Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Mutagenesis: Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of Salmonella typhimurium strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the Drosophila sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister

Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 mcg/mL, and in the Aspergillus nidulans non-disjunction assay at an unspecified concentration.

Impairment of Fertility: Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

Teratogenicity: Studies in which hydrochlorothiazide was orally administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3000 and 1000 mg hydrochlorothiazide/kg, respectively, provided no evidence of harm to the fetus.

7. Description

LOSTAT-H Tablets are orange colored, circular, biconvex, film coated tablets plain on both the sides.

LOSTAT-H Tablets contains 50 mg of losartan potassium and 12.5 mg of hydrochlorothiazide for oral administration in adults.

Losartan Potassium

Losartan potassium is the potassium salt of losartan, a non-peptide angiotensin II receptor antagonist with antihypertensive activity.

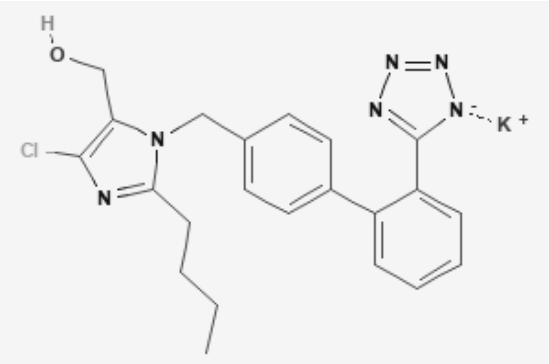
Losartan potassium is a white to off-white powder.

Molecular Weight: 461 g/mol.

Molecular Formula: C22H22ClKN6O.

Chemical Name: Potassium;[2-butyl-5-chloro-3-[[4-[2-(1,2,3-triaza-4-azanidacyclopenta-2,5-dien-5-yl)phenyl]phenyl]methyl]imidazol-4-yl]methanol.

Structural Formula:



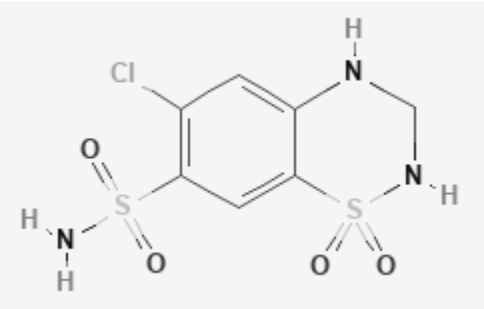
Hydrochlorothiazide

Hydrochlorothiazide is short acting thiazide class of diuretic used for the treatment of hypertension and congestive heart failure.

Hydrochlorothiazide is a white or practically white crystalline powder.

Molecular Weight: 297.7 g/mol.

Molecular Formula: C7H8ClN3O4S2.
Chemical Name: 6-chloro-1,1-dioxo-3,4-dihydro-2H-1λ6,2,4-benzothiadiazine-7-sulfonamide.
Structural Formula:



Inactive ingredients (excipients) of LOSTAT-H Tablets contain Microcrystalline Cellulose, Lactose, Colloidal Silicon Dioxide, Sodium Starch Glycolate, Magnesium Stearate, Instacoat Aqua III, and Purified Water.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life

24 months.

8.3Packaging Information

15 tablets per strip.

8.4Storage and Handling Instructions

Store protected from light and moisture at a temperature not exceeding 30°C.
Keep out of reach of children.

9. Patient Counseling Information

Instructions to Patients

- Instruct patients to take this medicine exactly as prescribed by your doctor. Do not change the dose or stop therapy without consulting doctor.
- Patients are advised to take LOSTAT-H Tablets once a day, with or without food. It may be easier to take your dose if you do it at the same time every day, such as with breakfast or dinner, or at bedtime. Do not take more than one dose at a time.

- If patients miss a dose, they can take it as soon as they remember. Do not take LOSTAT-H Tablets if it has been more than 12 hours since the last missed dose. Wait and take the next dose at regular scheduled time.
- Pregnant women and breastfeeding mothers should strictly avoid use of this medicine.
- Use of this medicine is not recommended in children.
- Patients should be informed that while taking LOSTAT-H Tablets do not stop taking other prescription medicines, including any other blood pressure medicines, without consulting their doctor.

10. Details of Manufacturer

Mepromax Lifesciences Pvt. Ltd.
16- Pharmacity, Selaqui, Dehradun – 248 011, Uttarakhand.

11. Details of Permission or License Number with Date

Mfg. Lic. No. : 23/UA/2007; Date of FDA Product Permission: 10/03/2017.

12. Date of Revision

February 2023.

Marketed by:
BLUE CROSS LABORATORIES PVT LTD.
A-12, M.I.D.C., NASHIK-422 010.
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