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 Tablets IP
(Brand Name: LOSTAT® 25 / 50 Tablets)

2. Qualitative and Quantitative Composition

Each film-coated tablet contains:
Losartan Potassium IP ……. 25 mg / 50 mg.
Excipients …… q.s.
Colour: Titanium Dioxide.

3. Dosage Form and Strength

Dosage Form: Tablets.
Dosage Strength: Losartan potassium 25 mg and 50 mg per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

1) Hypertension

LOSTAT Tablets are indicated for the treatment of hypertension in adults to lower blood pressure. Lowering blood pressure lowers the risk of fatal and non-fatal cardiovascular (CV) events, primarily strokes and myocardial infarction (MI).

2) Hypertensive Patients with Left Ventricular Hypertrophy

LOSTAT Tablets are indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy.

3) Nephropathy in Hypertensive Type 2 Diabetes Patients

LOSTAT Tablets are indicated for the treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria in patients with type 2 diabetes and a history of hypertension. In these patients losartan reduces the rate of progression of nephropathy.

4.2Posology and Method of Administration

For oral administration in adults.

1) Hypertension

The usual starting dose of losartan is 50 mg once daily. The dosage can be increased to a maximum dose of 100 mg once daily, as needed.
A starting dose of 25 mg is recommended for patients with possible intravascular depletion (e.g., on diuretic therapy).

2) <u>Hypertensive Patients with Left Ventricular Hypertrophy</u>

The usual starting dose of losartan is 50 mg once daily. Based on response to blood pressure, hydrochlorothiazide should be added and/or the dose of losartan should be increased up to 100 mg once daily.

3) <u>Nephropathy in Hypertensive Type 2 Diabetes Patients</u>

The usual starting dose of losartan is 50 mg once daily. The dose should be increased to 100 mg once daily based on blood pressure response.

LOSTAT Tablets may be given with other antihypertensive drugs. LOSTAT Tablets may be administered with or without food.
Or, as prescribed by the physician.

4.3Contraindications

LOSTAT Tablets are contraindicated in the following:

- Hypersensitivity to losartan or to any component of the formulation.
- During 2nd and 3rd trimester of pregnancy.
- Severe hepatic impairment.
- The concomitant use of losartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^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 losartan. Do not use LOSTAT Tablets as initial therapy in patients with intravascular volume depletion. Correct volume or salt depletion prior to losartan therapy.
Renal Function Deterioration: Changes in renal function including acute renal failure can be caused by drugs that inhibit the RAAS. 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 losartan therapy. Monitor renal function periodically in these patients. Consider withholding or discontinuing losartan therapy in patients who develop a clinically significant decrease in renal function.

Electrolyte Imbalance/Hyperkalemia: 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 as compared to the placebo group. Serum potassium should be monitored periodically and treated appropriately. Dosage reduction or discontinuation of losartan may be required.

Hypersensitivity: Patients with a history of angioedema (swelling of the face, lips, throat, and/or tongue) should be closely monitored.

Potassium Supplements: As this product contains potassium salt of losartan, patients are advised not to use potassium supplements or salt substitutes containing potassium without consultation with physician.

4.5Drug Interactions

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).

4.6Use in Special Populations

Pregnant Women

Pregnancy Category D. 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. Thus, when pregnancy is detected or planned, LOSTAT 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 have been observed in rat 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

LOSTAT Tablets are not intended for use in children. Oliguria or hypotension may occur in neonates with a history of *in utero* exposure to losartan. Safety and effectiveness have not been established in paediatric patients below 6 years old or in paediatric patients with glomerular filtration rate <30 ml/min/1.73 m^2.

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. In general, dose selection for an elderly patient should be cautious and usually a lower initial dose may be required, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant diseases and/or other drug therapy.

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 is necessary in patients with renal impairment unless a patient is also volume-depleted. No initial dosage adjustment is necessary in hemodialysis patients.

Hepatic Impairment Patients

Following oral administration 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. Thus, in patients with mild-to-moderate hepatic impairment, the recommended starting dose of losartan is 25 mg. Losartan has not been studied in patients with

severe hepatic impairment. Therefore, LOSTAT 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. However, when driving vehicles or operating machinery it must be borne in mind that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy, in particular during initiation of treatment or when the dose is increased.

4.8Undesirable Effects

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.

4.9Overdose

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.

5. Pharmacological Properties

5.1 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 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.

5.2Pharmacodynamic Properties

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.

5.3Pharmacokinetic Properties

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.

6. Nonclinical Properties

6.1 Animal Toxicology

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.

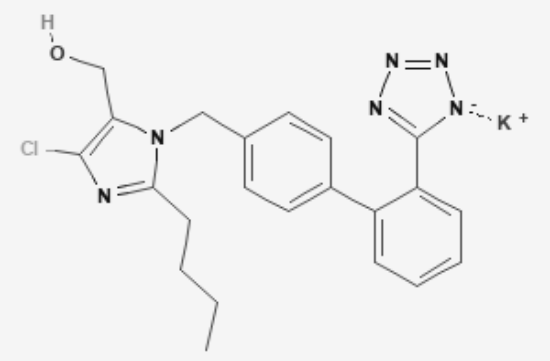
7. Description

LOSTAT 25 Tablets are off-white, circular, biconvex, uncoated tablet with “LK” engraved on one side and plain on the other side.

LOSTAT 50 Tablets are off-white, circular, biconvex, uncoated tablet with “LK” engraved on one side and plain on the other side.

LOSTAT Tablets contains 25 mg and 50 mg of losartan potassium for oral administration in adults.

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:



Inactive ingredients (excipients) of LOSTAT 25 and 50 Tablets contain Microcrystalline Cellulose, Lactose, Polyvinyl Pyrrolidone K–30, Isopropyl Alcohol, Sodium Starch Glycolate, Colloidal Silicon Dioxide, Magnesium Stearate, Instacoat Aqua – III(White), Purified Water, and Talc.

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.
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 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 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 Tablets do not stop taking other prescription medicines, including any other blood pressure medicines, without consulting their doctor.

10. Details of Manufacturer

Blue Cross Laboratories Pvt. Ltd.
A – 12, MIDC, Ambad, Nashik – 422 010 Maharashtra.

11. Details of Permission or License Number with Date

Lostat 25 Tablet: Mfg. Lic. No. : BD/25; Date of FDA Product Permission: 03/02/2004.
Lostat 50 Tablet: Mfg. Lic. No. : BD/25; Date of FDA Product Permission: 03/02/2004.

12. Date of Revision

February 2023.

MADE IN INDIA BY
BLUE CROSS LABORATORIES PVT LTD.
A-12, M.I.D.C., NASHIK-422 010.
Regd. Off.: Peninsula Chambers, G. K. Marg, Mumbai-400 013.