SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal Product

Losartan Potassium 50 mg & Hydrochlorothiazide 12.5 mg Tablets USP

2. Qualitative and Quantitative Composition

Sr. No.	Ingredients Chemical Name
01	Losartan Potassium
02	Hydrochlorothiazide
03	Microcrystalline Cellulose
04	Croscarmellose Sodium
05	Magnesium Stearate
06	Purified Talc
07	Sodium Starch Glycolate
08	Colour Quinoline Yellow SC-SP 2299
09	Isopropyl Alcohol
10	Dichloromethane

3. Pharmaceutical Form

Oral Tablet

Yellow coloured, round shaped, biconvex, film coated tablets, plain on both side.

4. Clinical Particulars

4.1 Therapeutic Indications

Losartan potassium and Hydrochlorothiazide Tablets are indicated for the treatment of hypertension and Reduced risk of stroke in hypertensive patients with left ventricular hypertrophy.

4.2 Posology and Method of Administration Hypertension:

Losartan and hydrochlorothiazide should be used in patients whose blood pressure is not adequately controlled by losartan potassium or hydrochlorothiazide alone. The usual dose is one tablet of Losartan potassium 50 mg with Hydrochlorothiazide 12.5 mg once daily. For patients who do not respond adequately to Losartan potassium 50 mg with Hydrochlorothiazide 12.5 mg, the dosage may be increased to one tablet of Losartan potassium 100 mg with Hydrochlorothiazide 25 mg once daily. The maximum dose is one tablet of Losartan potassium 100 mg with Hydrochlorothiazide 25 mg once daily.

Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy:
Treatment should be initiated with losartan potassium tablets 50 mg once daily. Hydrochlorothiazide 12.5 mg should be added or Losartan Potassium 50mg and Hydrochlorothiazide tablets 12.5 mg substituted if the blood pressure reduction is inadequate. If additional blood pressure reduction is needed, than given a dose of Losartan Potassium and Hydrochlorothiazide tablets 100 mg/25 mg.

4.3 Contraindications

Losartan potassium and Hydrochlorothiazide Tablets are contraindicated in patients with hypersensitivity to any component of the formulation. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

4.4 Special Warnings and Special Precautions for Use

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 Losartan potassium and Hydrochlorothiazide Tablets.

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.

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

Hypersensitivity Reaction: 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.

Hepatic and renal impairment: Losartan potassium / Hydrochlorothiazide Tablets is not recommended for patients with hepatic impairment or moderate to severe renal impairment.

Pregnancy: Category C (first trimester); Category D (second and third trimester). Losartan that act on the angiotensin system can cause injury and death to the developing fetus when used in the second and third trimesters. When pregnancy is detected, discontinue the therapy as soon as possible.

Lactation: It is not known whether losartan is excreted in human milk, but significant levels of losartan and its active metabolite were shown to be present in rat 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.

4.5 Interaction with other medicinal products and other forms of interaction

Losartan potassium:

Lithium: Plasma levels of lithium may be elevated, increasing the risk of toxicity.

Rifamycins (e.g., rifampin): May lead to reduced plasma Losartan levels, decreasing the antihypertensive effects.

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine.

Fluconazole: May decrease the metabolism of Losartan.

Hydrochlorothiazide:

Alcohol, barbiturates, or narcotics: Potentiating of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin): Dosage adjustment of the ant diabetic drug may be required.

Other antihypertensive drugs: There may be an additive effect.

Cholestyramine and colestipol resins: Absorption of hydrochlorothiazide may be impaired.

Corticosteroids, ACTH: There may be intensified electrolyte depletion, particularly hypokalaemia.

Nondepolarizing skeletal muscle relaxants (eg, turbocurarine): Responsiveness to muscle relaxant may be increased.

Lithium: Plasma levels of lithium may be elevated, increasing the risk of toxicity.

Non-steroidal anti-inflammatory drugs: Antihypertensive, diuretic, and natriuretic effects of hydrochlorothiazide may be reduced.

4.6 Fertility, Pregnancy and Lactation

Pregnancy: Category C (first trimester); Category D (second and third trimester). Losartan that act on the angiotensin system can cause injury and death to the developing fetus when used in the second and third trimesters. When pregnancy is detected, discontinue the therapy as soon as possible.

Lactation: It is not known whether losartan is excreted in human milk, but significant levels of losartan and its active metabolite were shown to be present in rat 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.

4.7 Effects on ability To Drive and use Machines

No data Available.

4.8 Undesirable Effects

Blood and lymphatic system disorders: Anaemia, ecchymosis, haemolysis, agranulocytosis, aplastic anaemia, haemolytic anaemia, leukopenia, purpura, thrombocytopenia.

Psychiatric disorders: Insomnia.

Nervous system disorders: Headache, dizziness.

Cardiac disorders: Hypotension, orthostatic hypotension, sternalgia, angina pectoris, grade II-AV block, cerebrovascular event, myocardial infarction, palpitation, arrhythmias.

Respiratory, thoracic and mediastinal disorders: Cough, upper respiratory infection, nasal congestion, sinusitis, sinus disorder.

Gastrointestinal disorders: Abdominal pain, nausea, diarrhoea, dyspepsia, constipation, dental pain, dry mouth, flatulence, gastritis, vomiting.

Skin and subcutaneous tissue disorders: Alopecia, dermatitis, dry skin, erythema, flushing, photosensitivity, pruritus, rash, urticaria, sweating.

Musculoskeletal and connective tissue disorders: Muscle cramp, back pain, leg pain, myalgia.

Renal and urinary disorders: Nocturia, urinary frequency, urinary tract infection, Glycosuria, interstitial nephritis, renal dysfunction, renal failure.

Others: Anorexia, gout, hyperkalaemia, mild reduction of haematocrit and haemoglobin.

4.9 Overdose

Losartan Potassium: Limited data are available in regard to overdosage in humans. 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

5. Pharmacological Properties

5.1 Pharmacodynamics Properties

Losartan potassium: 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. Angiotensin II binds to the AT1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys, and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. 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. Affinity of losartan for the AT1 receptor is 1000 times greater than the AT2 receptor.

Hydrochlorothiazide: Hydrochlorothiazide is a diuretic and antihypertensive. It affects the distal renal tubular mechanism of electrolyte reabsorption. Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate.

5.2 Pharmacokinetic Properties

Losartan potassium: Losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. Both losartan and its active metabolite are ≥ 99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 L. About 14% of an orally-administered dose of losartan is converted to its active metabolite (carboxylosartan) by CYP2C9 and CYP3A4. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. Plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6-9 hours, respectively.

Hydrochlorothiazide: After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours. 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% of the oral dose is eliminated unchanged within 24 hours.

5.3 Preclinical Safety Data

Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, genotoxicity and carcinogenic potential. The toxic potential of the combination of losartan/hydrochlorothiazide was evaluated in chronic toxicity studies for up to six months duration in rats and dogs after oral administration, and the changes observed in these studies with the combination were mainly produced by the losartan component. The administration of the losartan/hydrochlorothiazide combination induced a decrease in the red blood cell parameters (erythrocytes, haemoglobin, haematocrit), a rise in ureaN in the serum, a decrease in heart weight (without a histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, haemorrhages). There was no evidence of teratogenicity in rats or rabbits treated with the losartan/hydrochlorothiazide combination.

Foetal toxicity in rats, as evidenced by a slight increase in supernumerary ribs in the F1 generation, was observed when females were treated prior to and throughout gestation. As observed in studies with losartan alone, adverse foetal and neonatal effects, including renal toxicity and foetal death, occurred when pregnant rates were treated with the losartan/hydrochlorothiazide combination during late gestation and/or lactation.

6. Pharmaceutical Particulars

6.1 List of Excipients

Microcrystalline Cellulose BP
Croscarmellose Sodium USP-NF
Magnesium Stearate BP
Purified Talc BP
Sodium Starch Glycolate BP
Colour Quinoline Yellow SC-SP 2299 IHS
Isopropyl Alcohol BP
Dichloromethane BP

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

36 months

6.4 Special Precautions for Storage

Store below 30°C. Protect from light & moisture.

6.5 Nature and Contents of Container

10 Tablets are packed in a Alu-Alu Blister Pack. Such 3 Alu-Alu Blisters are packed in a printed Carton with Packing Insert.

6.6 Special precaution for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder And Manufacturing Site Addresses

Name and Address of Marketing Authorization Holder

Lincoln Pharmaceuticals Limited
Trimul Estate, Khatraj, Taluka: Kalol,
District: Gandhinagar Gujarat, India.
Telephone no.: +91-02764-665000
Fax: +91-02764-281809
Email: info@lincolnpharma.com
Website: www.lincolnpharma.com

7.1.1.1.1 Name and Address of manufacturing site(s)

Lincoln Pharmaceuticals Limited
Trimul Estate, Khatraj, Taluka: Kalol,
District: Gandhinagar Gujarat, India.
Telephone no.: +91-02764-665000
Fax: +91-02764-281809
Email: info@lincolnpharma.com
Website: www.lincolnpharma.com

8. Marketing Authorization Number

06837/6058/NMR/2018

9. Date of First <Registration> / Renewal of The <Registration>

Nov 28, 2021

10. **Date of Revision of the Text**