1.6 Product Information

1.6.1 Prescribing Information (Summary of Product Characteristics)

1. Name of the Medicinal Product

1.1 Trade Name : **LOZISART 50**
(Losartan Potassium Tablets USP 50 mg)

1.2 Strength : 50 mg

1.3 Pharmaceutical Form : Film Coated Tablets

2. Qualitative and Quantitative Composition

S. No	Name of Ingredients	Quantity/ Tablets (mg)
Active Substance		
1	Losartan Potassium USP	50.00
Inactive Substance		
2	Colloidal Anhydrous silica BP	2.00
3	Maize Starch BP	59.00
4	Lactose Monohydrate BP	42.60
5	Microcrystalline Cellulose BP	11.90
6	Povidone BP	1.60
7	Magnesium Stearate BP	3.00
8	Purified Talc BP	5.00
9	Croscarmellose Sodium USP-NF	9.90
10	Tartrazine Lake In-house	0.40
11	Opadry White In-house	4.60
12	Isopropyl Alcohol BP	Q. S.
13	Purified Water BP	Q. S.
	Total	**190.00 mg**

3. Pharmaceutical Form

Film coated tablets

Yellow, circular, slightly biconvex, film coated tablets, engraved with 'Zim' on one side and breakline on other side.

4. Clinical Particulars

4.1 Therapeutic indications

Losartan Potassium is indicated for the:

• Treatment of essential hypertension in adults and in children and adolescents 6 - 18 years of age.

• Treatment of renal disease in adult patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment.

• Reduction in the risk of stroke in adult hypertensive patients with left ventricular hypertrophy documented by ECG.

4.2 Posology and method of administration

Posology

Hypertension: The usual starting and maintenance dose is 50 mg once daily for most patients. The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy. Some patients may receive an additional benefit by increasing the dose to 100 mg once daily (in the morning).

Losartan may be administered with other antihypertensive agents, especially with diuretics (e.g. hydrochlorothiazide).

Hypertensive type II diabetic patients with proteinuria ≥ 0.5 g/day: The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily based on blood pressure response from one month onwards after initiation of therapy. Losartan may be administered with other antihypertensive agents (e.g. diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycemic agents (e.g. sulfonylureas, glitazones and glucosidase inhibitors).

Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG: The usual starting dose is 50 mg of losartan once daily. A low dose of hydrochlorothiazide should be added and/or the dose of losartan should be increased to 100 mg once daily based on blood pressure response.

Use in patients with intravascular volume depletion: For patients with intravascular volume-depletion (e.g. those treated with high-dose diuretics), a starting dose of 25mg once daily should be considered.

Use in patients with renal impairment and haemodialysis patients: No initial dosage adjustment is necessary in patients with renal impairment and in haemodialysis patients.

Use in patients with hepatic impairment:
A lower dose should be considered for patients with a history of hepatic impairment. There is no therapeutic experience in patients with severe hepatic impairment. Therefore, losartan is contraindicated in patients with severe hepatic impairment.

Use in Elderly
Although consideration should be given to initiating therapy with 25mg in patients over 75 years of age, dosage adjustment is not usually necessary for the elderly.

Method of administration
Losartan tablets should be swallowed whole with a glass of water. Losartan tablets may be administered with or without food.

4.3 Contraindication
• Hypersensitivity to the active substance or to any of the excipients of Losartan Potassium Tablet.
• 2^{nd} and 3^{rd} 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).

4.4 Special warnings and special precautions for use
Hypersensitivity:
Angiooedema: Patients with a history of angiooedema (swelling of the face, lips, throat, and/or tongue) should be closely monitored.

Hypotension and Electrolyte/Fluid Imbalance: Symptomatic hypotension, especially after the first dose and after increasing of the dose, may occur in patients who are volume- and/or sodium-depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. These conditions should be corrected prior to administration of losartan, or a lower starting dose should be used. This also applies to children 6 to 18 years of age.

Electrolyte imbalances: Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. The plasma concentrations of potassium as well as creatinine clearance values should be closely monitored, especially patients with heart failure and a creatinine clearance between 30-50 ml/min should be closely monitored.

The concomitant use of potassium-sparing diuretics, potassium supplements and potassium-containing salt substitutes with losartan is not recommended.

Hepatic impairment: There is no therapeutic experience with losartan in patients with severe hepatic impairment. Therefore losartan must not be administered in patients with severe hepatic impairment.
Losartan is not recommended in children with hepatic impairment.

Renal impairment: As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported (in particular, in patients whose renal function is dependent on the renin- angiotensin-aldosterone system such as those with severe cardiac insufficiency or pre-existing renal dysfunction). As with other medicinal products that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy. Losartan should be used with caution in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Use in paediatric patients with renal impairment: Losartan is not recommended in children with glomerular filtration rate < 30 ml/min/1.73 m^2 as no data are available.

Renal function should be regularly monitored during treatment with losartan as it may deteriorate. This applies particularly when losartan is given in the presence of other conditions (fever, dehydration) likely to impair renal function.

Concomitant use of losartan and ACE-inhibitors has shown to impair renal function. Therefore, concomitant use is not recommended.

Renal transplantation: There is no experience in patients with recent kidney transplantation.

Primary hyperaldosteronism: Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of losartan is not recommended.

Coronary heart disease and cerebrovascular disease: As with any antihypertensive agents, excessive blood pressure decrease in patients with ischaemic cardiovascular and cerebrovascular disease could result in a myocardial infarction or stroke.

Heart failure: In patients with heart failure, with or without renal impairment, there is - as with other medicinal products acting on the renin-angiotensin system - a risk of severe arterial hypotension, and (often acute) renal impairment.

There is no sufficient therapeutic experience with losartan in patients with heart failure and concomitant severe renal impairment, in patients with severe heart failure (NYHA class IV) as

well as in patients with heart failure and symptomatic life-threatening cardiac arrhythmias. Therefore, losartan should be used with caution in these patient groups. The combination of losartan with a beta-blocker should be used with caution.
Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy: As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Excipients: This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Pregnancy: Losartan should not be initiated during pregnancy. Unless continued losartan therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with losartan should be stopped immediately, and, if appropriate, alternative therapy should be started.

Other warnings and precautions: As observed for angiotensin converting enzyme inhibitors, losartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS): There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia, and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended.

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

4.5 Interaction with other medicinal products and other forms of interaction
Other antihypertensive agents may increase the hypotensive action of losartan. Concomitant use with other substances which may induce hypotension as an adverse reaction (like tricyclic antidepressants, antipsychotics, baclofen and amifostine) may increase the risk of hypotension.

Losartan is predominantly metabolised by cytochrome P450 (CYP) 2C9 to the active carboxy-acid metabolite. It was found that fluconazole (inhibitor of CYP2C9) decreases the exposure to the active metabolite by approximately 50%. It was found that concomitant treatment of losartan

with rifampicin (inducer of metabolism enzymes) gave a 40% reduction in plasma concentration of the active metabolite. The clinical relevance of this effect is unknown. No difference in exposure was found with concomitant treatment with fluvastatin (weak inhibitor of CYP2C9).
As with other medicinal products that block angiotensin II or its effects, concomitant use of other medicinal products which retain potassium (e.g. potassium-sparing diuretics: amiloride, triamterene, spironolactone) or may increase potassium levels (e.g. heparin), potassium supplements or salt substitutes containing potassium may lead to increases in serum potassium. Co-medication is not advisable.

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Very rare cases have also been reported with angiotensin II receptor antagonists. Co-administration of lithium and losartan should be undertaken with caution. If this combination proves essential, serum lithium level monitoring is recommended during concomitant use.
When angiotensin II antagonists are administered simultaneously with NSAIDs (i.e. selective COX-2 inhibitors, acetylsalicylic acid at anti-inflammatory doses and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of angiotensin II antagonists or diuretics and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia, and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.

4.6 Pregnancy and lactation

Pregnancy: The use of losartan is not recommended during the first trimester of pregnancy. The use of losartan is contraindicated during the 2nd and 3rd trimester of pregnancy.
When pregnancy is diagnosed, treatment with losartan should be stopped immediately and, if appropriate, alternative therapy should be started. You must tell your doctor if you think you are (or might become) pregnant.
Lactation: Because no information is available regarding the use of losartan during breastfeeding, losartan is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, when driving vehicles or operating machines 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.

4.8 Undesirable effects

The frequency of adverse reactions listed below is defined using the following convention: Very common (≥ 1/10); common (≥ 1/100, to < 1/10); uncommon (≥ 1/1,000, to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

Common: Dizziness, vertigo, hyperkalemia, asthenia, fatigue, anaemia, renal impairment, renal failure, increase in blood urea, serum creatinine, serum potassium, hypoglycemia.
Uncommon: Somnolence, headache, sleep disorders, palpitations, angina pectoris, (orthostatic) hypotension (including dose- related orthostatic effects), abdominal pain, obstipation, rash, oedema, headache, dyspnoea, cough, diarrhoea, nausea, vomiting, urticaria, pruritus.
Rare: Increased alanine aminotransferase (ALT) paraesthesia, syncope, atrial fibrillation, cerebrovascular accident, hypersensitivity reactions, anaphylactic reactions, angiooedema and vasculitis, hepatitis
Frequency not known: Anemia, thrombocytopenia, depression, migraine, dysgeusia, tinnitus, pancreatitis, liver function abnormalities, photosensitivity, myalgia, arthralgia, rhabdomyolysis, erectile dysfunction / impotence, malaise, hyponatraemia.

4.9 Overdose

Symptoms of intoxication: Limited data are available with regard to overdose in humans. The most likely manifestation of overdose would be hypotension and tachycardia. Bradycardia could occur from parasympathetic (vagal) stimulation.
Treatment of intoxication: If symptomatic hypotension should occur, supportive treatment should be instituted.
Measures are depending on the time of medicinal product intake and kind and severity of symptoms. Stabilisation of the cardiovascular system should be given priority. After oral intake, the administration of a sufficient dose of activated charcoal is indicated. Afterwards, close monitoring of the vital parameters should be performed. Vital parameters should be corrected if necessary.
Neither losartan nor the active metabolite can be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Angiotensin II antagonists.
ATC Code: C09CA01.

Losartan is a synthetic oral angiotensin-II receptor (type AT_1) antagonist. Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin/angiotensin system and an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT_1 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. Angiotensin II also stimulates smooth muscle cell proliferation.

Losartan selectively blocks the AT_1 receptor. *In vitro* and *in vivo* losartan and its pharmacologically active carboxylic acid metabolite E-3174 block all physiologically relevant actions of angiotensin II, regardless of the source or route of its synthesis.

Losartan does not have an agonist effect nor does it block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, there is no potentiation of undesirable bradykinin-mediated effects.

During administration of losartan, removal of the angiotensin II negative feedback on renin secretion leads to increased plasma renin activity (PRA). Increase in the PRA leads to an increase in angiotensin II in plasma. Despite these increases, antihypertensive activity and suppression of plasma aldosterone concentration are maintained, indicating effective angiotensin II receptor blockade. After discontinuation of losartan, PRA and angiotensin II values fell within three days to the baseline values.

Both losartan and its principal active metabolite have a far greater affinity for the AT_1-receptor than for the AT_2-receptor. The active metabolite is 10- to 40- times more active than losartan on a weight for weight basis.

5.2 Pharmacokinetic Properties

Absorption: Following oral administration, 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.

Distribution: Both losartan and its active metabolite are ≥99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres.

Biotransformation: About 14% of an orally-administered dose of losartan is converted to its active metabolite. Following oral administration of 14C-labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about one percent of individuals studied. In addition to the active metabolite, inactive metabolites are formed.

Elimination: Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. 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. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.

Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially, with a terminal half-life of about 2 hours and 6-9 hours, respectively. During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.

Both biliary and urinary excretions contribute to the elimination of losartan and its metabolites.

Following an oral dose administration of 14C-labelled losartan in man, about 35% / 43% of radioactivity is recovered in the urine and 58%/ 50% in the faeces.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, genotoxicity and carcinogenic potential. In repeated dose toxicity studies, the administration of losartan induced a decrease in the red blood cell parameters (erythrocytes, haemoglobin, haematocrit), a rise in urea-N in the serum and occasional rises in serum creatinine, a decrease in heart weight (without a histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, haemorrhages). Like other substances that directly affect the renin-angiotensin system, losartan has been shown to induce adverse reactions on the late foetal development, resulting in foetal death and malformations.

6. Pharmaceutical Particulars

6.1 List of excipients

Colloidal Anhydrous silica(E551)
Maize Starch (E1442)
Lactose Monohydrate
Microcrystalline Cellulose (E460)
Povidone (E1201)
Magnesium Stearate (E572)
Purified Talc (E553b)
Croscarmellose Sodium(E468)
Tartrazine Lake
Opadry White

6.2 Incompatibilities

None

6.3 Shelf life
3 years from the date of manufacture

6.4 Special precautions for storage
Store at a temperature not exceeding 30°C, protect from moisture.
Keep out of the reach of children.

6.5 Nature and contents of container
10 × 10 Tablets in Alu- Alu Blister Pack

6.6 Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder
ZIM Laboratories Limited
B-21/22, MIDC Area,
Kalmeshwar, Nagpur 441501
Maharashtra State,
India.

8. Number(S) In the National Register of Finished pharmaceutical products
NA

9. Date of First Authorization/Renewal of the Authorization
NA

10. Date of Revision of the Text
04 May 2019