SUMMARY OF PRODUCT CHARACTERISTICS
LOSARGOOD 50 (Losartan Potassium Tablets BP 50 mg)

1. NAME OF THE MEDICINAL PRODUCT

LOSARGOOD 50 (Losartan Potassium Tablets BP 50 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains losartan potassium BP 50 mg.

Excipients with known effect:

Contains lactose. For warnings, see section 4.4.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White, round, biconcave, film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LOSARGOOD 50 is indicated for:

- Treatment of essential hypertension in adults and in children and adolescents aged 6–18 years.
- 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 regimen.
- Treatment of chronic heart failure in adult patients when treatment with ACE inhibitors is not considered suitable due to incompatibility, especially cough, or contraindication. Patients with heart failure who have been stabilised with an ACE inhibitor should not be switched to losartan. Patients should have a left ventricular ejection fraction ≤40% and should be clinically stable on an established heart failure treatment regimen.
- Reduction in the risk of stroke in adult hypertensive patients with left ventricular hypertrophy documented by ECG (LIFE study).

4.2 Posology and method of administration

Hypertension

The usual starting and maintenance dose is 50 mg once daily. The maximal antihypertensive effect is attained 3–6 weeks after initiation of therapy. Some patients may receive additional benefit from increasing the dose to 100 mg once daily. Losartan may be administered with other antihypertensive agents, especially diuretics (e.g. hydrochlorothiazide).

Hypertensive type 2 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 after initiation of therapy. Losartan may be administered with other antihypertensive agents, insulin and other commonly used hypoglycaemic agents.

Heart failure

The usual initial dose is 12.5 mg once daily. The dose should generally be titrated at weekly intervals (12.5 mg, 25 mg, 50 mg once daily) as tolerated by the patient, with a target maintenance dose of 50 mg once daily.

Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy

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

Special populations

Intravascular volume depletion:

A starting dose of 25 mg once daily should be considered.

Renal impairment and haemodialysis:

No initial dosage adjustment is necessary in patients with renal impairment or in haemodialysis patients.

Hepatic impairment:

A lower dose should be considered for patients with a history of hepatic impairment. Losartan is contraindicated in patients with severe hepatic impairment.

Elderly patients:

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

Paediatric population (6 to 18 years)

For patients who can swallow tablets: body weight >20 kg to <50 kg: 25 mg once daily (may be increased to a maximum of 50 mg once daily); body weight >50 kg: 50 mg once daily (may be increased to a maximum of 100 mg once daily). Doses above 1.4 mg/kg/day (or 100 mg/day) have not been studied. Losartan is not recommended for children under 6 years of age or in children with GFR <30 ml/min/1.73 m². Losartan is not recommended in children with hepatic impairment.

Method of administration

Oral. Tablets should be swallowed whole with a glass of water. May be taken with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Second and third trimesters of pregnancy (see section 4.6).
- Severe hepatic impairment.
- Concomitant use of losartan with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m²).

4.4 Special warnings and precautions for use

Angioedema

Patients with a history of angioedema should be closely monitored.

Hypotension and electrolyte/fluid imbalance

Symptomatic hypotension, especially after the first dose and after dose increases, 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 aged 6–18 years.

Electrolyte imbalances

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In type 2 diabetic patients with nephropathy, the incidence of hyperkalaemia was higher in the losartan group than in placebo. Plasma potassium concentrations and creatinine clearance values should be closely monitored — especially patients with heart failure and creatinine clearance between 30–50 ml/min. Concomitant use of potassium-sparing diuretics, potassium supplements, potassium-containing salt substitutes, or other drugs that may increase serum potassium with losartan is not recommended.

Hepatic impairment

Based on pharmacokinetic data demonstrating significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered in patients with a history of hepatic impairment. Losartan must not be administered in patients with severe hepatic impairment.

Renal impairment

Changes in renal function, including renal failure, have been reported as a consequence of inhibiting the renin-angiotensin system — particularly in patients whose renal function is dependent on the RAAS (e.g. severe cardiac insufficiency or pre-existing renal dysfunction). 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. Use losartan with caution in these patients. Concomitant use of losartan and ACE inhibitors has shown to impair renal function and is not recommended.

Dual blockade of the RAAS

The concomitant use of ACE inhibitors, angiotensin II receptor blockers (AIIRAs) or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade is therefore not recommended. If considered absolutely necessary, it should occur only under specialist supervision with frequent monitoring of renal function, electrolytes and blood pressure. ACE inhibitors and AIIRAs should not be used concomitantly in patients with diabetic nephropathy.

Primary aldosteronism

Patients with primary aldosteronism generally will not respond to antihypertensive agents acting through inhibition of the RAAS; losartan is not recommended in this population.

Coronary heart disease and cerebrovascular disease

Excessive blood pressure reduction in patients with ischaemic cardiovascular and cerebrovascular disease could result in myocardial infarction or stroke.

Heart failure

Risk of severe arterial hypotension and renal impairment exists in patients with heart failure, with or without renal impairment. There is insufficient experience in patients with heart failure and severe concomitant renal impairment, NYHA class IV heart failure, or symptomatic life-threatening cardiac arrhythmias; losartan should be used with caution in these 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 these conditions.

Pregnancy

AIIRAs should not be initiated during pregnancy. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments with established safety in pregnancy. When pregnancy is diagnosed, losartan should be stopped immediately and, if appropriate, alternative therapy started (see sections 4.3 and 4.6).

Ethnic differences

Losartan and other angiotensin antagonists are apparently less effective in lowering blood pressure in Black people than in non-Black patients, possibly because of higher prevalence of low-renin states.

Lactose content

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

4.5 Interaction with other medicinal products and other forms of interaction

Other antihypertensive agents:

May increase the hypotensive action of losartan.

CYP2C9 inhibitors and inducers:

Losartan is predominantly metabolised by CYP2C9 to its active carboxylic acid metabolite. Fluconazole (CYP2C9 inhibitor) decreases exposure to the active metabolite by approximately 50%. Rifampicin reduces plasma concentrations of the active metabolite by approximately 40%.

Potassium-raising agents:

Concomitant use of potassium-sparing diuretics, potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium. Co-medication is not advisable.

Lithium:

Reversible increases in serum lithium concentrations and toxicity have been reported with AIIRAs. If the combination proves essential, serum lithium levels should be monitored during concomitant use.

NSAIDs:

Attenuation of the antihypertensive effect may occur. Concomitant use of AIIRAs or diuretics with NSAIDs may increase the risk of worsening renal function, including possible acute renal failure, and increase in serum potassium, especially in the elderly. Patients should be adequately hydrated and renal function monitored.

Dual RAAS blockade:

Associated with a higher frequency of hypotension, hyperkalaemia and decreased renal function compared with RAAS monotherapy (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Use of losartan is not recommended during the first trimester of pregnancy. Use is contraindicated during the second and third trimesters (see section 4.3). Exposure to AIIRAs during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). Should exposure have occurred from the second trimester, ultrasound examination of renal function and skull is recommended. Infants whose mothers have taken losartan should be closely observed for hypotension.

Breast-feeding

Because no information is available regarding the use of losartan during breast-feeding, losartan is not recommended. Alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Fertility

No relevant data available.

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. Dizziness or drowsiness may occasionally occur when taking antihypertensive therapy, particularly during initiation or when the dose is increased.

4.8 Undesirable effects

The most common adverse event across clinical studies was dizziness. The adverse reaction profile of losartan in paediatric patients appears to be similar to that seen in adults, though data are limited.

System Organ Class	Adverse Reaction	Frequency
Nervous system	Dizziness	Common
Nervous system	Somnolence, headache, sleep disorders	Uncommon
Ear and labyrinth	Vertigo	Common
Cardiac	Palpitations, angina pectoris	Uncommon
Vascular	Symptomatic hypotension, hypotension	Uncommon
Gastrointestinal	Abdominal pain, constipation	Uncommon
Skin	Rash	Uncommon
General	Asthenia, fatigue, oedema	Uncommon
Investigations	Hyperkalaemia	Common
Investigations	Elevated ALT (usually resolved on discontinuation)	Rare
Blood/lymphatic	Anaemia, thrombocytopenia	Not known
Immune system	Anaphylactic reactions, angioedema (larynx, glottis, face, lips, pharynx, tongue), vasculitis including Henoch-Schönlein purpura	Rare
Ear/labyrinth	Tinnitus	Not known
Respiratory	Cough	Not known
Gastrointestinal	Diarrhoea, pancreatitis	Not known
Hepatobiliary	Hepatitis; liver function abnormalities	Rare / Not known
Skin	Urticaria, pruritus, rash, photosensitivity	Not known
Musculoskeletal	Myalgia, arthralgia, rhabdomyolysis	Not known
Reproductive system	Erectile dysfunction/impotence	Not known
Psychiatric	Depression	Not known
Investigations	Hyponatraemia	Not known

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the National Regulatory Authority.

4.9 Overdose

The most likely manifestations of overdose are hypotension and tachycardia; bradycardia could occur from parasympathetic stimulation. If symptomatic hypotension occurs, supportive treatment should be instituted.

After oral intake, administration of activated charcoal is indicated. Close monitoring of vital parameters and correction as necessary. Neither losartan nor the active metabolite can be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonists, plain. ATC code: C09CA01.

Losartan is a synthetic oral angiotensin II receptor (type AT1) antagonist. Angiotensin II is a potent vasoconstrictor and the primary active hormone of the renin-angiotensin system. It binds to the AT1 receptor found in many tissues and elicits vasoconstriction, aldosterone release and smooth muscle cell proliferation. Losartan selectively blocks the AT1 receptor. In vitro and in vivo, losartan and its pharmacologically active carboxylic acid metabolite block all physiologically relevant actions of angiotensin II, regardless of the source or route of synthesis. Losartan does not have agonist activity, does not block other hormone receptors or ion channels important in cardiovascular regulation, and does not inhibit ACE (kininase II). Consequently, there is no potentiation of bradykinin-mediated effects.

Key clinical studies: LIFE study (9,193 hypertensive patients with LVH, aged 55–80 years) showed a 13% risk reduction in the primary composite cardiovascular endpoint vs atenolol, attributable mainly to a 25% reduction in stroke risk. The benefit did not apply to Black patients (see section 4.4). RENAAL study (1,513 type 2 diabetic patients with proteinuria) showed a 16.1% risk reduction in the primary composite endpoint of doubling of serum creatinine, end-stage renal failure or death. HEAAL study showed that 150 mg losartan reduced the primary composite endpoint (all-cause death or hospitalisation for HF) by 10.1% relative to 50 mg losartan, mainly due to a 13.5% reduction in hospitalisation for HF.

5.2 Pharmacokinetic properties

Absorption: Losartan is well absorbed following oral administration and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. Systemic bioavailability approximately 33%. Mean peak concentrations of losartan and its active metabolite reached at 1 hour and 3–4 hours, respectively. Distribution: Both losartan and its active metabolite are ≥99% bound to plasma proteins, primarily albumin. Volume of distribution of losartan: 34 litres. Biotransformation: Approximately 14% of a dose is converted to the active metabolite; CYP2C9 is the primary enzyme. Elimination: Plasma clearance of losartan and active metabolite approximately 600 ml/min and 50 ml/min, respectively. Terminal half-life of losartan approximately 2 hours; active metabolite 6–9 hours. Approximately 35% of dose excreted in urine and 58% in faeces. Neither losartan nor the active metabolite can be removed by haemodialysis. In hepatic cirrhosis: losartan AUC is 5-fold and active metabolite AUC 1.7-fold higher than in healthy young males.

5.3 Preclinical safety data

No special hazard for humans based on conventional studies of general pharmacology, genotoxicity and carcinogenic potential. Losartan induces adverse effects on late foetal development, resulting in foetal death and malformations. Decrease in red blood cell parameters, rise in urea-N and creatinine, decrease in heart weight and gastrointestinal changes were observed in repeated dose toxicity studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Starch, povidone K-30, isopropyl alcohol, magnesium stearate, purified talc, sodium starch glycolate, croscarmellose sodium, microcrystalline cellulose (MCCP 102), Kyron-314 (cross-linked polyacrylic acid — dissolution enhancer), titanium dioxide (film coat), methylene dichloride.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 30°C. Protect from light. Keep out of the reach and sight of children.

6.5 Nature and contents of container

10 tablets per ALU blister; 3 such blisters packed in one carton with package insert. Pack size: 30 tablets.

6.6 Special precautions for disposal and other handling

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

ZAIN PHARMA LTD.

Plot No. 209/13741, Colchester Park,

Go-Down No. 1, 2, 3, Off Mombasa Road,

Behind Nice and Lovely House,

P.O. Box: 100167-00101, Nairobi, Kenya.

8. MARKETING AUTHORISATION NUMBER (PPB REGISTRATION NUMBER)

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