SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the finished product:

LOSARVA 25 TABLET (Losartan Potassium TabletsUSP 25 mg)

2. Qualitative and Quantitative composition:

COMPOSITION:

Each Film coated tablet contains:
Losartan Potassium USP ..… 25 mg
Excipients..... q.s.

1.	Losartan Potassium
2.	Microcrystalline Cellulose (Avicel PH 102)
3.	Lactose Monohydrate (Spray dried)
4.	Sodium Starch Glycolate
5.	Colloidal Silicon Dioxide (Aerosil-200)
6.	Magnesium Stearate
7.	Opadry 200 White (200F280000)
8.	Opadry Yellow (200F520042)
9.	Opadry Red (200F550020)
10.	Purified Water

3. Pharmaceutical Form: Film coated tablet

4. Clinical Particulars:

4.1 Therapeutic Indications:

Hypertension

Losarva (Losartan Potassium) is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents (eg. thiazide diuretics).

Renal Protection in Typt-2 Diabetic Patients with Proteinuria

Losarva (Losartan Potassium) is indicated to delay the progression of renal disease in hypertensive type-2 diabetics with proteinuria, defined as urinary albumin to creatinine ratio >300 mg/g.

4.2 Posology and method of administration:

The usual starting and maintenance dose is 50 mg once daily for most patients. If the antihypertensive effect using 50 mg once daily is inadequate, 25 mg twice daily is recommended prior to increasing the dose. For patients with intravascular volume-depletion (e.g., those treated with high-dose diuretics), a starting dose of 25 mg once daily should be considered. Losartan Potassium can be administered once or twice daily. The total daily dose ranges from 25 mg to 100 mg.

4.3 Contraindications

Losartan Potassium is contraindicated in pregnant women and in patients who are hypersensitive to any component of this product, Losartan Potassium should not be administered with Aliskiren in patients with diabetes.

4.4 Special warnings and 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 Potassium Tablets, 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. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalaemia was higher in the group treated with Losartan Potassium Tablets ' as compared to the placebo group. Therefore, 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

Based on pharmacokinetic data, which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with a history of 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 also not recommended in children with hepatic impairment.

Renal function 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 rennin- 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 pediatric patients with renal function impairment

Losartan is not recommended in children with glomerular filtration rate < 30ml/ min/ 1.73 m^2as 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 drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of Losartan tablets 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 drugs 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.

Precautions
Use of Losartan Potassium during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. In patients who are intravascularly volume-depleted (e.g. those treated with high-dose diuretics). Symptomatic hypotension may occur. Plasma concentration of Losartan Potassium is significantly increased in cirrhotic patients. Changes in renal function including renal failure have been reported in renal impaired patient.

4.5 Interaction with other medicinal products and other forms of interaction
Agents Increasing Serum Potassium:
Coadministration of losartan with other drugs that raise serum potassium levels may result in hyperkalemia. Monitor serum potassium in such patients.

Lithium:
Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists. 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, coadministration 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 System (RAS):
Dual blockade of the RAS with angiotensin receptor blockers, 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.

4.6 Pregnancy and Lactation:
Pregnancy Category D. The risk to the fetus increases if Losartan Potassium is administered during the second or third trimesters of pregnancy. It is not known whether Losartan Potassium is excreted in human milk. as many drugs are excreted in human milk and 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 the 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 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.

4.8 Undesirable effects:
The side effects with the use of Losartan Potassium are mild and transient in nature. The most common side effects are dizziness, diarrhea, nasal congestion, cough, upper respiratory infection. Other side effects are fatigue. oedema, abdominal pain, chest pain, nausea, headache & pharyngitis.

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 drug intake and kind and severity of symptoms. Stabilisation of the circulatory 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 Particulars:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II Receptor 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 bradykininmediated effects.

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 intravenously- or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of 14C-labeled 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 600mL/min and 50mL/min, respectively. Renal clearance of losartan and its active metabolite is about 74mL/min and 26mL/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.

5.3 Pre-clinical Safety:
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 effects on the late foetal development, resulting in foetal death and malformations.

6. Pharmaceutical Particulars:

6.1 List of Excipients:

Microcrystalline Cellulose (Avicel PH 102)	BP
Lactose Monohydrate (Spray dried)	BP
Sodium Starch Glycolate	BP
Colloidal Silicon Dioxide (Aerosil-200)	USPNF
Magnesium Stearate	BP
Opadry 200 White (200F280000)	IH
Opadry Yellow (200F520042)	IH
Opadry Red (200F550020)	IH
Purified Water	BP

6.2 Incompatibilities: Nil

6.3 Shelf Life: 24 months

6.4 Special Precautions for storage:
Do not store above 30°C. Keep out of sight and reach of children.

6.5 Nature and contents of container:
5 Alu-PVDC Blisters of 10 tablets each packed in a primary carton along with pack insert.

6.6 Special precautions for disposal and other handling
None

7. Marketing Authorization Holder:
NIPRO JMI Pharma Ltd.
Unique Heights, Level-6
117, Kazi Nazrul Islam Avenue,
Ramna, Dhaka-1217
Country: Bangladesh

8. Marketing Authorization Number: --

06442/07138/NMR/2018

9. Date of first Authorization /renewal of the authorization:

Aug 3, 2021

10. Date of revision of text:

May 2018