SARANTO
P1524177

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SUMMARY OF PRODUCT CHARACTERISTICS
SARANTO
Losartan Potassium Tablets 25 mg, 50 mg and 100 mg.
R_x Only

NAME OF DRUG PRODUCT : Losartan Potassium Tablets 25 mg.
Losartan Potassium Tablets 50 mg.
Losartan Potassium Tablets 100 mg.

(TRADE) NAME OF PRODUCT : SARANTO 25
SARANTO 50
SARANTO 100

STRENGTH : 25 mg, 50 mg and 100 mg.

QUALITATIVE AND QUANTITATIVE COMPOSITIONS:

Losartan Potassium Tablets 25 mg
Each film-coated tablet contains Losartan Potassium Ph. Eur. 25 mg.

Losartan Potassium Tablets 50 mg
Each film-coated tablet contains Losartan Potassium Ph. Eur. 50 mg.

Losartan Potassium Tablets 100 mg
Each film-coated tablet contains Losartan Potassium Ph. Eur. 100 mg.

PHARMACEUTICAL FORM:

Losartan Potassium Tablets 25 mg: White to off-white, oval shaped, biconvex film-coated tablets debossed with '5' and '7' on either side of score line on one side and 'J' with a scoreline on other side..

Losartan Potassium Tablets 50 mg:* White to off-white, oval shaped, biconvex film-coated tablets debossed with 'E' on one side and '4' and '6' separated by score line on other side.

'the tablet can be divided into equal halves'.

Losartan Potassium Tablets 100 mg: White to off-white, oval shaped, biconvex film-coated tablets debossed with 'E' on one side and '47' on the other side.

CLINICAL PARTICULARS:

Therapeutic indications

Hypertension

Losartan Potassium is indicated for the treatment of hypertension.

Hypertensive Patients with Left Ventricular Hypertrophy

Losartan Potassium is indicated for the reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy (see RACE).

Renal Protection in Type 2 Diabetic Patients with Proteinuria

Losartan Potassium is indicated to delay the progression of renal disease as measured by a reduction in the incidence of doubling of serum creatinine and end stage renal disease (need for dialysis or renal transplantation), and to reduce proteinuria.

Dosage and administration

Losartan tablets may be administered with or without food.

Losartan Potassium may be administered with other antihypertensive agents.

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 .

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

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 (see PRECAUTIONS).

No initial dosage adjustment is necessary for elderly patients up to 75 years of age, or for patients with mild renal impairment. For patients above 75 years of age, patients with moderate to severe renal impairment and patients on dialysis, a lower starting dose of 25mg is recommended. A lower dose should be considered for patients with a history of hepatic impairment (see PRECAUTIONS).

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

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.

Renal Protection in Type 2 Diabetic Patients with Proteinuria

The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily based on blood pressure response. Losartan Potassium 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).

Paediatric Use

Safety and effectiveness in children have not been established.

Neonates with a history of in utero exposure to Losartan Potassium:

If oliguria or hypotension occur, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

Use in Elderly

In clinical studies there was no age-related difference in the efficacy or safety profile of losartan.

Presently there is limited clinical experience in patients above 75 years of age; a lower starting dose of 25 mg once daily is recommended.

Race

Based on the LIFE (Losartan Intervention For Endpoint reduction in hypertension) study, the benefits of Losartan Potassium on cardiovascular morbidity and mortality compared to atenolol do not apply to Black patients with hypertension and left ventricular hypertrophy although both treatment regimens effectively lowered blood pressure in Black patients. In the overall LIFE study population (n=9193), treatment with Losartan Potassium resulted in a 13.0% risk reduction (p=0.021) as compared to atenolol for patients reaching the primary composite endpoint of the combined incidence of cardiovascular death, stroke, and myocardial infarction. In this study, Losartan Potassium decreased the risk of cardiovascular morbidity and mortality compared to atenolol in non-Black, hypertensive patients with left ventricular hypertrophy (n=8660) as measured by the primary endpoint of the combined incidence of cardiovascular death, stroke, and myocardial infarction (p=0.003). In this study, however, Black patients treated with atenolol were at lower risk of experiencing the primary composite endpoint compared with Black patients treated with Losartan Potassium (p=0.03). In the subgroup of Black patients (n=533; 6% of the LIFE study patients), there were 29 primary endpoints among 263 patients on atenolol (11%, 25.9 per 1000 patient-years) and 46 primary endpoints among 270 patients (17%, 41.8 per 1000 patient-years) on Losartan Potassium.

Contraindications

Losartan Potassium is contraindicated in patients who are hypersensitive to any component of this product. 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).

Precautions

Fetal Toxicity

Use of drugs that act on the renin-angiotensin system during the second and third trimester 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 deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Losartan Potassium as soon as possible. See PREGNANCY.

Hypersensitivity: Angioedema. See SIDE EFFECTS.

Hypotension and Electrolyte/Fluid Imbalance

In patients who are intravascularly volume-depleted (e.g., those treated with high-dose diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of Losartan Potassium, or a lower starting dose should be used (see DOSAGE AND ADMINISTRATION).

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 Potassium as compared to the placebo group; however, few patients discontinued therapy due to hyperkalemia (see SIDE EFFECTS and Laboratory Test Findings).

Concomitant use of other drugs that may increase serum potassium may lead to hyperkalemia (see DRUG INTERACTIONS).

Liver Function 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 (see DOSAGE AND ADMINISTRATION).

Renal Function Impairment

As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported in susceptible individuals; these changes in renal function may be reversible upon discontinuation of therapy.

Other drugs that affect the renin-angiotensin system may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. Similar effects have been reported with Losartan Potassium; these changes in renal function may be reversible upon discontinuation of therapy.

No initial dosage adjustment is necessary in patients with mild renal impairment (i.e. creatinine clearance 20-50 ml/min). For patients with moderate to severe renal impairment (i.e. creatinine clearance <20 ml/min) or patients on dialysis, a lower starting dose of 25 mg once daily is recommended.

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 (see DRUG INTERACTIONS).

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.

Drug Interactions

In clinical pharmacokinetic trials, no drug interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbital, ketoconazole, and erythromycin. Rifampin and fluconazole have been reported to reduce levels of active metabolite. The clinical consequences of these interactions have not been evaluated.

As with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, salt substitutes containing potassium, or other drugs that may increase serum potassium (e.g.,trimethoprim-containing products) may lead to increases in serum potassium.

As with other drugs which affect the excretion of sodium, lithium excretion may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be co-administered with angiotensin II receptor antagonists.

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of diuretics and other antihypertensive drugs. Therefore, the antihypertensive effect of angiotensin II receptor antagonists or ACE inhibitors may be attenuated by NSAIDs including selective COX-2 inhibitors.

In some patients with compromised renal function (e.g., elderly patients or patients who are volume-depleted, including those on diuretic therapy) who are being treated with non-steroidal anti-inflammatory drugs, including selective cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists or ACE inhibitors may result in a further deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Therefore, the combination should be administered with caution in patients with compromised renal function.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) 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) as compared to monotherapy. Closely monitor blood pressure, renal function, and electrolytes in patients on Losartan Potassium and other agents that affect the RAAS. (See CONTRAINDICATIONS and PRECAUTIONS).

Pregnancy

Although there is no experience with the use of Losartan Potassium in pregnant women, animal studies with losartan potassium have demonstrated fetal and neonatal injury and death, the mechanism of which is believed to be pharmacologically mediated through effects on the renin-angiotensin system. In humans, fetal renal perfusion, which is dependent upon the development of the renin-angiotensin system, begins in the second trimester; thus, risk to the fetus increases if Losartan Potassium is administered during the second or third trimesters of pregnancy.

Use of drugs that act on the renin-angiotensin system 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 deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Losartan Potassium as soon as possible.

These adverse outcomes are usually associated with the use of these drugs in the second and third trimesters of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue Losartan Potassium, unless it is considered life-saving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to Losartan Potassium for hypotension, oliguria, and hyperkalemia.

Nursing mothers

It is not known whether losartan is excreted in human milk. Because 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.

Side effects

Losartan Potassium has been found to be generally well tolerated in controlled clinical trials for hypertension; side effects have usually been mild and transient in nature and have not required discontinuation of therapy. The overall incidence of side effects reported with Losartan Potassium was comparable to placebo.

In controlled clinical trials for essential hypertension, dizziness was the only side effect reported as drug related that occurred with an incidence greater than placebo in one percent or more of patients treated with Losartan Potassium. In addition, dose-related orthostatic effects were seen in less than one percent of patients. Rarely, rash was reported, although the incidence in controlled clinical trials was less than placebo.

A/s: 280 x 360 mm ■ Black

AUROBINDO Packaging Development		Product Name	Component	Item Code	Date & Time
		Saranto Tablets	Leaflet	P1524177	19.10.2021 & 12.20 pm
		Country	Version No.	Reason of Issue	Reviewed / Approved by
		Singapore_U3	07	Submission	
Team Leader	Kiran K	Dimensions (mm)	Colours: 01		
Initiator	Shirisha N	A/s: 280 x 360 mm			
Artist	Sree Designers	Pharmacode: 24177			
Additional Information: VB					

24177

In these double-blind controlled clinical trials for essential hypertension, the following adverse experiences reported with Losartan Potassium occurred in ≥1 percent of patients, regardless of drug relationship:

	Losartan Potassium (n=2085)	Placebo (n=535)
Body as a Whole		
Abdominal pain	1.7	1.7
Asthenia/fatigue	3.8	3.9
Chest pain	1.1	2.6
Edema/swelling	1.7	1.9
Cardiovascular		
Palpitation	1.0	0.4
Tachycardia	1.0	1.7
Digestive		
Diarrhea	1.9	1.9
Dyspepsia	1.1	1.5
Nausea	1.8	2.8
Musculoskeletal		
Back pain	1.6	1.1
Muscle cramps	1.0	1.1
Nervous/Psychiatric		
Dizziness	4.1	2.4
Headache	14.1	17.2
Insomnia	1.1	0.7
Respiratory		
Cough	3.1	2.6
Nasal congestion	1.3	1.1
Pharyngitis	1.5	2.6
Sinus disorder	1.0	1.3
Upper respiratory infection	6.5	5.6

Losartan Potassium was generally well tolerated in a controlled clinical trial in hypertensive patients with left ventricular hypertrophy. The most common drug-related side effects were dizziness, asthenia/fatigue, and vertigo.

In the LIFE study, among patients without diabetes at baseline, there was a lower incidence of new onset diabetes mellitus with Losartan Potassium as compared to atenolol (242 patients versus 320 patients, respectively,p<0.001). Because there was no placebo group included in the study, it is not known if this represents a beneficial effect of Losartan Potassium or an adverse effect of atenolol.

Losartan Potassium was generally well tolerated in a controlled clinical trial in type 2 diabetic patients with proteinuria. The most common drug-related side effects were asthenia/fatigue, dizziness, hypotension and hyperkalemia (see PRECAUTIONS, Hypotension and Electrolyte/Fluid Imbalance).

The following additional adverse reactions have been reported in post-marketing experience:

Hypersensitivity: Anaphylactic reactions, 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; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Vasculitis, including Henoch-Schoenlein purpura, has been reported rarely.

Gastrointestinal: Hepatitis (reported rarely), liver function abnormalities, vomiting.

General disorders and administration site conditions: Malaise.

Hematologic: Anemia, thrombocytopenia (reported rarely).

Musculoskeletal: Myalgia, arthralgia.

Nervous System/Psychiatric: Migraine, dysgeusia.

Reproductive system and breast disorders: Erectile dysfunction/impotence.

Respiratory: Cough.

Skin: Urticaria, pruritus, erythroderma, photosensitivity.

Laboratory Test Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Losartan Potassium. Hyperkalemia (serum potassium >5.5 mEq/L) occurred in 1.5% of patients in the hypertension clinical trials. In a clinical study conducted in type 2 diabetic patients with proteinuria, 9.9% of patients treated with Losartan Potassium and 3.4% of patients treated with placebo developed hyperkalemia (see PRECAUTIONS, Hypotension and Electrolyte/Fluid Imbalance). Serum potassium should be monitored, particularly in the elderly and patients with renal impairment. Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy.

Over dosage

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.

PHARMACOLOGICAL PROPERTIES

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

Pharmacodynamic properties

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 AT1-receptor than for the AT2-receptor. The active metabolite is 10- to 40- times more active than losartan on a weight for weight basis.

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 ^{14}C-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 excretion contribute to the elimination of Losartan and its metabolites. Following an oral dose/ intravenous administration of ^{14}C-labelled Losartan in man, about 35%/43% of radioactivity is recovered in the urine and 58%,50% in the faeces.

Characteristics in patients

In elderly hypertensive patients the plasma concentrations of losartan and its active metabolite do not differ essentially from those found in young hypertensive patients.

In female hypertensive patients the plasma levels of losartan were up to twice as high as in male hypertensive patients, while the plasma levels of the active metabolite did not differ between men and women.

In patients with mild to moderate alcohol-induced hepatic cirrhosis, the plasma levels of losartan and its active metabolite after oral administration were respectively 5 and 1.7 times higher than in young male volunteers.

Plasma concentrations of losartan are not altered in patients with a creatinine clearance above 10 ml/minute. Compared to patients with normal renal function, the AUC for losartan is about 2-times higher in haemodialysis patients.

The plasma concentrations of the active metabolite are not altered in patients with renal impairment or in haemodialysis patients.

Neither losartan nor the active metabolite can be removed by haemodialysis.

PHARMACEUTICAL PARTICULARS

List of excipients

Tablet core:

Cellulose microcrystalline, Lactose monohydrate, Starch Pregelatinised, Low substituted hydroxy propyl cellulose, Magnesium stearate.

Tablet coat:

Hydroxypropyl cellulose (E463), Hypromellose 6cP (E464), Titanium Dioxide (E171).

Incompatibilities

None known.

Shelf life

36 months.

Special precautions for storage

Store in a dry place below 30° C.

Nature and contents of container

Blister Pack

25 mg - 3 x 10's Tablets
50 mg - 3 x 10's Tablets
100 mg - 3 x 10's Tablets

The container is a White Opaque PVC/PVdC-Aluminium foil blister pack

Not all presentations may be available locally

MANUFACTURED BY:

Aurobindo Pharma Ltd., Unit-III,
Survey No. 313 & 314, Bachupally, Bachupally Mandal,
Medchal-Malkajgiri District,
Telangana State, India.

PRODUCT OWNER

AUROBINDO

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Telangana state, India.

DATE OF PREPARATION OF LEAFLET

October 2021.

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