1. NAME OF THE MEDICINAL PRODUCT

1.1 Brand Name : LORZIDE

1.2 Generic Name : Losartan Potassium and Hydrochlorothiazide Tablets USP

1.3 Strength: Each Film Coated Tablet Contains:

Losartan Potassium USP 50 mg

Hydrochlorothiazide USP 12.5 mg

Colour: Sunset Yellow Lake

1.4 Pharmaceutical Form: Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

S. No.	Ingredients	Claim	Specification	Quantity(mg)/ Tablet	Overages %	Reason For Inclusion
Premix Materials						
1.	*Losartan Potassium	50 mg	USP	51.02	-----	API
2.	*Hydrochlorothiazide	12.5 mg	USP	12.50	-----	API
3.	Microcrystalline Cellulose	-----	BP	36.53	-----	Diluent
4.	Lactose Monohydrate	-----	BP	39.05	-----	Diluent
5.	Maize Starch	-----	BP	27.75	-----	Diluent
Binder Materials						
6.	Hydroxy Propyl Cellulose	-----	BP	03.80	-----	Binder
7.	Isopropyl Alcohol (IPA)	-----	BP	82.40	-----	Solvent
Lubrication Materials						
8.	AC Di Sol	-----	IH	07.60	-----	Disintegrant
9.	Colloidal Anhydrous Silica	-----	BP	00.95	-----	Glidant
10.	Sodium Lauryl Sulphate	-----	BP	02.00	-----	Lubricant
11.	Purified Talc	-----	BP	01.90	-----	Antiadherent
12.	Magnesium Stearate	-----	BP	01.90	-----	Lubricant
		Actual weight		**185.00 mg**		
Film Coating						
1.	Hypromellose (HPMC E15)	-----	BP	07.60	-----	Film Former
2.	Polyethylene Glycol (PEG 6000)	-----	BP	01.05	-----	Plasticizer
3.	Col. Sunset Yellow FCF Lake	-----	IH	00.34	-----	Colorants
4.	Purified Talc	-----	BP	00.59	-----	Antiadherent
5.	Titanium Dioxide	-----	BP	00.40	-----	Opacifier
6.	Isopropyl Alcohol (IPA)	-----	BP	27.20	-----	Solvent
7.	Dichloromethane	-----	BP	62.51	-----	Solvent
		Theoretical weight **Actual weight**		**194.98 mg** **(190.00 mg)** **(after process loss during coating)**		

3. PHARMACEUTICAL FORM:

Film Coated Tablets

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS:

For the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on losartan or hydrochlorothiazide alone.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Hypertension

The usual maintenance dose is one tablet once daily. For patients who do not respond adequately to 50 mg/12.5 mg, the dosage may be increased to one tablet of 100 mg/25 mg once daily. The maximum dose is one tablet 100 mg/25 mg once daily.

Use in patients with renal impairment and haemodialysis patients

No initial dosage adjustment is necessary in patients with moderate renal impairment (i.e. creatinine clearance 30-50 ml/min). Losartan and hydrochlorothiazide tablets are not recommended for haemodialysis patients. Losartan/HCTZ tablets must not be used in patients with severe renal impairment.

Use in patients with intravascular volume depletion

Volume and /or sodium depletion should be corrected prior to administration of losartan/HCTZ tablets.

Use in patients with hepatic impairment.

Losartan/HCTZ is contraindicated in patients with severe hepatic impairment.

Use in the elderly

Dosage adjustment is not usually necessary for the elderly.

Use in children and adolescents (< 18 years)

There is no experience in children and adolescents. Therefore, losartan/hydrochlorothiazide should not be administered to children and adolescents.

4.3 CONTRAINDICATIONS

Therapy resistant hypokalaemia or hypercalcaemia
Severe hepatic impairment; Cholestasis and biliary obstructive disorders
Refractory hypernatremia
Symptomatic hyperuricaemia/gout
Second and third trimester of pregnancy
Severe renal impairment (i.e. creatinine clearance <30 ml/min)
Anuria

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Angiooedema

Patients with a history of Angiooedema (swelling of the face, lips, throat, and/or tongue) should be closely monitored.

Hypotension and intravascular volume depletion

Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/ or sodium-depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of Losartan/Hydrochlorothiazide.

Electrolyte imbalances

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. Therefore, the plasma concentrations of potassium and 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.

Liver function impairment

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, Losartan/Hydrochlorothiazide should be used with caution in patients with a history of mild to moderate hepatic impairment. There is no therapeutic experience with losartan in patients with severe hepatic impairment.

Renal function impairment

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function, including renal failure, have been reported.

As with other drugs 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.

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 Losartan/Hydrochlorothiazide 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.

Pregnancy

Losartan/Hydrochlorothiazide should not be initiated during pregnancy. Unless continued losartan/hydrochlorothiazide 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/Hydrochlorothiazide should be stopped immediately, and, if appropriate, alternative therapy should be started.

Hydrochlorothiazide

Hypotension and electrolyte/fluid imbalance

As with all antihypertensive therapy, symptomatic hypotension may occur in some patients. Patients should be observed for clinical signs of fluid or electrolyte imbalance, e.g., volume depletion, hypernatremia, hypochloremic alkalosis, hypomagnesaemia or hypokalemia which may occur during intercurrent diarrhoea or vomiting. Periodic determination of serum electrolytes should be performed at appropriate intervals in such patients. Dilutional hyponatraemia may occur in oedematous patients in hot weather.

Metabolic and endocrine effects

Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required. Latent diabetes mellitus may become manifest during thiazide therapy.

Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcemia may be evidence of hidden hyperparathyroidism.

Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Thiazide therapy may precipitate hyperuricaemia and/or gout in certain patients. Because losartan decreases uric acid, losartan in combination with hydrochlorothiazide attenuates the diuretic-induced hyperuricaemia.

Hepatic impairment

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, as it may cause intrahepatic , cholestasis, and since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Losartan/Hydrochlorothiazide is contraindicated for patients with severe hepatic impairment.

4.5 INTERATION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS

Losartan

Rifampicin 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, or salt substitutes containing potassium may lead to increases in serum potassium. Co-medication is not advisable.

As with other medicines 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.

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.

In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, including selective, cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists may result in a further deterioration of renal function.

These effects are usually reversible.

Other substances inducing hypotension like tricyclic antidepressants, antipsychotics, baclofene, and amifostine: Concomitant use with these drugs that lower blood pressure, as main or side-effect, may increase the risk of hypotension.

Hydrochlorothiazide

When given concurrently, the following drugs may interact with thiazide diuretics:

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

Antidiabetic drugs (oral agents and insulin): The treatment with a thiazide may influence the glucose tolerance. Dosage adjustment of the antidiabetic drug may be required. Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

Cholestyramine and colestipol resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either Cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g. adrenaline): Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g. tubocurarine): Possible increased responsiveness to the muscle relaxant.

Lithium: Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity; concomitant use is not recommended.

Medicinal products used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol): Dosage adjustment of uricosuric medicinal products may be necessary since hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Coadministration of a thiazide may increase the incidence of hypersensitivity reactions to allopurinol.

Anticholinergic agents (e.g. atropine, biperiden): Increase of the bioavailability to thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate.

Cytotoxic agents (e.g. cyclophosphamide, methotrexate): Thiazides may reduce the renal excretion of cytotoxic medicinal products and potentiate their myelo suppressive effects.

Salicylates: In case of high dosages of salicylates hydrochlorothiazide may enhance the toxic effect of the salicylates on the central nervous system.

Methyldopa: There have been isolated reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

Cyclosporine: Concomitant treatment with cyclosporine may increase the risk of hyperuricaemia and gout-type complications.

Digitalis glycosides: Thiazide-induced hypokalaemia or hypomagnesaemia may favour the onset of digitalis-induced cardiac arrhythmias.

Calcium salts: Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements must be prescribed, serum calcium levels should be monitored and calcium dosage should be adjusted accordingly.

4.6 PREGNANCY AND LACTATION

Pregnancy

Losartan

The use of AIIRAs is not recommended during the first trimester of pregnancy. The use of AIIRAs is contraindicated during the second and third trimester of pregnancy.

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRAs 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 AIIRAs should be stopped immediately and, if appropriate, alternative therapy should be started.

Losartan/Hydrochlorothiazide therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, and hyperkalaemia).

Hydrochlorothiazide

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient.

Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Lactation

Losartan

Because no information is available regarding the use of Losartan/hydrochlorothiazide during breastfeeding, Losartan/hydrochlorothiazide is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a New born or preterm infant.

Hydrochlorothiazide

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production.

The use of Losartan hydrochlorothiazide Tablets during breast feeding is not recommended.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINE

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

Anaemia, Henoch-Schönlein purpura, Ecchymosis, Haemolysis, Insomnia, Headache, Dizziness, Cough, Upper respiratory infection, Nasal congestion, Sinusitis, Sinus disorder, Abdominal pain, Nausea, Diarrhoea, Dyspepsia, Muscle cramp, Back pain, Leg pain, Myalgia, Asthenia,

Fatigue, Chest pain, Hyperkalemia, Mild reduction of hematocrit and Haemoglobin, Cephalalgia

4.9 OVERDOSE

Losartan

Limited data are available in regard to overdose in humans. The most likely manifestation of overdose 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 the 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMICS PROPERTIES

Losartan is a synthetically produced oral angiotensin-II receptor (type AT) antagonist. Angiotensin II, a potent vasoconstrictor, is the primary 1 active hormone of the renin-angiotensin system and an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT receptor found in many tissues and elicits several important biological actions, including vasoconstriction and the release of 1 aldosterone. Angiotensin II also stimulates smooth-muscle cell proliferation.

Hydrochlorothiazide is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity and increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium.

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%. Hydrochlorothiazide is well absorbed (65% to 75%) following oral administration.

Distribution

Both losartan and its active metabolite are ≥99% bound to plasma proteins, primarily albumin. Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Metabolism

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.

Hydrochlorothiazide is not metabolized.

Elimination

Following an oral dose of 14C-labeled losartan in man, about 35% is recovered in the urine and 58% in the feces. Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney.

5.3 PRECLINICAL SAFETY DATA

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline Cellulose	BP
Lactose Monohydrate	BP
Maize Starch	BP
Hydroxy Propyl Cellulose	BP
Isopropyl Alcohol (IPA)	BP
AC Di Sol	IH
Colloidal Anhydrous Silica	BP
Sodium Lauryl Sulphate	BP
Purified Talc	BP
Magnesium Stearate	BP
Hypromellose (HPMC E15)	BP
Polyethylene Glycol (PEG 6000)	BP
Col. Sunset Yellow FCF Lake	IH
Purified Talc	BP
Titanium Dioxide	BP
Dichloromethane	BP

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

24 Months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C, protected from light & moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

10 Tablets packed in Alu- Alu Blister.

6.6 SPECIAL PRECAUTION FOR DISPOSAL

Not Applicable

7. MARKETING AUTHORIZATION HOLDER

Name	:	UNOSOURCE PHARMA NIGERIA LIMITED,
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Phone	:	002348038540440 002348129126660
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NAME AND ADDRESS OF THE MANUFACTURER

Name	Akums Drugs & Pharmaceuticals Ltd.
Address	Plot no. 19, 20,21, Sector 6A, IIE, SIDCUL, Ranipur, Haridwar-249403,Uttarakhand, India.
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