1. Name Of The Medicinal Product

Losartan and Hydrochlorothiazide

ANGIZAAR H

2. Qualitative and Quantitative Composition

Each film-coated tablet contains:

Losartan Potassium USP .....50 mg

Hydrochlorothiazide USP .....12.5 mg

For excipients, see 6.1.

3. Pharmaceutical Form

Film-coated tablets

Orange coloured, circular, bi-convex, film-coated tablets with 'MICRO' engraved on both the sides

4. Clinical Particulars

4.1 Therapeutic indications

Losartan and Hydrochlorothiazide is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure lowers the risk of fatal and non-fatal cardiovascular (CV) events, primarily strokes and myocardial infarction. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes including losartan and hydrochlorothiazide.

Hypertensive Patients with Left Ventricular Hypertrophy

Losartan and Hydrochlorothiazide is indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy, but there is evidence that this benefit does not apply to Black patients.

4.2 Posology and method of administration

Hypertension

The usual starting dose of Losartan and Hydrochlorothiazide is 50/12.5 (losartan 50 mg/hydrochlorothiazide 12.5 mg) once daily. The dosage can be increased after 3 weeks of therapy to a maximum of 100/25 (losartan 100 mg/hydrochlorothiazide 25 mg) once daily as needed to control blood pressure.

Initiate a patient whose blood pressure is not adequately controlled with losartan 50 mg monotherapy with Losartan and Hydrochlorothiazide 50/12.5 once daily. If blood pressure remains uncontrolled after about 3 weeks of therapy, the dosage may be increased to two tablets of Losartan and Hydrochlorothiazide 50/12.5 once daily or one tablet of Losartan and Hydrochlorothiazide 100/25 once daily.

Initiate a patient whose blood pressure is not adequately controlled with losartan 100 mg monotherapy with Losartan and Hydrochlorothiazide 100/12.5 (losartan 100 mg/hydrochlorothiazide 12.5 mg) once daily. If blood pressure remains uncontrolled after about 3 weeks of therapy, increase the dose to two tablets of Losartan and Hydrochlorothiazide 50/12.5 once daily or one tablet of Losartan and Hydrochlorothiazide 100/25 once daily.

Initiate a patient whose blood pressure is inadequately controlled with hydrochlorothiazide 25 mg once daily, or is controlled but who experiences hypokalemia with this regimen, on Losartan and Hydrochlorothiazide 50/12.5 once daily, reducing the dose of hydrochlorothiazide without reducing the overall expected antihypertensive response. Evaluate the clinical response to Losartan and Hydrochlorothiazide 50/12.5 and, if blood pressure remains uncontrolled after about 3 weeks of therapy, increase the dose to two tablets of Losartan and Hydrochlorothiazide 50/12.5 once daily or one tablet of Losartan and Hydrochlorothiazide 100/25 once daily.

Hypertensive Patients with Left Ventricular Hypertrophy

In patients whose blood pressure is not adequately controlled on 50 mg losartan potassium, initiate treatment with Losartan and Hydrochlorothiazide 50/12.5. If additional blood pressure reduction is

needed, increase the dose to Losartan and Hydrochlorothiazide 100/12.5, followed by Losartan and Hydrochlorothiazide 100/25. For further blood pressure reduction add other antihypertensive.

4.3 Contraindications

Losartan and Hydrochlorothiazide is contraindicated:

- In patients who are hypersensitive to any component of this product.
- In patients with anuria
- For coadministration with aliskiren in patients with diabetes

4.4 Special warnings and precautions for use

Fetal Toxicity

Losartan and Hydrochlorothiazide can cause fetal harm when administered to a pregnant woman. 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 and Hydrochlorothiazide as soon as possible.

Thiazides cross the placental barrier and appear in cord blood. Adverse reactions include fetal or neonatal jaundice, thrombocytopenia

Hypotension in Volume- or Salt-Depleted Patients

In patients with an activated renin-angiotensin system, such as volume- or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of treatment with Losartan and Hydrochlorothiazide. Correct volume or salt depletion prior to administration of Losartan and Hydrochlorothiazide. Do not use Losartan and Hydrochlorothiazide as initial therapy in patients with intravascular volume depletion.

Impaired Renal Function

Changes in renal function including acute renal failure can be caused by drugs that inhibit the renin-angiotensin system and by diuretics. Patients whose renal function may depend in part on the activity of the renin-angiotensin system (e.g., patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) may be at particular risk of developing acute renal failure on Losartan and Hydrochlorothiazide. Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on Losartan and Hydrochlorothiazide.

Hypersensitivity

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

Electrolyte and Metabolic Effects

In double-blind clinical trials of various doses of losartan potassium and hydrochlorothiazide, the incidence of hypertensive patients who developed hypokalemia (serum potassium <3.5 mEq/L) was 6.7% versus 3.5% for placebo; the incidence of hyperkalemia (serum potassium >5.7 mEq/L) was 0.4% versus 0% for placebo.

Losartan and Hydrochlorothiazide contains hydrochlorothiazide which can cause hypokalemia, hyponatremia and hypomagnaesemia. Hypomagnaesemia can result in hypokalemia which may be difficult to treat despite potassium repletion. Losartan and Hydrochlorothiazide also contains losartan which can cause hyperkalemia. Monitor serum electrolytes periodically.

Concomitant use of other drugs that may increase serum potassium may lead to hyperkalemia.
Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides.

Hyperuricaemia may occur or frank gout may be precipitated in patients receiving thiazide therapy. Because losartan decreases uric acid, losartan in combination with hydrochlorothiazide attenuates the diuretic-induced hyperuricaemia.

Hydrochlorothiazide decreases urinary calcium excretion and may cause elevations of serum calcium. Monitor calcium levels.

Acute Myopia and Secondary Angle-Closure Glaucoma

Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Systemic Lupus Erythematosus

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of hydrochlorothiazide could act as a possible mechanism for NMSC.

Patients taking hydrochlorothiazide should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of hydrochlorothiazide may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

Other

In patients receiving thiazides, hypersensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

Choroidal effusion, acute myopia and secondary angle-closure glaucoma:

Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

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 with concomitant use of angiotensin II receptor antagonists or thiazide diuretics. Monitor lithium levels in patients receiving Losartan and Hydrochlorothiazide and lithium.

Non-Steroidal Anti-Inflammatory Agents Including Selective Cyclooxygenase-2 Inhibitors

Losartan Potassium

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.

Hydrochlorothiazide

The administration of a non-steroidal anti-inflammatory agent including a selective COX-2 inhibitor can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when Losartan and Hydrochlorothiazide and non-steroidal anti-inflammatory agents including selective COX-2 inhibitors are used concomitantly, observe closely to determine if the desired effect of the diuretic is obtained.

In patients receiving diuretic therapy, coadministration of NSAIDs with angiotensin receptor blockers, 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 hydrochlorothiazide, losartan, and NSAID therapy.

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.

The Veterans Affairs Nephropathy in Diabetes (VANEPHRON-D) trial enrolled 1448 patients with type 2 diabetes, elevated urinary-albumin-to-creatinine ratio, and decreased estimated glomerular filtration rate (GFR 30 to 89.9 mL/min), randomized them to lisinopril or placebo on a background of losartan therapy and followed them for a median of 2.2 years. Patients receiving the combination of losartan and lisinopril did not obtain any additional benefit compared to monotherapy for the combined endpoint of decline in GFR, end-stage renal disease, or death, but experienced an increased incidence of hyperkalemia and acute kidney injury compared with the monotherapy group.

Closely monitor blood pressure, renal function, and electrolytes in patients on Losartan and Hydrochlorothiazide and other agents that affect the RAS.

Do not coadministered aliskiren with Losartan and Hydrochlorothiazide in patients with diabetes. Avoid use of aliskiren with Losartan and Hydrochlorothiazide in patients with renal impairment (GFR <60 mL/min).

The Use of Hydrochlorothiazide with Other Drugs

When administered concurrently, the following drugs may interact with thiazide diuretics.

Antidiabetic drugs (oral agents and insulin) — dosage adjustment of the antidiabetic drug may be required.

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. Stagger the dosage of hydrochlorothiazide and the resin such that hydrochlorothiazide is administered at least 4 hours before or 4 to 6 hours after the administration of the resin.

4.6 Fertility, pregnancy and lactation

Pregnancy

Losartan and Hydrochlorothiazide can cause fetal harm when administered to a pregnant woman. 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. 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. When pregnancy is detected, discontinue Losartan and Hydrochlorothiazide as soon as possible.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated Maternal and/or Embryo/Fetal Risk

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

Fetal/Neonatal Adverse Reactions

Losartan:

Use of drugs that act on the renin-angiotensin system in the second and third trimesters of pregnancy can result in the following: oligohydramnios, reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension, and death.

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 and Hydrochlorothiazide tablets, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of gestation. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe neonates with histories of *in utero* exposure to Losartan and Hydrochlorothiazide tablets for hypotension, oliguria, and hyperkalemia. In neonates with a history of *in utero* exposure Losartan and Hydrochlorothiazide tablets if oliguria or hypotension occurs, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and replacing renal function.

Hydrochlorothiazide:

Thiazides can cross the placenta, and concentrations reached in the umbilical vein approach those in the maternal plasma. Hydrochlorothiazide, like other diuretics, can cause placental hypoperfusion. It accumulates in the amniotic fluid, with reported concentrations up to 19 times higher than in umbilical vein plasma. Use of thiazides during pregnancy is associated with a risk of fetal or neonatal jaundice or thrombocytopenia. Since they do not alter the course of pre-eclampsia, these drugs should not be used to treat hypertension in pregnant women. The use of hydrochlorothiazide for other indications in pregnancy should be avoided.

Lactation

It is not known whether losartan is excreted in human milk, but significant levels of losartan and its active metabolite were shown to be present in rat milk. Thiazides appear in human milk. 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.

Lactation

Risk Summary

It is not known whether losartan is excreted in human milk, but significant levels of losartan and its active metabolite were shown to be present in rat milk. Thiazides appear in human milk. 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.

Pediatric Use

Safety and effectiveness of Losartan and Hydrochlorothiazide tablets in pediatric patients have not been established.

Neonates with a history of *in utero* exposure to Losartan and Hydrochlorothiazide tablets: If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Geriatric Use

In a controlled clinical study for the reduction in the combined risk of cardiovascular death, stroke and myocardial infarction in hypertensive patients with left ventricular hypertrophy, 2857 patients (62%) were 65 years and over, while 808 patients (18%) were 75 years and over. In an effort to control blood pressure in this study, patients were coadministered losartan and hydrochlorothiazide 74% of the total time they were on study drug. No overall differences in effectiveness were observed between these patients and younger patients. Adverse events were somewhat more frequent in the elderly compared to non-elderly patients for both the losartan-hydrochlorothiazide and the control groups.

Race

In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, Black patients with hypertension and left ventricular hypertrophy treated with atenolol had a lower risk of stroke, the primary composite endpoint, as compared with Black patients treated with losartan (both cotreated with hydrochlorothiazide in the majority of patients). 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%, 26 per 1000 patient-years) and 46 primary endpoints among 270 patients (17%, 42 per 1000 patient-years) on losartan. This finding could not be explained on the basis of differences in the populations other than race or on any imbalances between treatment groups. In addition, blood pressure reductions in both treatment groups were consistent between Black and non-Black patients. Given the difficulty in interpreting subset differences in large trials, it cannot be known whether the observed difference is the result of chance. However, the LIFE study provides no evidence that the benefits of losartan on reducing

the risk of cardiovascular events in hypertensive patients with left ventricular hypertrophy apply to Black patients.

Hepatic Impairment

Initiation of Losartan and Hydrochlorothiazide tablets is not recommended for patients with hepatic impairment because the appropriate starting dose of losartan, 25 mg, is not available.

Renal Impairment

Changes in renal function have been reported in susceptible individuals. Safety and effectiveness of Losartan and Hydrochlorothiazide tablets in patients with severe renal impairment (creatinine clearance <30 mL/min) have not been established.

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 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

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Losartan potassium-hydrochlorothiazide has been evaluated for safety in 858 patients treated for essential hypertension and 3889 patients treated for hypertension and left ventricular hypertrophy. Most adverse reactions have been mild and transient in nature and have not required discontinuation of therapy. In controlled clinical trials, discontinuation of therapy due to clinical adverse events was required in only 2.8% and 2.3% of patients treated with the combination and placebo, respectively.

In these double-blind controlled clinical trials, adverse reactions occurring in greater than 2% of subjects treated with losartan-hydrochlorothiazide and at a greater rate than placebo were: back pain (2.1% vs 0.6%), dizziness (5.7% vs 2.9%), and upper respiratory infection (6.1% vs 4.6%).

The following additional adverse reactions have been reported in clinical trials with Losartan and Hydrochlorothiazide and/or the individual components:

Blood and the lymphatic system disorders: Anemia, aplastic anemia, hemolytic anemia, leukopenia, agranulocytosis.

Metabolism and nutrition disorders: Anorexia, hyperglycemia, hyperuricaemia, electrolyte imbalance including hyponatremia and hypokalemia.

Psychiatric disorders: Insomnia, restlessness.

Nervous system disorders: Dysgeusia, headache, migraine, paraesthesias.

Eye disorders: Xanthopsia, transient blurred vision.

Cardiac disorders: Palpitation, tachycardia.

Vascular disorders: Dose-related orthostatic effects, necrotizing angiitis (Vasculitis, cutaneous Vasculitis).

Respiratory, thoracic and mediastinal disorders: Nasal congestion.

Gastrointestinal disorders: Dyspepsia, abdominal pain, gastric irritation, cramping, nausea, vomiting, pancreatitis, sialoadenitis.

Hepato-biliary disorders: Jaundice (intrahepatic cholestatic jaundice).

Skin and subcutaneous tissue disorders: Rash, pruritus, purpura, toxic epidermal necrolysis, urticaria, photosensitivity, cutaneous lupus erythematosus.

Musculoskeletal and connective tissue disorders: Muscle cramps, muscle spasm.

Renal and urinary disorders: Glycosuria, renal dysfunction, interstitial nephritis, renal failure.

Reproductive system and breast disorders: Erectile dysfunction/impotence.

General disorders and administration site conditions: Chest pain, malaise, weakness.

Investigations: Liver function abnormalities.

Cough

Persistent dry cough has been associated with ACE-inhibitor use and in practice can be a cause of discontinuation of ACE-inhibitor therapy. Two prospective, parallel-group, double-blind, randomized, controlled trials were conducted to assess the effects of losartan on the incidence of cough in hypertensive patients who had experienced cough while receiving ACE-inhibitor therapy. Patients who had typical ACE-inhibitor cough when challenged with lisinopril, whose cough disappeared on placebo, were randomized to losartan 50 mg, lisinopril 20 mg, or either placebo (one study, n=97) or 25 mg

hydrochlorothiazide (n=135). The double-blind treatment period lasted up to 8 weeks. The incidence of cough is shown in Table 1 below.

Table 1:

Study 1*	HCTZ	Losartan	Lisinopril
Cough	25%	17%	69%
Study 2†	Placebo	Losartan	Lisinopril
Cough	35%	29%	62%

* Demographics = (89% Caucasian, 64% female)

† Demographics = (90% Caucasian, 51% female)

These studies demonstrate that the incidence of cough associated with losartan therapy, in a population that all had cough associated with ACE-inhibitor therapy, is similar to that associated with hydrochlorothiazide or placebo therapy.

Cases of cough, including positive re-challenges, have been reported with the use of losartan in postmarketing experience.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Losartan and Hydrochlorothiazide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or to establish a causal relationship to drug exposure.

Digestive: Hepatitis has been reported rarely in patients treated with losartan.

Hematologic: Thrombocytopenia.

Hypersensitivity: 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-Schönlein purpura, has been reported with losartan. Anaphylactic reactions have been reported.

Musculoskeletal: Rhabdomyolysis.

Skin: Erythroderma

Non-melanoma Skin Cancer: Hydrochlorothiazide is associated with an increased risk of non-melanoma skin cancer. In a study conducted in the Sentinel System, increased risk was predominantly for squamous cell carcinoma (SCC) and in white patients taking large cumulative doses. The increased risk for SCC in the overall population was approximately 1 additional case per 16,000 patients per year, and for white patients taking a cumulative dose of ≥50,000mg the risk increase was approximately 1 additional SCC case for every 6,700 patients per year.

Hydrochlorothiazide

Chlortalidone- and indapamide-containing products:

Eye disorders: choroidal effusion (frequency not known)

For bendroflumethiazide, cicletanine, clopamide, cyclopenthiazide, hydroflumethiazide, metipamide, metolazone, xipamide-containing products (choroidal effusion has not yet been reported but is considered a class effect):

Description of selected adverse reactions:

Cases of choroidal effusion with visual field defect have been reported after the use of thiazide and thiazide-like diuretics.

4.9 Overdose

Losartan Potassium

Significant lethality was observed in mice and rats after oral administration of 1000 mg/kg and 2000 mg/kg, respectively, about 44 and 170 times the maximum recommended human dose on a mg/m^2 basis.

Limited data are available in regard to over dosage in humans. The most likely manifestation of over dosage 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 its active metabolite can be removed by hemodialysis.

Hydrochlorothiazide

The oral LD_{50} of hydrochlorothiazide is greater than 10 g/kg in both mice and rats. The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremic, hyponatreamia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

5. Pharmacological Properties

5.1 Pharmacodynamic properties:

Mechanism of Action

Losartan Potassium

Angiotensin II [formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II)], is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues (e.g., vascular smooth muscle, adrenal gland). There is also an AT2 receptor found in many tissues but it is not known to be associated with cardiovascular homeostasis. Neither losartan nor its principal active metabolite exhibits any partial agonist activity at the AT1 receptor, and both have much greater affinity (about 1000-fold) for the AT1receptor than for the AT2 receptor. *In vitro* binding studies indicate that losartan is a reversible, competitive inhibitor of the AT1 receptor. The active metabolite is 10 to 40 times more potent by weight than losartan and appears to be a reversible, non-competitive inhibitor of the AT1 receptor.
Neither losartan nor its active metabolite inhibits ACE (kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin), nor do they bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics. The mechanism of the antihypertensive effect of thiazides is unknown.

Pharmacodynamics

Losartan Potassium

Losartan inhibits the pressor effect of angiotensin II (as well as angiotensin I) infusions. A dose of 100 mg inhibits the pressor effect by about 85% at peak with 25-40% inhibition persisting for 24 hours. Removal of the negative feedback of angiotensin II causes a doubling to tripling in plasma renin activity and consequent rise in angiotensin II plasma concentration in hypertensive patients. Losartan does not affect the response to bradykinin, whereas ACE inhibitors increase the response to bradykinin. Aldosterone plasma concentrations fall following losartan administration. In spite of the effect of losartan on aldosterone secretion, very little effect on serum potassium was observed.

The effect of losartan is substantially present within one week but in some studies the maximal effect occurred in 3-6 weeks. In long-term follow-up studies (without placebo control) the effect of losartan appeared to be maintained for up to a year. There is no apparent rebound effect after abrupt withdrawal of losartan. There was essentially no change in average heart rate in losartan-treated patients in controlled trials.

Hydrochlorothiazide

After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours, and lasts about 6 to 12 hours.

Drug Interactions

Hydrochlorothiazide

Alcohol, barbiturates, or narcotics — potentiation of orthostatic hypotension may occur.

Other antihypertensive drugs — additive effect or potentiation.

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

Corticosteroids, ACTH, or glycyrrhizin (found in liquorice) — intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine) — possible decreased response to pressor amines but not sufficient to preclude their use.

5.2 Pharmacokinetic properties*:*

Losartan Potassium

Absorption: Following oral administration, losartan is well absorbed and undergoes substantial first-pass metabolism. The systemic bioavailability of losartan is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. While maximum plasma concentrations of losartan and its active metabolite are approximately equal, the AUC (area under the curve) of the metabolite is about 4 times as great as that of losartan. A meal slows absorption of losartan and decreases its C_{max} but has only minor effects on losartan AUC or on the AUC of the metabolite (~10% decrease). The pharmacokinetics of losartan and its active metabolite are linear with oral losartan doses up to 200 mg and do not change over time.

Distribution: The volume of distribution of losartan and the active metabolite is about 34 liters and 12 liters, respectively. Both losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2%, respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Metabolism: Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. It is converted, in part, to an active carboxylic acid metabolite that is responsible for most of the angiotensin II receptor antagonism that follows losartan treatment. About 14% of an orally-administered dose of losartan is converted to the active metabolite. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed. *In vitro* studies indicate that cytochrome P450 2C9 and 3A4 are involved in the biotransformation of losartan to its metabolites.

Elimination: Total plasma clearance of losartan and the active metabolite is about 600 mL/min and 50 mL/min, respectively, with renal clearance of about 75 mL/min and 25 mL/min, respectively. The terminal half-life of losartan is about 2 hours and of the metabolite is about 6-9 hours. After single doses of losartan administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% is

excreted in urine as active metabolite. Biliary excretion contributes to the elimination of losartan and its metabolites. Following oral 14C-labeled losartan, about 35% of radioactivity is recovered in the urine and about 60% in the feces. Following an intravenous dose of 14C-labeled losartan, about 45% of radioactivity is recovered in the urine and 50% in the feces. Neither losartan nor their metabolites accumulate in plasma upon repeated once-daily dosing.

Hydrochlorothiazide

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Specific Populations

Geriatric and Gender

Losartan pharmacokinetics have been investigated in the elderly (65-75 years) and in both genders. Plasma concentrations of losartan and its active metabolite are similar in elderly and young hypertensives. Plasma concentrations of losartan were about twice as high in female hypertensives as male hypertensives, but concentrations of the active metabolite were similar in males and females.

Race

Pharmacokinetic differences due to race have not been studied.

Hepatic Insufficiency

Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5 times and about 1.7 times those in young male volunteers. Compared to normal subjects, the total plasma clearance of losartan in patients with hepatic insufficiency was about 50% lower, and the oral bioavailability was about doubled. The lower starting dose of losartan recommended for use in patients with hepatic impairment cannot be given using Losartan and Hydrochlorothiazide. Its use in such patients as a means of losartan titration is, therefore, not recommended.

Renal Insufficiency

Losartan

Following oral administration, plasma concentrations and AUCs of losartan and its active metabolite are increased by 50-90% in patients with mild (creatinine clearance of 50 to 74 mL/min) or moderate (creatinine clearance 30 to 49 mL/min) renal insufficiency. In this study, renal clearance was reduced by 55-85% for both losartan and its active metabolite in patients with mild or moderate renal insufficiency. Neither losartan nor its active metabolite can be removed by hemodialysis.

Hydrochlorothiazide

Following oral administration, the AUC for hydrochlorothiazide is increased by 70 and 700% for patients with mild and moderate renal insufficiency, respectively. In this study, renal clearance of hydrochlorothiazide decreased by 45 and 85% in patients with mild and moderate renal impairment, respectively.

Use the usual regimens of therapy with Losartan and Hydrochlorothiazide as long as the patient's creatinine clearance is greater than 30 mL/min. Safety and effectiveness of Losartan and Hydrochlorothiazide in patients with severe renal impairment (creatinine clearance less than 30 mL/min) have not been established.

Drug Interactions

Losartan Potassium

No clinically significant drug interactions have been found in studies of losartan potassium with hydrochlorothiazide, digoxin, warfarin, cimetidine and phenobarbital. However, rifampin has been shown to decrease the AUC of losartan and its active metabolite by 30% and 40%, respectively. Fluconazole, an inhibitor of cytochrome P450 2C9, decreased the AUC of the active metabolite by approximately 40%, but increased the AUC of losartan by approximately 70% following multiple doses. Conversion of losartan to its active metabolite after intravenous administration is not affected by ketoconazole, an inhibitor of P450 3A4.The AUC of active metabolite following oral losartan was not affected by erythromycin, an inhibitor of P450 3A4, but the AUC of losartan was increased by 30%.

The pharmacodynamic consequences of concomitant use of losartan and inhibitors of P450 2C9 have not been examined. Subjects who do not metabolize losartan to active metabolite have been shown to have a specific, rare defect in cytochrome P450 2C9. These data suggest that the conversion of losartan to its active metabolite is mediated primarily by P450 2C9 and not P450 3A4.

5.3 Preclinical safety data

Losartan Potassium-Hydrochlorothiazide

No carcinogenicity studies have been conducted with the losartan potassium-hydrochlorothiazide combination.

Losartan potassium-hydrochlorothiazide when tested at a weight ratio of 4:1, was negative in the Ames microbial mutagenesis assay and the V-79 Chinese hamster lung cell mutagenesis assay. In addition, there was no evidence of direct genotoxicity in the *in vitro* alkaline elution assay in rat hepatocytes and *in vitro* chromosomal aberration assay in Chinese hamster ovary cells at noncytotoxic concentrations.

Losartan potassium, coadministered with hydrochlorothiazide, had no effect on the fertility or mating behavior of male rats at dosages up to 135 mg/kg/day of losartan and 33.75 mg/kg/day of hydrochlorothiazide. These dosages have been shown to provide respective systemic exposures (AUCs) for losartan, its active metabolite and hydrochlorothiazide that are approximately 60, 60 and 30 times greater than those achieved in humans with 100 mg of losartan potassium in combination with 25 mg of hydrochlorothiazide. In female rats, however, the coadministration of doses as low as 10 mg/kg/day of losartan and 2.5 mg/kg/day of hydrochlorothiazide was associated with slight but statistically significant decreases in fecundity and fertility indices. AUC values for losartan, its active metabolite and hydrochlorothiazide, extrapolated from data obtained with losartan administered to rats at a dose of 50 mg/kg/day in combination with 12.5 mg/kg/day of hydrochlorothiazide, were approximately 6, 2, and 2 times greater than those achieved in humans with 100 mg of losartan in combination with 25 mg of hydrochlorothiazide.

Losartan Potassium

Losartan potassium was not carcinogenic when administered at maximally tolerated dosages to rats and mice for 105 and 92 weeks, respectively. Female rats given the highest dose (270 mg/kg/day) had a slightly higher incidence of pancreatic acinar adenoma. The maximally tolerated dosages (270 mg/kg/day in rats, 200 mg/kg/day in mice) provided systemic exposures for losartan and its pharmacologically active metabolite that were approximately 160 and 90 times (rats) and 30 and 15 times (mice) the exposure of a 50 kg human given 100 mg per day.

Losartan potassium was negative in the microbial mutagenesis and V-79 mammalian cell mutagenesis assays and in the *in vitro* alkaline elution and *in vitro* and *in vivo* chromosomal aberration assays. In addition, the active metabolite showed no evidence of genotoxicity in the microbial mutagenesis, *in vitro* alkaline elution, and *in vitro* chromosomal aberration assays.

Fertility and reproductive performance were not affected in studies with male rats given oral doses of losartan potassium up to approximately 150 mg/kg/day. The administration of toxic dosage levels in females (300/200 mg/kg/day) was associated with a significant ($p<0.05$) decrease in the number of corpora lutea/female, implants/female, and live fetuses/female at C-section. At 100 mg/kg/day only a decrease in the number of corpora lutea/female was observed. The relationship of these findings to drug-treatment is uncertain since there was no effect at these dosage levels on implants/pregnant female, percent post-implantation loss, or live animals/litter at parturition. In nonpregnant rats dosed at 135 mg/kg/day for 7 days, systemic exposure (AUCs) for losartan and its active metabolite were approximately 66 and 26 times the exposure achieved in man at the maximum recommended human daily dosage (100 mg).

Hydrochlorothiazide

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 mcg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation.

6. Pharmaceutical Particulars

6.1 List of excipients

Maize Starch

Microcrystalline cellulose

Colloidal anhydrous silica

Methyl hydroxy benzoate

Propyl hydroxy benzoate

Crospovidone

Talc

Magnesium stearate

Tabcoat TC 2052/3835 (ORANGE)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months from the date of manufacture

6.4 Special precautions for storage

Store below 30°C. Keep away from reach of children

6.5 Nature and contents of container

Alu/Alu Pack of 10 Tablets

6.6 Special precautions for disposal and other handling

No special requirements

7. Marketing Authorization Holder

MICRO LABS LIMITED
31, race course road
Bangalore-560001
INDIA

9. Date of first authorization/renewal of authorization

Not applicable

10. Date of revision of text

May 2022