SUMMARY OF PRODUCT CHARACTERISTIC (SPC)

1. NAME OF THE MEDICINAL PRODUCT

1.1 Name of the medicinal product

LOSACAR H 50/12.5 & 100/25

Losartan Potassium and Hydrochlorothiazide Tablets USP 50mg/12.5mg & 100mg/25mg

1.2 Strength

50mg/12.5mg & 100mg/25mg per Tablet

1.3 Pharmaceutical Form

Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LOSACAR H 50/12.5

Losartan Potassium and Hydrochlorothiazide USP Tablets 50mg/12.5mg

Each film coated tablet contains:

Losartan Potassium USP	50mg
Hydrochlorothiazide USP	12.5mg

Color: Titanium Dioxide

LOSACAR H 100/25

Losartan Potassium and Hydrochlorothiazide USP Tablets 100mg/25mg

Each film coated tablet contains:

Losartan Potassium USP	100mg
Hydrochlorothiazide USP	25mg

Color: Titanium Dioxide

For full list excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film coated Tablets.

Losartan Potassium and Hydrochlorothiazide Tablets USP 50mg/12.5mg: White to off white, capsule shaped, film coated tablets debossed with "Z31" on one side plain on other side.

Losartan Potassium and Hydrochlorothiazide Tablets USP 100mg/25mg: White to off white, capsule shaped, film coated tablets debossed with "Z32" on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension

Losartan potassium and hydrochlorothiazide tablets are 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.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than 1 drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

This fixed dose combination is not indicated for initial therapy of hypertension, except when the hypertension is severe enough that the value of achieving prompt blood pressure control exceeds the risk of initiating combination therapy in these patients.

Losartan potassium and hydrochlorothiazide tablets may be administered with other antihypertensive agents.

Hypertensive Patients with Left Ventricular Hypertrophy

Losartan potassium and hydrochlorothiazide tablets are 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

Posology

Hypertension

The usual starting dose of losartan potassium and hydrochlorothiazide tablets are 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 potassium and hydrochlorothiazide tablets 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 potassium and hydrochlorothiazide 50/12.5 once daily or one tablet of losartan potassium and hydrochlorothiazide 100/25 once daily.

Initiate a patient whose blood pressure is not adequately controlled with losartan 100 mg monotherapy with losartan potassium and hydrochlorothiazide tablets 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 potassium and hydrochlorothiazide 50/12.5 once daily or one tablet of losartan potassium 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 potassium and hydrochlorothiazide tablets 50/12.5 once daily, reducing the dose of hydrochlorothiazide without reducing the overall expected antihypertensive response. Evaluate the clinical response to losartan potassium and hydrochlorothiazide tablets 50/12.5 and, if blood pressure remains uncontrolled after about 3 weeks of therapy, increase the dose to two tablets of losartan potassium and hydrochlorothiazide 50/12.5 once daily or one tablet of losartan potassium 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 potassium and hydrochlorothiazide tablets 50/12.5. If additional blood pressure reduction is needed, increase the dose to losartan potassium and hydrochlorothiazide tablets 100/12.5, followed by losartan potassium and hydrochlorothiazide tablets 100/25. For further blood pressure reduction add other anti hypertensives.

Method of administration: Oral use

Special populations

Pediatric Use

Safety and effectiveness of losartan potassium and hydrochlorothiazide in pediatric patients have not been established.

Neonates with a history of *in utero* exposure to losartan potassium and hydrochlorothiazide: 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 potassium and hydrochlorothiazide 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 potassium and hydrochlorothiazide in patients with severe renal impairment (creatine clearance <30 mL/min) have not been established.

4.3 Contraindications

Losartan potassium and hydrochlorothiazide is contraindicated:

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

4.4 Special warnings and precautions for use

Fetal Toxicity

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 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 potassium and hydrochlorothiazide. Correct volume or salt depletion prior to administration of losartan potassium and hydrochlorothiazide. Do not use losartan potassium 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 potassium 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 potassium 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 potassium and hydrochlorothiazide contains hydrochlorothiazide which can cause hypokalemia, hyponatremia and hypomagnesemia. Hypomagnesemia can result in hypokalemia which may be difficult to treat despite potassium repletion. Losartan potassium and hydrochlorothiazide also contains losartan which can cause hyperkalemia. Monitor serum electrolytes periodically.

Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides.

Hyperuricemia 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 hyperuricemia.

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.

Postsympathectomy Patients

The antihypertensive effects of the drug may be enhanced in the post sympathectomy patient.

4.5 Interaction with other medicinal products and other forms of interaction

Agents Increasing Serum Potassium

Co administration 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 potassium 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, co administration 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 potassium 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, co administration 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 (VA NEPHRON-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 potassium and hydrochlorothiazide and other agents that affect the RAS.

Do not co administer aliskiren with losartan potassium and hydrochlorothiazide in patients with diabetes. Avoid use of aliskiren with losartan potassium 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 Pregnancy and lactation

Pregnancy

Pregnancy Category D

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 as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester 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 and hydrochlorothiazide, unless it is considered lifesaving 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 and hydrochlorothiazide for hypotension, oliguria, and hyperkalemia.

There was no evidence of teratogenicity in rats or rabbits treated with a maximum losartan potassium dose of 10 mg/kg/day in combination with 2.5 mg/kg/day of hydrochlorothiazide. At these dosages, respective exposures (AUCs) of losartan, its active metabolite, and hydrochlorothiazide in rabbits were approximately 5, 1.5, and 1.0 times those achieved in humans with 100 mg losartan in combination with 25 mg hydrochlorothiazide. 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. Fetal toxicity in rats, as evidenced by a slight increase in supernumerary ribs, was observed when females were treated prior to and throughout gestation with 10 mg/kg/day losartan in combination with 2.5 mg/kg/day hydrochlorothiazide. As also observed in studies with losartan alone, adverse fetal and neonatal effects, including decreased body weight, renal toxicity, and mortality, occurred when pregnant rats were treated during late gestation and/or lactation with 50 mg/kg/day losartan in combination with 12.5 mg/kg/day hydrochlorothiazide. Respective AUCs for losartan, its active metabolite and hydrochlorothiazide at these dosages in rats were approximately 35, 10 and 10 times greater than those achieved in humans with the administration of 100 mg of losartan in combination with 25 mg hydrochlorothiazide. When hydrochlorothiazide was administered without losartan to pregnant mice and rats during their respective periods of major organogenesis, at doses up to 3000 and 1000 mg/kg/day, respectively, there was no evidence of harm to the fetus.

Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Nursing Mothers

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.

4.7 Effects on ability to drive and use machines

No studies on the reactions 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 potassium 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, hyperuricemia, 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, pharyngitis, sinus disorder, respiratory distress (including pneumonitis and pulmonary edema).

Gastrointestinal disorders: Dyspepsia, abdominal pain, gastric irritation, cramping, diarrhea, constipation, 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, myalgia, arthralgia. *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, edema/swelling, malaise, fever, 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

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 post marketing experience.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of losartan potassium 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

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 LD50 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, hypochloremia, hyponatremia) 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

Pharmacotherapeutic group: Angiotensin II antagonists and diuretics

ATC code: C09DA01

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 AT1 receptor 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.

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 to 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 Cmax 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 to 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 its metabolite 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.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

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 non pregnant 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

- Lactose Monohydrate,
- Corn Starch
- Microcrystalline Cellulose,
- Hydroxy propyl cellulose (Low substitute)
- Colloidal Silicon Dioxide
- Sodium Starch Glycolate

- Magnesium Stearate,
- Opadry White 03F58991

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

STORE UPTO 30ºC.

PROTECT FROM LIGHT

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Blister pack of 10's (Pack Size: 3x10 Tablets)

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. REGISTRANT

Marketing Authorization holder

Name : Cadila Healthcare Limited

Address : Zydus Tower, Satellite Cross Roads, Ahmedabad 380 015, INDIA

Tel. No. : +91-79-2686 8100 (20 lines)

Fax No. : +91-79-2686 2365 / 66

8. MANUFACTURER

Name : Cadila Healthcare Limited

Address : Kundaim Industrial Estate, Plot No. 203-213, Kundaim, Goa - 403 115, INDIA

Tel. No. : +91-832-6615401/6615123/6615124

Fax No. : +91-832-2395203

9. DATE OF REVISION OF THE TEXT

To be included after first registration.