SUMMARY OF PRODUCT CHARACTERISTIC (SPC)

1. NAME OF THE MEDICINAL PRODUCT

LOSACAR H 50/12.5

Losartan Potassium and Hydrochlorothiazide Tablets USP 50mg/12.5mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Losartan Potassium USP	50mg
Hydrochlorothiazide USP	12.5mg

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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

4.2 Hypertension

Indicated for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on Losartan or Hydrochlorothiazide alone. Lowering blood pressurelowers the risk of fatal and non-fatal cardiovascular (CV) events, primarily strokes andmyocardial infarction. These benefits have been seen in controlled trials of antihypertensivedrugs 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, antithromboticthерapy, smoking cessation, exercise, and limited sodium intake. Many patients will require morethan 1 drug to achieve blood pressure goals. For specific advice on goals and management, seepublished guidelines, such as those of the National High Blood Pressure Education Program’sJoint 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, patientswith 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.

4.3 Posology and method of administrationPosology

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. Ifblood 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 populationsPediatric 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.

4.4 Contraindications

- Hypersensitivity to losartan, sulphonamide-derived substances (as hydrochlorothiazide) or to any of the excipients listed in section 6.1;
- Therapy resistant hypokalaemia or hypercalcaemia;
- Severe hepatic impairment; cholestasis and biliary obstructive disorders;
- Refractory hyponatraemia;
- Symptomatic hyperuricaemia/gout;
- 2nd and 3rd trimesters of pregnancy (see sections 4.4 and 4.6);

- Severe renal impairment (i.e. creatinine clearance <30 ml/min);
- Anuria;
- The concomitant use of Cozaar Comp with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2) (see sections 4.5 and 5.1).

4.5 Special warnings and precautions for use

Losartan

Angioedema

Patients with a history of angioedema (swelling of the face, lips, throat, and/or tongue) should be closely monitored (see section 4.8).

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 Cozaar Comp tablets (see sections 4.2 and 4.3).

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.

The concomitant use of potassium-sparing diuretics, potassium supplements, potassium containing salt substitutes, or other drugs that may increase serum potassium (e.g., trimethoprim-containing products) with losartan/hydrochlorothiazide is not recommended (see section 4.5).

Liver function impairment

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, Cozaar Comp 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. Therefore Cozaar Comp is contraindicated in patients with severe hepatic impairment (see sections 4.2, 4.3 and 5.2).

Renal function impairment

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function, including renal failure, have been reported (in particular, in patients whose renal function is dependent on the renin-angiotensin-aldosterone system, such as those with severe cardiac insufficiency or pre-existing renal dysfunction).

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 of Cozaar Comp tablets is not recommended.

Coronary heart disease and cerebrovascular disease

As with any antihypertensive agents, excessive blood pressure decrease in patients with ischaemic cardiovascular and cerebrovascular disease could result in a myocardial infarction or stroke.

Heart failure

In patients with heart failure, with or without renal impairment, there is - as with other drugs acting on the renin-angiotensin system - a risk of severe arterial hypotension, and (often acute) renal impairment.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Ethnic differences

As observed for angiotensin converting enzyme inhibitors, losartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

Pregnancy

AIIRAs should not be initiated during pregnancy. Unless continued AIIRA 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 (see sections 4.3 and 4.6).

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia, and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

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, hyponatraemia, hypochloraemic alkalosis, hypomagnesaemia or hypokalaemia 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 (see section 4.5). 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 hyperuricemia.

Eye disorders

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.

Acute Respiratory Toxicity

Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, Cozaar Comp should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

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.

Cozaar Comp is contraindicated for patients with severe hepatic impairment (see sections 4.3 and 5.2).

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. Photosensitising 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 minimise 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.

Excipient

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine**.**

4.6 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 possibleacute 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 ona background of losartan therapy and followed them for a median of 2.2 years. Patients receivingthe 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, butexperienced 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 potassiumand 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 withrenal 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. Singledoses 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.

4.7 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 itis 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 inhumans 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 treatedprior 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 majororganogenesis, 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 thedrug to the mother.

4.8 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.

4.9 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 trialsof 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 ventricularhypertrophy. 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 toclinical 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, electrolyteimbalance 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, renalfailure.
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 causeof 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* Cough	HCTZ 25%	Losartan 17%	Lisinopril 69%
Study 2† Cough	Placebo 35%	Losartan29%	Lisinopril62%

*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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.10Overdose

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 diureticsATC 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 appearsto 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-aldosteronelink 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

5.3

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 inthe 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 thefeces. 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.

5.4 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of FertilityLosartan 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 atnoncytotoxic 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, 60and 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 ofdoses as low as 10 mg/kg/day of losartan and 2.5 mg/kg/day of hydrochlorothiazide wasassociated with

slight but statistically significant decreases in fecundity and fertility indices.AUC values for losartan, its active metabolite and hydrochlorothiazide, extrapolated from dataobtained with losartan administered to rats at a dose of 50 mg/kg/day in combination with 12.5mg/kg/day of hydrochlorothiazide, were approximately 6, 2, and 2 times greater than thoseachieved 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/litterat 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 at the temperature below 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. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

TAN 20 HM 0391

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25th September, 2020

10. DATE OF REVISION OF THE TEXT

Not applicable (first approval)