1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT:

1.1 Product name: Presartan H 50

(Losartan Potassium & Hydrochlorothiazide Tablets**)**

1.2 Strength:

Each film coated tablet contains:

Losartan Potassium USP…..….50mg

Hydrochlorothiazide BP….. ….12.5mg

1.3 Pharmaceutical dosage form:

Solid dosage form (Film Coated Tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

2.1 Qualitative Declaration:

Losartan potassium is chemically described as 2-butyl-4-chloro-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl) benzyl] imidazole-5-methanol monopotassium salt.

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

2.2 Quantitative Declaration:

Each film coated tablet contains:

Losartan Potassium USP…..….50mg

Hydrochlorothiazide BP/ EP….12.5mg

3. PHARMACEUTICAL FORM:

Presartan H 50

"Yellow colored, oval, biconvex, film coated tablets."

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications:

Hypertension

Losartan potassium and hydrochlorothiazide combination is indicated for the treatment of hypertension. It is not for use as initial therapy, but in patients whose

blood pressure is not adequately controlled by losartan potassium or hydrochlorothiazide alone.

The combination may be administered with other antihypertensive agents.

Hypertensive patients with left ventricular hypertrophy

Losartan potassium and hydrochlorothiazide combination 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:

Losartan potassium and hydrochlorothiazide tablets may be administered with or without food. It may be administered with other antihypertensive agents. It should be swallowed with a glass of water.

Hypertension Dose titration with the individual components (losartan and hydrochlorothiazide) is recommended.

When clinically appropriate, direct change from monotherapy to the fixed combination may be considered in patients whose blood pressure is not adequately controlled.

The usual starting dose is one tablet of Losartan potassium and hydrochlorothiazide tablets (50mg + 12.5mg) once daily. If blood pressure remains uncontrolled after about 3 weeks of therapy, the dose may be increased gradually to two tablets of Losartan potassium and hydrochlorothiazide tablets (50mg + 12.5mg) once daily. More than two tablets of Losartan potassium and hydrochlorothiazide tablets (50mg + 12.5mg) once daily are not recommended. The maximal antihypertensive effect is attained about 3 weeks after initiation of therapy.

Use in patients with renal impairment: The usual regimens of therapy with the combination may be followed as long as the patient's creatinine clearance is >30 mL/min. Losartan potassium and hydrochlorothiazide tablets must not be used in patients with severe renal impairment (i.e. creatinine clearance <30 ml/min). The tablets are not recommended for haemodialysis patients.

Use in patients with hepatic impairment: Losartan potassium and hydrochlorothiazide tablets (50mg + 12.5mg) is not recommended in patients with hepatic impairment because the appropriate 25 mg starting dose of losartan cannot be given.

Use in patients with intravascular volume depletion: Losartan potassium and hydrochlorothiazide tablets (50mg + 12.5mg) are also not recommended for use as initial therapy in patients with intravascular volume depletion (e.g., patients treated with diuretics). Volume and/or sodium depletion should be corrected prior to administration of Losartan potassium and hydrochlorothiazide tablets.

Use in elderly patients: No initial dosage adjustment for Losartan potassium and hydrochlorothiazide tablets (50mg + 12.5mg) is necessary for elderly patients. The dose of 2 tablets of Losartan potassium and hydrochlorothiazide (50mg + 12.5mg) should not be used as the initial dose in elderly patients.

Use in children and adolescents (<18 years): There is no experience in children and adolescents. Therefore, Losartan potassium and hydrochlorothiazide tablets should not be administered to children and adolescents.

Hypertensive patients with left ventricular hypertrophy

Treatment should be initiated with Losartan 50mg once daily. Losartan potassium and hydrochlorothiazide (50mg + 12.5mg) should be substituted if the blood pressure reduction is inadequate. If additional blood pressure reduction is needed, the dose should be increased to two tablets of Losartan potassium and hydrochlorothiazide (50mg + 12.5mg). For further blood pressure reduction other antihypertensive should be added.

4.3 Contraindications:

Losartan potassium and hydrochlorothiazide tablets are contraindicated in:

- Patients who are hypersensitive to any component of this product or to other sulfonamide-derived drugs.
- Patients with anuria
- Therapy resistant hypokalaemia or hypercalcaemia
- Severe hepatic impairment, cholestasis and biliary obstructive disorders

- Refractory hyponatraemia
- Symptomatic hyperuricaemia/gout
- Second and third trimester of pregnancy
- Severe renal impairment (i.e. creatinine clearance <30 ml/min)

Do not co-administer aliskiren with losartan potassium and hydrochlorothiazide combination in patients with diabetes

4.4 Special warning and precautions for use:

WARNINGS

Fetal/neonatal morbidity and mortality - Drugs that act directly 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, losartan potassium and hydrochlorothiazide combination should be discontinued as soon as possible.

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

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

Hypotension - In patients with an activated rennin-angiotensin system, such as volume- or salt-depleted patients (e.g. those being treated with high dose of diuretics, dietary salt restriction, diarrhea or vomiting), symptomatic hypotension may occur after initiation of treatment with losartan potassium and hydrochlorothiazide combination. These conditions should be corrected prior to administration of the drug. Do not use losartan potassium and hydrochlorothiazide tablets as initial therapy in patients with intravascular volume depletion.

A patient receiving the combination should be cautioned that light headedness can occur, especially during the first days of therapy, and that it should be reported to

the prescribing physician. The patients should be told that if syncope occurs, the combination should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Impaired hepatic function – Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, Losartan potassium and hydrochlorothiazide tablets should be used with caution in patients with a history of mild to moderate hepatic impairment.

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

Losartan potassium and hydrochlorothiazide tablets (50mg + 12.5mg) is not recommended in patients with mild to moderate hepatic impairment because the appropriate 25 mg starting dose of losartan cannot be given. It is contraindicated in patients with severe hepatic impairment.

Hypersensitivity - Angioedema can occur rarely. 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.

Systemic lupus erythematosus - The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

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 Losartan potassium and hydrochlorothiazide 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 nonblacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

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 the drug 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.

Precautions

Impaired renal function - As a consequence of inhibiting the renin-angiotensin-aldosterone system, 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-aldosterone system (e.g., patients with severe congestive heart failure, renal artery stenosis, chronic kidney disease or volume depletion), may be at particular risk of developing acute renal failure on losartan potassium and hydrochlorothiazide tablets. 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 tablets.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. Similar effects have been reported with losartan; in some patients, these effects were 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.

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.

Renal transplantation - There is no experience in patients with recent kidney transplantation.

Electrolyte imbalance – 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 creatinine clearance between 30-50ml/min should be closely monitored.

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: namely, hyponatremia, hypo-chloremic alkalosis, hypomagnesemia and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

Although any chloride deficit is generally mild and usually does not require specific treatment, except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia - 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.

Hyperglycemia - Thiazide therapy may impair glucose tolerance. In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

Hypomagnesemia - Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia. Hypomagnesemia can result in hypokalemia which may be difficult to treat despite potassium repletion.

Hypercalcemia - Thiazides decreases urinary calcium excretion and may cause elevations of serum calcium. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Monitor calcium levels. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

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

Postsympathectomy patients - The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

Effect 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.

Usage in pregnancy and lactation

The use of angiotensin receptor blockers is not recommended during the first trimester of pregnancy. It is contra-indicated during the 2^{nd} and 3^{rd} trimester of pregnancy. When pregnancy is detected, should be discontinued as soon as possible.

Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy.

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 rennin-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 tablets, 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 tablets for hypotension, oliguria, and hyperkalemia 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.

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

Usage in paediatrics

Safety and effectiveness in paediatric patients have not been established. Therefore, losartan potassium and hydrochlorothiazide combination should not be administered to children and adolescents.

Neonates with a history of in utero exposure to losartan potassium 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.

Usage in geriatrics

No overall differences in effectiveness or safety were observed between elderly patients and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

4.5 Drug interactions

Losartan

Digoxin and warfarin - No significant drug-drug pharmacokinetic interactions have been found with digoxin and warfarin.

Cimetidine - Coadministration of losartan and cimetidine led to an increase in AUC of losartan but did not affect the pharmacokinetics of its active metabolite.

Phenobarbital - Coadministration of losartan and phenobarbital led to a reduction in the AUC of losartan and that of its active metabolite.

Rifampin - Rifampin, an inducer of drug metabolism, decreased the AUC of losartan and its active metabolite by 30% and 40% respectively.

Cytochrome P450 inhibitors - Potent inhibitors of cytochrome P450 3A4 and 2C9 have not been studied clinically but *in vitro* studies show significant inhibition of the formation of the active metabolite by inhibitors of P450 3A4 (ketoconazole, troleandomycin, gestodene), or P450 2C9 (sulfaphenazole) and nearly complete inhibition by the combination of sulfaphenazole and ketoconazole. In humans, ketoconazole, an inhibitor of P450 3A4, did not affect the conversion of losartan to the active metabolite after intravenous administration of losartan. Inhibitors of cytochrome P450 2C9 have not been studied clinically. The pharmacodynamic consequences of concomitant use of losartan and inhibitors of P450 2C9 have not been examined. The AUC of active metabolite following oral losartan was not affected by erythromycin, another inhibitor of P450 3A4, but the AUC of losartan was increased.

Fluconazole, an inhibitor of cytochrome P450 2C9, decreased the AUC of the active metabolite, but increased the AUC of losartan following multiple doses. The clinical consequences of these interactions have not been evaluated.

Potassium sparing diuretics, potassium supplements - As with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium. Co-medication is not advisable.

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

1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) - 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 combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

The antihypertensive effect of angiotensin II receptor antagonists, including losartan, may be attenuated by NSAIDs, including selective COX-2 inhibitors

Blood pressure lowering drugs - Concomitant use with these drugs that lower blood pressure, like tricyclic antidepressants, antipsychotics, baclofene, amifostine, may increase the risk of hypotension.

Grape fruit - Grape fruit slows down and decreases the extent of conversion of losartan to its active metabolite. The therapeutic effectiveness of the combination is to be monitored if losartan and hydrochlorothiazide combination is used concomitantly with grapefruit juice.

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. Closely monitor blood pressure, renal function, and electrolytes in patients on losartan potassium and hydrochlorothiazide combination and other agents that affect the RAS. Do not co-administer aliskiren with the combination in patients with diabetes. Avoid use of aliskiren with losartan potassium and hydrochlorothiazide combination in patients with renal impairment (GFR <60 ml/min).

1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS

Hydrochlorothiazide

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

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

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

Other antihypertensive drugs - Additive effect or potentiation.

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. 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.

Amphotericin B (parenteral), corticosteroids, ACTH or stimulant laxatives 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.

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

Non-Steroidal Anti-inflammatory Drugs - The administration of a non-steroidal anti-inflammatory agent including a selective cyclooxygenase-2 inhibitor can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when losartan potassium and hydrochlorothiazide combination and non-steroidal anti-inflammatory agents, including selective cyclo-oxygenase -2 inhibitors are used concomitantly, the

patient should be observed 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.

Lithium – Should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.

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

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

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

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

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

Ciclosporin - Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout-type complications.

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

1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS

Medicinal products affected by serum potassium disturbances - Periodic monitoring of serum potassium and ECG is recommended when losartan potassium and hydrochlorothiazide tablets are administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides and antiarrhythmics) and with the following torsades de pointes (ventricular tachycardia)-inducing medicinal products (including some antiarrhythmics), hypokalaemia being a predisposing factor to torsades de pointes (ventricular tachycardia):

• Class Ia antiarrythmics (e.g. quinidine, hydroquinidine, disopyramide).

• Class III antiarrythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide).

•Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol).

• Others (e.g. bepridil, cisapride, diphemanil, erythromycin IV, halofantrine, mizolastin, pentamidine, terfenadine, vincamine IV).

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

Carbamazepine - Risk of symptomatic hyponatremia. Clinical and biological monitoring is required.

Iodine contrast media - In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of the iodine product. Patients should be rehydrated before the administration.

Laboratory test interactions - Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function.

4.6 Pregnancy and lactation:

The use of angiotensin receptor blockers is not recommended during the first trimester of pregnancy. It is contra-indicated during the 2^{nd} and 3^{rd} trimester of pregnancy. When pregnancy is detected, should be discontinued as soon as possible.

1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS

Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy.

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 rennin-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 tablets, 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 tablets for hypotension, oliguria, and hyperkalemia 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.

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. Hydrochlorothiazide is excreted in human milk. Thiazides in high doses causing intense diuresis can inhibit the milk production. 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 Effect on ability to drive and use machine:

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

1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS

4.8 Adverse Effects:

No adverse reactions peculiar to the combination of Losartan potassium and hydrochlorothiazide were observed. The adverse reactions were restricted to those which were formerly observed with losartan potassium and/or hydrochlorothiazide. In general, treatment with losartan potassium and hydrochlorothiazide combination is well tolerated. For the most part, adverse experiences have been mild and transient in nature and have not required discontinuation of therapy.

Frequencies are defined as: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, ≤1/100); rare (≥1/10000, ≤1/1000), very rare (≤1/10000), not known (<1/10000).

Adverse effects reported with the combination are as follows:

Hepato-biliary disorders - *Rare:* Hepatitis

Investigations - *Rare*: Hyperkalaemia, elevation of ALT

Nervous system disorders – *Common:* Dizziness

Additional adverse reactions that have been seen with one of the individual components and may be potential adverse reactions with losartan potassium/hydrochlorothiazide are the following:

Losartan

Blood and lymphatic system disorders - *Uncommon:* Anaemia, Henoch-Schönlein purpura, ecchymosis, haemolysis

Cardiac disorders - *Uncommon:* Hypotension, orthostatic hypotension, sternalgia, angina pectoris, grade II-AV block, cerebrovascular event, myocardial infarction, palpitation, arrhythmias (atrial fibrillations, sinus bradycardia, tachycardia, ventricular tachycardia, ventricular fibrillation)

Ear and labyrinth disorders - *Uncommon:* Vertigo, tinnitus

Eye disorders - *Uncommon:* Blurred vision, burning/stinging in the eye, conjunctivitis, decrease in visual acuity

Gastrointestinal disorders - *Common:* Abdominal pain, nausea, diarrhoea, dyspepsia; *Uncommon:* Constipation, dental pain, dry mouth, flatulence, gastritis, vomiting

General disorders and administration site conditions - *Common*: Asthenia, fatigue, chest pain; *Uncommo*n: Facial oedema, fever; *Not known:* Malaise, weakness, edema/swelling

Hepato-biliary disorders – *Rare:* Hepatitis; *Not known:* Liver function abnormalities

Immune system disorders - *Rare:* Anaphylactic reactions, angioedema, urticaria

Investigations - *Common:* Hyperkalaemia, mild reduction of haematocrit and haemoglobin; *Uncommon:* Mild increase in urea and creatinine serum levels. *Very rare:* Increase in hepatic enzymes and bilirubin, because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid hormone. *Not known:* Hyponatremia

Metabolism and nutrition disorders - *Uncommon:* Anorexia, gout

Musculoskeletal and connective tissue disorders - *Common:* Muscle cramp, back pain, leg pain, myalgia; *Uncommon:* Arm pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, coxalgia, fibromyalgia, muscle weakness; *Rare:* Rhabdomyolysis

Nervous system disorders - *Common:* Headache, dizziness. *Uncommon:* Nervousness, paraesthesia, peripheral neuropathy, tremor, migraine, syncope; *Not known:* Dysgeusia

Psychiatric disorders - *Common:* Insomnia. *Uncommon:* Anxiety, anxiety disorder, panic disorder, confusion, depression, abnormal dreams, sleep disorder, somnolence, memory impairment

Renal and urinary disorders - *Uncommon:* Nocturia, urinary frequency, urinary tract infection

Reproductive system and breast disorders - *Uncommon:* Decreased libido, impotence, erectile dysfunction

Respiratory, thoracic and mediastinal disorders - *Common:* Cough, upper respiratory infection, nasal congestion, sinusitis, sinus disorder; *Uncommon:* Pharyngeal discomfort, pharyngitis, laryngitis, dyspnoea, bronchitis, epistaxis, rhinitis, respiratory congestion

Skin and subcutaneous tissue disorders - *Uncommon:* Alopecia, dermatitis, dry skin, erythema, flushing, photosensitivity, pruritus, rash, urticaria, sweating; *Not known:* Erythroderma

Vascular disorders - *Uncommon:* Vasculitis

Hydrochlorothiazide

Blood and lymphatic system disorders - *Uncommon:* Agranulocytosis, aplastic anaemia, haemolytic anaemia, leukopenia, purpura, thrombocytopenia

Eye disorders - *Uncommon:* Transient blurred vision, xanthopsia

Gastrointestinal disorders - *Uncommon:* Sialoadenitis, spasms, stomach irritation, nausea, vomiting, diarrhoea, constipation

General disorders and administration site conditions - *Uncommon:* Fever, dizziness

Hepato-biliary disorders - *Uncommon:* Jaundice (intrahepatic cholestatic jaundice), pancreatitis

Immune system disorders - *Rare:* Anaphylactic reaction

Metabolism and nutrition disorders - *Uncommon:* Anorexia, hyperglycaemia, hyperuricaemia, hypokalaemia, hyponatraemia

Musculoskeletal and connective tissue disorders - *Uncommon:* Muscle cramps

Nervous system disorders - *Common:* Cephalalgia

Psychiatric disorders - *Uncommon:* Insomnia, restlessness

Respiratory, thoracic and mediastinal disorders - *Uncommon:* Respiratory distress including pneumonitis and pulmonary oedema

Renal and urinary disorders - *Uncommon:* Glycosuria, interstitial nephritis, renal dysfunction, renal failure

Skin and subcutaneous tissue disorders - *Uncommon:* Photosensitivity, urticaria, toxic epidermal necrolysis; *Not known:* Cutaneous lupus erythematosus

Vascular disorders - *Uncommon:* Necrotising angiitis (vasculitis, cutaneous vasculitis)

4.9 Overdose:

No specific information is available on the treatment of overdosage with the combination. Treatment is symptomatic and supportive. Therapy with the combination should be discontinued and the patient observed closely. Suggested

measures include induction of emesis if ingestion is recent and correction of dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures.

Losartan

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 overdosage in humans. The most likely manifestation of overdosage 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, 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:

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 AT_1 receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland). Both losartan and its principal active

metabolite do not exhibit any partial agonist activity at the AT_1 receptor and have much greater affinity (about 1000-fold) for the AT_1 receptor than for the AT_2 receptor. *In vitro* binding studies indicate that losartan is a reversible, competitive inhibitor of the AT_1 receptor. The active metabolite is 10 to 40 times more potent by weight than losartan and appears to be a reversible, noncompetitive inhibitor of the AT_1 receptor.

During the administration of losartan the removal of the angiotensin II negative feedback on renin secretion leads to increased plasma-renin activity (PRA). Increase in the PRA leads to an increase in angiotensin II in plasma. Despite these increases, antihypertensive activity and suppression of the plasma aldosterone concentration are maintained, indicating effective angiotensin II receptor blockade. After the discontinuation of losartan, PRA and angiotensin II values fell within 3 days to the baseline values.

In nondiabetic hypertensive patients with proteinuria, the administration of losartan potassium significantly reduces proteinuria, fractional excretion of albumin and IgG. Losartan maintains glomerular filtration rate and reduces filtration fraction. Generally losartan causes a decrease in serum uric acid (usually <0.4 mg/dL) which was persistent in chronic therapy.

Losartan has no effect on autonomic reflexes and no sustained effect on plasma norepinephrine.

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.

Despite the significant decrease in blood pressure, administration of losartan had no clinically significant effect on heart rate.

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

and bicarbonate loss, and decreases in serum potassium. The mechanism of the antihypertensive effect of thiazides is unknown.

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

The components of Presartan-H (losartan potassium and hydrochlorothiazide) have been shown to have an additive effect on blood pressure reduction, reducing blood pressure to a greater degree than either component alone. This effect is thought to be a result of the complimentary actions of both components. Further, as a result of its diuretic effect, hydrochlorothiazide increases plasma renin activity, increases aldosterone secretion, decreases serum potassium, and increases the levels of angiotensin II. Administration of losartan blocks all the physiologically relevant actions of angiotensin II and through inhibition of aldosterone could tend to attenuate the potassium loss associated with the diuretic.

Losartan has been shown to have a mild and transient uricosuric effect. Hydrochlorothiazide has been shown to cause modest increases in uric acid; the combination of losartan and hydrochlorothiazide tends to attenuate the diuretic-induced hyperuricemia.

The antihypertensive effect of the combination is sustained for a 24-hour period. In at least one year's duration, the antihypertensive effect was maintained with continued therapy. Despite the significant decrease in blood pressure, administration of Losartan Potassium/Hydrochlorothiazide had no clinically significant effect on heart rate.

Losartan Potassium/Hydrochlorothiazide is effective in reducing blood pressure in males and females, blacks and non-blacks and in younger (<65 years) and older (≥65 years) patients and is effective in all degrees of hypertension.

5.2 Pharmacokinetic properties:

Losartan

Following oral administration, losartan is well absorbed. The systemic bioavailability of losartan is approximately 33%. It 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 the orally

administered dose of losartan is converted to the active metabolite. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed. 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 (about 10% decreased). Both losartan and its active metabolite are highly bound to plasma proteins (≥99%). Plasma protein binding is constant over the concentration range achieved with recommended doses. Losartan crosses the blood-brain barrier poorly, if at all.

When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% is excreted in urine as active metabolite. The terminal half-life of losartan is about 2 hours and of the metabolite is about 6-9 hours. Biliary excretion contributes to the elimination of losartan and its metabolites.

Hydrochlorothiazide

Hydrochlorothiazide is absorbed from the GI tract. Food does not affect absorption of 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:

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6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Lactose Monohydrate, Microcrystalline Cellulose, Pregelatinised Starch, Maize Starch, Colloidal Silicon Dioxide, Magnesium Stearate, Hydroxy Propylmethyl Cellulose-15 cps, Titanium Dioxide, Purified Talc, Polyethylene Glycol (PEG 6000), Quinoline Yellow Lake.

6.2 Incompatibilities:

Not applicable

6.3 Shelf – life:

24 months

6.4 Special precautions for storage:

Store below 30°C in a dry place.

6.5 Nature and contents of container:

Blister strip of 14 tablets. Such 2 blister strips in a printed showbox along with leaflet.

7. MARKETING AUTHORIZATION HOLDER

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Mumbai 400 067,
India.