SUMMARY OF PRODUCT CHARACTERISTICS

NUSAR-H

(Losartan Potassium & Hydrochlorothiazide Tablets)

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1. NAME OF THE MEDICINAL PRODUCT

Nusar-H is a film coated tablet containing the fixed dose combination of Losartan Potassium and Hydrochlorothiazide

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredients of Nusar-H are Losartan Potassium and Hydrochlorothiazide.

Each tablet of Nusar-H contains :

Losartan potassium USP…….. 50 mg

Hydrochlorothiazide BP…….. 12.5 mg

3. PHARMACEUTICAL FORM

Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nusar-H is indicated for the treatment of hypertension.

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

4.2 Posology and method of administration

Titration of individual drugs is recommended as far as possible. Combination therapy with Nusar-H is recommended only if patients do not respond to monotherapy with either drug. The starting dose of Nusar-H for initial treatment of severe hypertension is one tablet of Nusar-H once daily

In Hypertensive Patients with Left Ventricular Hypertrophy, treatment should be initiated with Losartan 50 mg once daily. If the blood pressure reduction is inadequate, hydrochlorothiazide 12.5 mg should be added or Nusar-H should be substituted. Further upward titration of the doses should be done if the anti-hypertensive response obtained is insufficient

Nusar-H may be administered with other antihypertensive agents.

Nusar-H may be administered with or without food.

Renal insufficiency: No dose adjustment is required in patients with mild renal impairment (creatinine clearance 20-50 ml/min). Therapy with Nusar-H is not recommended in patients with moderate to severe renal impairment (creatinine clearance <20 ml/ min)

Liver disease: Nusar-H is not recommended in patients with hepatic impairment

Use in patients with intravascular volume depletion: Nusar-H should not be initiated in patients who are intravascularly volume depleted (e.g. those treated with high-dose diuretics).

Use in the elderly: Patients over 75 years: Presently there is limited clinical experience in this group. Any therapy involving the angiotensin II antagonist, losartan, should be initiated with 25 mg losartan in these patients.

Use in children: Safety and efficacy of Nusar-H in children has not been established.

4.3 Contraindications

Nusar-H is contraindicated in patients who are hypersensitive to any component of this product. Nusar-H is also contraindicated in pregnant patients. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

4.4 Special warnings and special precautions for use:

Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, Nusar-H should be discontinued as soon as possible.

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.

Hypotension - Volume-Depleted Patients

In patients who are intravascularly volume-depleted (e.g., those treated with diuretics), symptomatic hypotension may occur after initiation of therapy with Nusar-H™. This condition should be corrected prior to administration of Nusar-H™.

Impaired Hepatic and Renal Function:

Nusar-H is not recommended for patients with hepatic impairment who require titration with losartan. Nusar-H is also not recommended in patients with moderate to severe renal impairment.

Hypersensitivity Reaction

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

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

Lithium Interaction: Lithium generally should not be given with thiazides.

4.5 Interaction with other medicinal products and other forms of Interaction

Losartan Potassium

No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, cimetidine, Phenobarbital,

ketoconazole and erythromycin. Rifampin decreased while fluconazole increased the concentrations of losartan and its active metabolite. However the clinical consequences of this interaction are unknown

As with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, and amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium

Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors : In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs (NSAIDs) including those that selectively inhibit cyclooxygenase-2 inhibitors (COX-2 inhibitors), the co-administration of angiotensin II receptor antagonists including losartan, may result in a further deterioration of renal function. These effects are usually reversible.

Reports suggest that NSAIDs including selective COX-2 inhibitors may diminish the antihypertensive effect of angiotensin II receptor antagonists, including losartan. This interaction should be given consideration in patients taking NSAIDs including selective COX-2 inhibitors concomitantly with angiotensin II receptor antagonists.

Hydrochlorothiazide

The following drugs may show interaction with thiazide diuretics if administered concomitantly:

Non-steroidal anti-inflammatory agents including a selective cyclooxygenase-2 inhibitor can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when Nusar-Hand non-steroidal anti-inflammatory agents including selective cyclooxygenase-2 inhibitors are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

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

occur.

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

Other antihypertensive drugs - Additive effect or potentiation may be seen

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

Corticosteroids, ACTH - Intensified electrolyte depletion, particularly hypokalemia may be seen.

Pressor amines (e.g., norepinephrine) - Possible decreased response to pressor amines may be seen, but it is not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine) - Possible increased responsiveness to the muscle relaxant may be noted.

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

4.6 Pregnancy

There is no clinical data supporting the use of Nusar-H during pregnancy. Animal studies with Losartan have demonstrated fetal and neonatal injury and death possibly because of the inhibition of the fetal rennin angiotensin system. The fetal renal circulation which depends on the renin angiotensin system begins to develop in the second trimester. Hence, risk to fetus increases in the second and third trimesters of pregnancy.

Thiazides cross the placental barrier and appear in cord blood. The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes

mother and fetus to unnecessary hazard, including fetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which have occurred in the adult. Diuretics do not prevent development of toxemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxemia.

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Nusar-H should be discontinued as soon as possible if pregnancy is detected.

Nursing Mothers

It is not known whether losartan is excreted in human milk, but significant levels of losartan and its active metabolite were shown to be present in rat milk. Thiazides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother

4.7 Effects on ability to drive and use machines

There are no data to suggest that Nusar-H affects the ability to drive and use machines.

4.8 Undesirable effects

In clinical trials with losartan potassium-hydrochlorothiazide, no adverse experiences peculiar to this combination have been observed. Adverse experiences have been limited to those that were reported previously with losartan potassium and/or hydrochlorothiazide. The overall incidence of adverse experiences reported with the combination was comparable to placebo.

In controlled clinical trials, rate of discontinuation of therapy with Nusar-H due to clinical adverse experiences was similar to placebo.

In controlled clinical trials for essential hypertension, dizziness was the only adverse experience reported as drug related that occurred with an incidence greater than placebo in 1% or more of patients treated with losartan potassium-

hydrochlorothiazide.
In a controlled trial in hypertensive patients with left ventricular hypertrophy, losartan used usually with hydrochlorothiazide was generally well tolerated. The most common drug-related side effects were dizziness, asthenia/fatigue, and vertigo.

The following adverse reactions have been reported in post-marketing experience:

Hypersensitivity/Anaphylactic reactions, 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-Schonlein purpura has been reported rarely with losartan.
Gastro-intestinal: Hepatitis has been reported rarely in patients treated with losartan, diarrhea.
Respiratory: Cough has been reported with losartan.
Skin: Urticaria
Additional side effects that have been seen with one of the individual components and may be potential side effects with Nusar-H are as follows:

Losartan
Dose-related orthostatic effects, liver function abnormalities, myalgia, migraine, rash, anemia, pruritus.

Hydrochlorothiazide
Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialoadenitis, vertigo, paraesthesiae, headache, xanthopsia, leucopenia, agranulocytosis, thrombocytopenia, aplastic anemia, hemolytic anemia, purpura, photosensitivity, fever, necrotizing angiitis, respiratory distress (including pneumonitis and pulmonary edema), anaphylactic reactions, toxic epidermal necrolysis, hyperglycemia, glycosuria, hyperuricaemia, electrolyte imbalance (including hyponatraemia and hypokalaemia), renal dysfunction, interstitial nephritis, renal failure, muscle spasm, weakness,

restlessness, transient blurred vision.

Laboratory test findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of losartan potassium-hydrochlorothiazide. Hyperkalaemia (serum potassium>5.5 mmol/l) occurred in 0.7% of patients, but in these trials discontinuation of losartan potassium-hydrochlorothiazide due to hyperkalaemia was not necessary. Serum potassium should be monitored, particularly in the elderly and patients with renal impairment. Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy.

4.9 Overdose

Nusar -H

There is no sufficient data regarding toxicity or overdose of Nusar-H in human beings. Treatment in cases of overdose is supportive and symptomatic. Patients should be closely monitored and appropriate measures must be instituted to tackle the resulting adverse effects like hypotension and electrolyte disturbances.

Losartan Potassium

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 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 and hydrochlorothiazide combination tablet

The components of Nusar-H 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 hyperuricaemia.

The antihypertensive effect of Nusar-H is sustained for a 24-hour period. In clinical studies of at least one year's duration, the antihypertensive effect was maintained with continued therapy. Despite the significant decrease in blood pressure, administration of Nusar-H had no clinically significant effect on heart rate. In clinical trials, after 12 weeks of therapy with losartan 50 mg/hydrochlorothiazide 12.5 mg, trough sitting diastolic blood pressure was reduced by an average of up to 13.2 mm Hg.

Nusar-His 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.

Losartan

Losartan is an oral, specific angiotensin-II receptor (type AT1) antagonist. Angiotensin II binds to the AT1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys, and the heart) and elicits several important biological

actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth-muscle proliferation. Based on binding and pharmacological bioassays, angiotensin II binds selectively to the AT1 receptor. In vitro and in vivo, both losartan and its pharmacologically active carboxylic acid metabolite (E-3174) block all physiologically relevant actions of angiotensin II, regardless of the source or route of synthesis.

During losartan administration, removal of angiotensin-II negative feedback on renin secretion leads to increased plasma-renin activity. Increases in plasma-renin activity lead to increases in angiotensin II in plasma. Even with these increases, antihypertensive activity and suppression of plasma-aldosterone concentration are maintained, indicating effective angiotensin-II receptor blockade.

Losartan binds selectively to the AT1 receptor and does not bind to or block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore, losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, effects not directly related to blocking the AT1 receptor, such as the potentiation of bradykinin-mediated effects or the generation of edema (losartan 1.7%, placebo 1.9%), are not associated with losartan.

Losartan has been shown to block responses to angiotensin I and angiotensin II without affecting responses to bradykinin, a finding which is consistent with the specific mechanism of action of losartan. In contrast, ACE inhibitors have been shown to block responses to angiotensin I and enhance responses to bradykinin without altering the response to angiotensin II, thus providing a pharmacodynamic distinction between losartan and ACE inhibitors.

In non-diabetic 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 which is persistent in chronic therapy.

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

Hydrochlorothiazide

The mechanism of the antihypertensive effect of thiazides is unknown. Thiazides do not usually affect normal blood pressure.

Hydrochlorothiazide is a diuretic and antihypertensive. It affects the distal renal tubular mechanism of electrolyte resorption. Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate.
After oral use, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

Clinical experience:

LIFE Study

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a randomized, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left ventricular hypertrophy. Patients were randomized to once daily Losartan 50 mg or atenolol 50 mg. If goal blood pressure (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of Losartan or atenolol was then increased to 100 mg once daily. Other antihypertensives (e.g., increase in dose of hydrochlorothiazide therapy to 25 mg or addition of other diuretic therapy, calcium channel blockers, alpha blockers, or centrally acting agents, but not ACE inhibitors, angiotensin II antagonists or beta-blockers) were added if necessary to reach the goal blood pressure. In efforts to control blood pressure, the patients in both arms of the LIFE study were co-administered hydrochlorothiazide the majority of time they were on study drug (73.9% and 72.4% of days in the losartan and atenolol arms respectively). The mean length of follow up was 4.8 years.
The primary endpoint was the composite of cardiovascular morbidity and mortality as measured by a reduction in the combined incidence of cardiovascular death, stroke and myocardial infarction. Blood pressure was significantly lowered to similar levels in the two groups. Treatment with Losartan' resulted in a 13.0% risk reduction (p=0.021, 95 % confidence interval 0.77-0.98) compared with atenolol for patients

reaching the primary composite endpoint. This was mainly attributable to a reduction of the incidence of stroke. Treatment with Losartan reduced the risk of stroke by 25% relative to atenolol (p=0.001 95% confidence interval 0.63-0.89). The rates of cardiovascular death and myocardial infarction were not significantly different between the treatment groups.

In another study, the safety and efficacy of losartan and hydrochlorothiazide was evaluated in elderly patients using ABPM (Eto K et. al. Nippon Ronen Igakkai Zasshi. 2002 Mar;39(2):181-6). Elderly hypertensive patients (mean age 75 +/- 2 years) were treated with either losartan (25-50 mg/day) or HCTZ (12.5 mg/day) for at least 4 weeks, and 24-hour blood pressure (BP) was measured by ABPM. Combination therapy with addition of other drug was initiated in 14 patients whose 24-hour systolic BP or daytime systolic BP was over 140 mmHg (160 mmHg for the patients of 80 years or older). After 4 weeks of the combination therapy, ABPM was repeated. Blood cell count and blood chemistry were also done before and after initiation of combination therapy. In the losartan-preceding group (n = 9), the combination therapy with HCTZ reduced 24-hour BP by 19.3 +/- 2.3/6.6 +/- 2.3 mmHg. Similarly, daytime and nighttime BP decreased by 21.4 +/- 4/8.4 +/- 2.8 mmHg and 15.2 +/- 4/4.2 +/- 2.4 mmHg, respectively. In the HCTZ-preceding group, the combination with losartan also decreased 24-hour BP by 12.2 +/- 4.8/3.4 +/- 1.4 mmHg. The decreases of daytime and nighttime BP were 13.8 +/- 6.6/4 +/- 1.1 mmHg and 10 +/- 4.7/3 +/- 2.4 mmHg, respectively. Heart rate did not change with combination therapy in the losartan-preceding group, while heart rate during daytime tended to decrease by addition of losartan in the HCTZ-preceding group (3.8 +/- 1.7/min). Serum electrolytes, uric acid, lipids, renal function and body weight did not change during the study period. Thus, combination therapy of losartan/hydrochlorothiazide was found to be useful in the treatment of elderly hypertensive patients, showing additive BP lowering effect without metabolic adverse effects.

In another study the antihypertensive efficacy and safety of losartan alone and in combination with hydrochlorothiazide was evaluated in African-American adult patients with mild to moderate hypertension (Flack JM et. al. Clin Ther. 2001 Aug;23(8):1193-208). This was a 12-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled study wherein 440 African American patients were

randomized in a 3:3:1 ratio to I of 3 treatment groups: placebo, losartan monotherapy (50 to 150 mg), or losartan plus HCTZ (50/0 to 50/12.5 to 100/25 mg). Doses were titrated at weeks 4 and 8 if sitting diastolic blood pressure (SiDBP) was > or = 90 mm Hg. Safety was assessed by determining the incidence of clinical and laboratory Adverse events and evaluating mean changes in pulse, body weight, electrocardiographic parameters, and laboratory test results. At week 12, the response rate with losartan monotherapy was 45.8%, with a significant (P < or = 0.01) lowering in mean SiDBP by 6.6 mm Hg compared with placebo; the response rate with placebo was 27.2%, with a mean SiDBP reduction of 3.9 mm Hg. Sitting systolic blood pressure (SiSBP) was significantly lowered with losartan monotherapy, by 6.4 mm Hg, compared with placebo (reduction of 2.3 mm Hg). The response rate with losartan/ HCTZ was 62.7%, with reductions in SiSBP and SiDBP of 16.8 mm Hg and 10.8 mm Hg, respectively (P < or = 0.01 vs. placebo and losartan monotherapy). The incidence of clinical adverse events was comparable in the 3 treatment groups. Thus losartan/ hydrochlorothiazide combination was shown to be well tolerated and significantly effective in lowering sitting systolic and diastolic blood pressure.

A 12-week, open-label, multicenter study assessed the efficacy and safety of losartan/hydrochlorothiazide (HCTZ), alone or in combination with other antihypertensive agents, in the treatment of patients with severe systemic hypertension (Oparil S et. al. Am J Cardiol. 2001 Mar 15;87(6):721-6). Patients received once-daily losartan/HCTZ 50/12.5 mg. Dose escalation was done, if required, to achieve blood pressure (BP) control (sitting diastolic BP <95 mm Hg); felodipine (extended release) and/or atenolol could be added if target sitting diastolic BP was not achieved with losartan/HCTZ alone. Mean sitting systolic BP of the 131 patients enrolled was 165.3 mm Hg at baseline and 139.8 mm Hg at final visit (reduction -25.4 mm Hg; p < or =0.01). Mean sitting diastolic BP was 111.9 mm Hg at baseline and 93.6 mm Hg at final visit (reduction -18.4 mm Hg; p < or =0.01). After 2 weeks of treatment, 63.8% of patients (83 of 130) were taking losartan/HCTZ 50/12.5 mg alone. By the final visit, one third of patients (35.1%; 46/131) were still only taking losartan/HCTZ. Most patients (48.1%; 63 of 131) were taking losartan/HCTZ 100/25 mg plus felodipine (extended release) at the final visit. Losartan/HCTZ was well tolerated. Thus, losartan/ HCTZ, alone or as part of a regimen with other standard antihypertensive agents, was shown to be effective and

well tolerated in the treatment of patients with severe hypertension.

5.2 Pharmacokinetic properties

Absorption

Losartan:

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. There was no clinically significant effect on the plasma-concentration profile of losartan when the drug was administered with a standardized meal.

Distribution

Losartan:

Both losartan and its active metabolite are 99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 liters. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Hydrochlorothiazide:

Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Biotransformation

Losartan:

About 14% of an intravenously or orally administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of 14C-labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about 1% of individuals studied.

In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N-2 tetrazole glucuronide.

Elimination

Losartan:

Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.

Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 69 hours, respectively. During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.

Both biliary and urinary excretions contribute to the elimination of losartan and its metabolites. Following an oral dose of 14C-labelled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the faeces.

Hydrochlorothiazide:

Hydrochlorothiazide is not metabolised 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% of the oral dose is eliminated unchanged within 24 hours.

Characteristics in Patients

Losartan and hydrochlorothiazide combination tablet:

The plasma concentrations of losartan and its active metabolite and the absorption of hydrochlorothiazide in elderly hypertensives are not significantly different from those in young hypertensives.

Losartan:

Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-fold and 1.7-fold greater than those seen in young male volunteers.

Neither losartan nor the active metabolite can be removed by haemodialysis.

5.3 Preclinical safety data

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

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

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

Losartan Potassium

Losartan potassium was not carcinogenic when administered at maximally tolerated dosages to rats and mice for 105 and 92 weeks, respectively. Female rats given the highest dose (270 mg/kg/day) had a slightly higher incidence of pancreatic acinar adenoma. The maximally tolerated dosages (270 mg/kg/day in rats, 200 mg/kg/day in

mice) provided systemic exposures for losartan and its pharmacologically active metabolite that were approximately 160 and 90 times (rats) and 30 and 15 times (mice) the exposure of a 50 kg human given 100 mg per day.

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

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

Hydrochlorothiazide

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

Hydrochlorothiazide was not genotoxic in vitro in the Ames mutagenicity assay of Salmonella typhimurium strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or in

vivo in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the Drosophila sex-linked recessive lethal trait gene. Positive test results were obtained only in the in vitro CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 g/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

Starch (USP)
Lactose monohydrate (BP)
Microcrystalline cellulose (BP)
Sodium Starch Glycolate (BP)
Crosscarmellose Sodium (USP)
Colloidal Silicon Dioxide (BP)
Magnesium Stearate (BP)
Purified water (BP)
Hydroxy Propyl methyl Cellulose (Hypromellose) (USP)
Polyethylene Glycol 6000 (Marogols)
Titanium Dioxide [E-171] (USP)
Talc (USP)
Methyl Hydroxy benzoate (Methyl Paraben) (BP)
Propyl Hydroxy benzoate (Propyl paraben) (BP)
Iron Oxide Red (In house)

6.2 Incompatibilities

None of the in-active ingredients of the formulation have been known to exhibit incompatibility with the active ingredients.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store in a dry and dark place, below 25°C.

6.5 Nature and contents of container

10 tablets are packed in a blister strip (VMCH coated printed Aluminium foil / PVC foil). 3 such strips are packed in a printed superchromoboard carton along with a package insert.

6.6 Instructions for use and handling

Store in a dry and dark place, below 25°C.

Keep away from the reach of children.

7. MARKETING AUTHORISATION HOLDER

Emcure Pharmaceuticals Ltd.

8. MARKETING AUTHORISATION NUMBER(S)

Shall be provided when available.

9. DATE OF AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not applicable.

10. DATE OF REVISION OF THE TEXT

Not applicable.