

1.3.1	Losartan/Hydrochlorothiazide
SPC, Labeling and Package Leaflet	MY-Malaysia

Lorista H ***Lorista HD***

Losartan potassium/Hydrochlorothiazide

NAME OF THE MEDICAL PRODUCT

Lorista H 50 mg/12.5 mg film-coated tablets
Lorista HD 100 mg/25 mg film-coated tablets

PRODUCT DESCRIPTION AND COMPOSITION

Each Lorista H film-coated tablet contains 50 mg losartan, potassium salt, and 12.5 mg hydrochlorothiazide.

Lorista H: Yellow, oval, slightly biconvex, one-side scored film coated tablets. The score line is not intended for breaking the tablet.

Each Lorista H tablet contains 59.98 mg lactose.

Each Lorista HD film-coated tablet contains 100 mg losartan, potassium salt, and 25 mg hydrochlorothiazide.

Lorista HD: Yellow, oval, slightly biconvex film coated tablets.

Each Lorista HD tablet contains 119.95 mg lactose.

DOSAGE FORM

Film-coated tablets

THERAPEUTICS INDICATIONS

Hypertension

Lorista H and Lorista HD is indicated for the treatment of hypertension, for patients in whom combination therapy is appropriate.

Hypertensive Patients with left ventricular hypertrophy

Lorista H and Lorista HD 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 (see SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE, PHARMACODYNAMIC PROPERTIES and POSOLOGY AND METHOD OF ADMINISTRATION.)

POSOLOGY AND METHOD OF ADMINISTRATION

Lorista H or Lorista HD may be administered with other antihypertensive agents.

Lorista H or Lorista HD should be swallowed with a glass of water.

Lorista H or Lorista HD may be administered with or without food.

Fixed dose combination is not indicated for initial therapy.

Hypertension

The usual starting and maintenance dose is one Lorista H (losartan 50 mg/HCTZ 12.5 mg) tablet once daily. For patients who do not respond adequately to Lorista H, the dosage may be increased to 2 Lorista H tablets or 1 Lorista HD (losartan 100 mg/HCTZ 25 mg) tablet once daily. The maximum

1.3.1	Losartan/Hydrochlorothiazide
SPC, Labeling and Package Leaflet	MY-Malaysia

recommended daily dose is 1 Lorista HD tablet or 2 Lorista H tablets once daily. In general, the antihypertensive effect is attained within three to four weeks after initiation of therapy.

Lorista H or Lorista HD should not be Initiated in patients who are intravascular volume-depleted (e.g., those treated with high-dose diuretics).

Lorista H or Lorista HD is not recommended for patients with severe renal impairment (creatinine clearance ≤ 30 ml) or for patients with hepatic impairment.

No initial dosage adjustment of Lorista H is necessary for elderly patients. Lorista HD should not be used as initial therapy in elderly patients.

Hypertensive Patients with left Ventricular Hypertrophy

The usual starting dose is 50 mg of losartan once daily. If goal blood pressure is not reached with losartan 50 mg, therapy should be titrated using a combination of losartan and a low dose of hydrochlorothiazide (12.5 mg) and, if needed, the dose should be increased to losartan 100 mg and hydrochlorothiazide 12.5 mg once daily. If necessary, the dose should be increased to losartan 100 mg and hydrochlorothiazide 25 mg once daily. Lorista H and Lorista HD are suitable alternative formulation in patients who would otherwise be treated concomitantly with losartan plus hydrochlorothiazide.

Route of administration

Oral

CONTRAINDICATIONS

- Hypersensitivity to losartan, sulphonamide-derived substances (as hydrochlorothiazide) or to any of the excipients
- Therapy resistant hypokalaemia or hypercalcaemia
- Severe hepatic impairment; cholestasis and biliary obstructive disorders
- Refractory hyponatraemia
- Symtomatic hyperuricaemia/gout
- 2nd and 3rd trimester of pregnancy.
- Severe renal impairment (i.e. creatinine clearance <30 ml/min)
- Anuria
- Lorista H or Lorista HD should not be administered with aliskiren in patients with diabetes.

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

Losartan/Hydrochlorothiazide

Fetal Toxicity

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and Increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Lorista H or Lorista HD as soon as possible. See PREGNANCY.

Hypersensitivity: Angioedema (see SIDE EFFECTS).

Hepatic and Renal impairment

Lorista H or Lorista HD is not recommended for patients with hepatic impairment or severe renal impairment (creatinine clearance ≤ 30 ml/min) (see DOSAGE AND ADMINISTRATION).

1.3.1	Losartan/Hydrochlorothiazide
SPC, Labeling and Package Leaflet	MY-Malaysia

Losartan

Renal Function Impairment

As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported in susceptible individuals; these changes in renal function may be reversible upon discontinuation of therapy.

Other drugs that affect the renin-angiotensin system may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. Similar effects have been reported with losartan; these changes in renal function may be reversible upon discontinuation of therapy.

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, hyponatremia, hypochloremic alkalosis, hypomagnesaemia or hypokalaemia which may occur during intercurrent diarrhea or vomiting. Periodic determination of serum electrolytes should be performed at appropriate intervals in such patients.

Metabolic and endocrine effects

Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required (see DRUG INTERACTIONS).

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 dysfunction.

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

Thiazide therapy may precipitate hyperuricemia and/or gout in certain patients. Because losartan decreases uric acid, losartan in combination with hydrochlorothiazide attenuates the diuretic-induced hyperuricemia.

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.

Use in the elderly

There were no clinically significant differences in the efficacy and safety profiles of losartan/hydrochlorothiazide in older ≥ 65 years) and younger patients (<65 years).

Race

The benefits of losartan on cardiovascular morbidity and mortality compared to atenolol do not apply to Black patients with hypertension and left ventricular hypertrophy although both treatment regimens effectively lowered blood pressure in Black patients.

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 (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

1.3.1	Losartan/Hydrochlorothiazide
SPC, Labeling and Package Leaflet	MY-Malaysia

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

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, Lorista H or Lorista HD should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

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.

Pediatric use

Safety and effectiveness in children have not been established.

Neonates with a history of *in utero* exposure to losartan/hydrochlorothiazide:

If oliguria or hypotension occur, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

Excipient

Lorista H and Lorista HD contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Losartan

Rifampicin and fluconazole have been reported to reduce levels of active metabolite. The clinical consequences of these interactions have not been evaluated.

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.

As with other medicines which affect the excretion of sodium, lithium excretion may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be co-administered with angiotensin II receptor antagonists.

1.3.1	Losartan/Hydrochlorothiazide
SPC, Labeling and Package Leaflet	MY-Malaysia

When angiotensin II antagonists are administered simultaneously with NSAIDs (i.e. selective COX-2 inhibitors, acetylsalicylic acid at anti-inflammatory doses) and non-selective NSAIDs, attenuation of the antihypertensive effect may occur. Concomitant use of angiotensin II antagonists or diuretics and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. 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.

In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, including selective cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists may result in a further deterioration of renal function. These effects are usually reversible.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) 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/hydrochlorothiazide and other agents that affect the RAAS. Do not co-administer aliskiren with Lorista H or Lorista HD in patients with diabetes. Avoid use of aliskiren with Lorista H or Lorista HD in patients with renal impairment (GFR <60 ml/min).

Other substances inducing hypotension like tricyclic antidepressants, antipsychotics, baclofene, amifostine: Concomitant use with these drugs that lower blood pressure, as main or side-effect, may increase the risk of hypotension.

Hydrochlorothiazide

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

Alcohol, barbiturates, narcotics or antidepressants
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.

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.

Pressor amines (e.g. adrenaline)
Possible decreased response to pressor amines but not sufficient to preclude their use.

1.3.1	Losartan/Hydrochlorothiazide
SPC, Labeling and Package Leaflet	MY-Malaysia

Skeletal muscle relaxants, nondepolarizing (e.g. tubocurarine)

Possible increased responsiveness to the muscle relaxant.

Lithium

Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity; concomitant use is not recommended.

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.

Cyclosporine

Concomitant treatment with cyclosporine 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.

Medicinal products affected by serum potassium disturbances

Periodic monitoring of serum potassium and ECG is recommended when losartan/hydrochlorothiazide is 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 antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide).
- Class III antiarrhythmics (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, halofantrin, mizolastin, pentamidine, terfenadine, vincamine IV).

Calcium salts

1.3.1	Losartan/Hydrochlorothiazide
SPC, Labeling and Package Leaflet	MY-Malaysia

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.

Laboratory Test Interactions

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

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.

Amphotericin B (parenteral), corticosteroids, ACTH, stimulant laxatives, or glycyrrhizin (found in liquorice)

Hydrochlorothiazide may intensify electrolyte imbalance, particularly hypokalaemia.

PREGNANCY AND LACTATION

Pregnancy

Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. When pregnancy is detected, discontinue Lorista H or Lorista HD as soon as possible.

Although there is no experience with the use of Lorista H or Lorista HD in pregnant women, animal studies with losartan potassium have demonstrated fetal and neonatal injury and death, the mechanism of which is believed to be pharmacologically mediated through effects *on* the renin-angiotensin system. In humans, fetal renal perfusion, which is dependent upon the development of *the* renin-angiotensin system, begins *in* the second trimester; thus, risk to the fetus increases if Lorista H or Lorista HD is administered during the second or third trimesters of pregnancy.

Use of drugs that act *on* the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increase 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 Lorista H or Lorista HD as soon as possible.

These adverse outcomes are usually associated with the use of these drugs in the second and third trimesters 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 Lorista H or Lorista HD, 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 Lorista H or Lorista HD for hypotension, oliguria, *and* hyperkalemia.

1.3.1	Losartan/Hydrochlorothiazide
SPC, Labeling and Package Leaflet	MY-Malaysia

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.

Lactation

It is not known whether losartan is excreted in human 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.

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.

UNDESIRABLE EFFECTS

In general, treatment with losartan potassium/hydrochlorothiazide was well tolerated. For the most part, adverse experiences have been mild and transient in nature and have not required discontinuation of therapy.

The following additional adverse reaction have been reported with individual components:

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Not known: Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)

Blood and the lymphatic system disorders: Thrombocytopenia, anemia. aplastic anemia, hemolytic anemia, leucopenia, agranulocytosis,

Immune system disorders: 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.

Metabolism and nutrition disorders: anorexia, hyperglycemia, hyperuricemia, electrolyte imbalance including hyponatremia and hypokalemia.

Psychiatric disorders: insomnia, restlessness

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

Eye disorders: Xanthopsia, transient blurred vision, acute angle-closure glaucoma, acute myopia, choroidal effusion.

Cardiac disorders: Palpitation, tachycardia.

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

1.3.1	Losartan/Hydrochlorothiazide
SPC, Labeling and Package Leaflet	MY-Malaysia

Respiratory, thoracic and mediastinal disorders: cough, nasal congestion, pharyngitis, sinus disorder, upper respiratory infection, respiratory distress (including pneumonitis *and* pulmonary edema), acute respiratory distress syndrome (ARDS).

Gastrointestinal disorders: dyspepsia, abdominal pain, gastric irritation, cramping, diarrhea, constipation, nausea, vomiting, pancreatitis, sialoadenitis.

Hepato-biliary disorders: hepatitis, jaundice (intrahepatic cholestatic jaundice).

Skin and subcutaneous tissue disorders: rash, pruritus, purpura (including Henoch-Schoenlein purpura), toxic epidermal necrolysis, urticaria, erythroderma, photosensitivity, cutaneous lupus erythematosus.

Musculoskeletal and connective tissue disorders: back pain, muscle cramps, muscle spasm, myalgia, arthralgia.

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

Reproductive system and breast disorders: erectile dysfunction/impotence.

General disorders and administration site conditions: chest pain, edema/swelling, malaise, fever, weakness.

Investigations: liver function abnormalities.

Description of selected adverse reactions

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed.

Laboratory test finding

Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy.

OVERDOSE

No specific information is available on the treatment of overdose with Lorista H or Lorista HD. Treatment is symptomatic and supportive. Therapy with Lorista H or Lorista HD 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

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

Hydrochlorothiazide

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hyponatremia, hypochloremia) 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.

1.3.1	Losartan/Hydrochlorothiazide
SPC, Labeling and Package Leaflet	MY-Malaysia

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: angiotensin II antagonists and diuretics, ATC code: C09DA01.

PHARMACODYNAMIC PROPERTIES

Mechanism of action

Losartan-Hydrochlorothiazide

The components of Lorista H and Lorista HD 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.

Pharmacodynamics

Losartan

Losartan inhibits systolic and diastolic pressor responses to angiotensin II infusions. At peak, 100 mg of losartan potassium inhibits these responses by approximately 85%; 24 hours after single and multiple-dose administration, inhibition is about 26-39%.

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. During chronic (6 weeks) treatment of hypertensive patients with 100 mg/day losartan, approximately 2-3 fold increases of plasma angiotensin II were observed at time of peak plasma drug concentrations. In some patients, greater increases were observed, particularly during short term (2 weeks) treatment. However, antihypertensive activity and suppression of plasma aldosterone concentration were apparent at 2 and 6 weeks, indicating effective angiotensin II receptor blockade. After discontinuation of losartan, plasma renin activity and angiotensin II levels declined to untreated levels within 3 days. Effects of losartan/hydrochlorothiazide on PRA and angiotensin II levels were similar to those observed with 50 mg of losartan.

Since losartan is a specific antagonist of the angiotensin II receptor type AT₁, it does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. In a study which compared the effects of 20 mg and 100 mg of losartan potassium and an ACE inhibitor on responses to angiotensin I, angiotensin II and bradykinin, losartan was shown to block responses to angiotensin I and angiotensin II without affecting responses to bradykinin. This finding is consistent with losartan's specific mechanism of action. In contrast, the ACE inhibitor was 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.

Plasma concentrations of losartan and its active metabolite and the antihypertensive effect of losartan increase with increasing dose. Since losartan and its active metabolite are both angiotensin II receptor antagonists, they both contribute to the antihypertensive effect.

1.3.1	Losartan/Hydrochlorothiazide
SPC, Labeling and Package Leaflet	MY-Malaysia

In a single-dose study in normal males, the administration of 100 mg of losartan potassium, under dietary high- and low-salt conditions, did not alter glomerular filtration rate, effective renal plasma flow or filtration fraction. Losartan had a natriuretic effect which was more pronounced on a low-salt diet and did not appear to be related to inhibition of early proximal reabsorption of sodium. Losartan also caused a transient increase in urinary uric acid excretion.

In nondiabetic hypertensive patients with proteinuria (≥ 2 g/24 hours) treated for 8 weeks, the administration of losartan potassium 50 mg titrated to 100 mg significantly reduced proteinuria by 42%. Fractional excretion of albumin and IgG also was significantly reduced. In these patients, losartan maintained glomerular filtration rate and reduced filtration fraction.

In postmenopausal hypertensive women treated for 4 weeks, 50 mg of losartan potassium had no effect on renal or systemic prostaglandin levels.

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

Losartan potassium, administered in doses of up to 150 mg once daily, did not cause clinically important changes in fasting triglycerides, total cholesterol or HDL-cholesterol in patients with hypertension. The same doses of losartan had no effect on fasting glucose levels.

Generally losartan caused a decrease in serum uric acid (usually <0.4 mg/dl) which was persistent with chronic therapy. In controlled clinical trials in hypertensive patients, no patients were discontinued due to increases in serum creatinine or serum potassium.

In a 12-week, parallel-design study in patients with left ventricular failure (New York Heart Association Functional Classes II-IV), most of whom were receiving diuretics and/or digitalis, losartan potassium administered in once-daily doses of 2.5, 10, 25 and 50 mg was compared to placebo. The 2.5-mg and 50-mg doses produced positive hemodynamic and neurohormonal effects which were maintained for the length of the study. Hemodynamic responses were characterized by an increase in cardiac index and decreases in: pulmonary capillary wedge pressure, systemic vascular resistance, mean systemic arterial pressure and heart rate. The occurrence of hypotension was dose related in these heart failure patients. Neurohormonal results were characterized by a reduction in circulating levels of aldosterone and norepinephrine.

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use ($\geq 50,000$ mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use ($\sim 25,000$ mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose ($\sim 100,000$ mg).

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

PI_Text032829_1	- Updated:	Page 11 of 13
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1.3.1	Losartan/Hydrochlorothiazide
SPC, Labeling and Package Leaflet	MY-Malaysia

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 $\geq 99\%$ 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 ^{14}C -labeled 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 one percent 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 6-9 hours, respectively. During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.

Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose of ^{14}C -labeled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the feces.

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.

Characteristics in Patients

Losartan-Hydrochlorothiazide

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.

1.3.1	Losartan/Hydrochlorothiazide
SPC, Labeling and Package Leaflet	MY-Malaysia

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.

Pharmacokinetic studies showed that the AUC of losartan in Japanese and non-Japanese healthy male subjects is not different. However, the AUC of the carboxylic acid metabolite (E-3174) appears to be different between the two groups, with an approximately 1.5 fold higher exposure in Japanese subjects than in non-Japanese subjects. The clinical significance of these results is not known.

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

Special precautions for storage

Do not store above 30°C. Store in the original package in order to protect from moisture.
Keep out of the reach of children.

Nature and contents of container

Blister pack (Al foil, OPA/Al/PVC foil): 28 Lorista H film-coated tablets in a folding box.
Blister pack (Al foil, OPA/Al/PVC foil): 28 Lorista HD film-coated tablets in a folding box.

PRODUCT REGISTRATION HOLDER

PAHANG PHARMACY SDN. BHD.
Lot 5979, Jalan Teratai, 5 ½ Miles, Off Jalan Meru, 41050 Klang, Selangor, Malaysia

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