PI for HYLOKAT TABLETS

SCHEDULING STATUS:

1. NAME OF THE MEDICINE

HYLOKAT 50/12,5 Tablets (film-coated tablets).

HYLOKAT 100/25 Tablets (film-coated tablets).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

HYLOKAT 50/12,5 mg

Each film-coated tablet contains:

Losartan potassium 50 mg and hydrochlorothiazide 12,5 mg

Contains sugar (62,5 mg lactose monohydrate).

HYLOKAT 100/25 mg

Each film-coated tablet contains:

Losartan potassium 100 mg and hydrochlorothiazide 25 mg

Contains sugar (125 mg lactose monohydrate).

Excipients:

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet.

HYLOKAT 50/12,5 mg

Yellow coloured, oval shaped, biconvex, film coated tablets having 'ML 43' debossed on one side and plain on other side.

HYLOKAT 100/25 mg

Yellow coloured, oval shaped, biconvex, film coated tablets having 'ML 44' debossed on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

HYLOKAT is indicated for the treatment of hypertension in patients established on identical doses of the individual medicines.

4.2 Posology and method of administration

The maximum dose is one tablet of **HYLOKAT** (100 mg losartan potassium and 25 mg hydrochlorothiazide) once daily. The maximum antihypertensive effect is attained within three weeks after initiation of therapy.

HYLOKAT should not be initiated in patients who are intravascularly volume-depleted (e.g. those treated with high-dose diuretics).

HYLOKAT is not recommended for patients with severe renal impairment or for patients with hepatic impairment (see section 4.4)

HYLOKAT should not be used as initial therapy in elderly patients.

HYLOKAT may be administered with other antihypertensive medicines, such as calcium channel blockers and beta-blockers.

HYLOKAT may be administered with or without food.

4.3 Contraindications

- Sensitivity to any of the components of **HYLOKAT**
- A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines.
- Hereditary or idiopathic angioedema
- Hypertrophic obstructive cardiomyopathy (HOCM)
- Severe renal function impairment (creatinine clearance less than 30ml/min)
- Bilateral renal artery stenosis
- Renal artery stenosis in patients with a single kidney
- Aortic stenosis
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride

- Porphyria
- Thiazide diuretics in (fixed dose) combination as with **HYLOKAT**, should not be given to patients with Addison's disease. This therapy is also contraindicated in patients with severe renal impairment or anuria, and in patients who show hypersensitivity to other sulphonamide-derived medicines.
- Lithium therapy: Concomitant administration with **HYLOKAT** may lead to toxic blood concentrations of lithium
- Pregnancy and lactation (see section 4.6)
- Hepatic impairment
- Paediatric Use: Safety and efficacy in children has not been established.
- The concomitant use of **HYLOKAT** with direct renin inhibitors such asaliskiren-containing products is contraindicated (see section 4.4 & 4.5)
- Concomitant use of fluoroquinolones with ACE inhibitors/ Renin-Angiotensin blockers is contraindicated in patients with moderate to severe renal impairment

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving **HYLOKAT**, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see section 4.3 and 4.6)

Hypotension and electrolyte/fluid imbalance:

In patients who are intravascularly volume-depleted (e.g. those treated with high-dose diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of **HYLOKAT**, or a lower starting dose should be used (see Section 4.2). Periodic determination of serum electrolytes must be performed at appropriate intervals.

Metabolic and endocrine effects:

Hydrochlorothiazide, a component of **HYLOKAT**, therapy may impair glucose tolerance. Dosage adjustment of antidiabetic medicine, including insulin, may be required (see Section 4.5).

Hydrochlorothiazide, a component of **HYLOKAT**, may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. **HYLOKAT** should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with hydrochlorothiazide, a component of **HYLOKAT**, therapy. Hydrochlorothiazide, a component of **HYLOKAT**, therapy may precipitate hyperuricaemia and/or gout in certain patients.

Concomitant use with Lithium:

Concomitant administration of lithium with **HYLOKAT** is contraindicated, because it may lead to toxic blood concentrations of lithium (see sections 4.3 and 4.5).

Hepatic and Renal impairment:

HYLOKAT is not recommended for patients with hepatic impairment or severe renal impairment (see section 4.2 and 4.3)

As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported. These changes in renal function may be reversible upon discontinuation of therapy. **HYLOKAT** 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 (see section 4.3).

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

There is evidence that the concomitant use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers or aliskiren may increase the risk of hypotension, hyperkalaemia and decreases renal function (including acute renal failure). Dual blockade of RAAS through the combined use of **HYLOKAT** and aliskiren is therefore contraindicated (see section 4.3).

HYLOKAT should not be used concomitantly with aliskiren (see section 4.3).

Concomitant use of fluoroquinolones

Concomitant use of fluoroquinolones and angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3). Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) whether used separately and/or concomitantly.

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitising actions of hydrochlorothiazide could act as a possible mechanism for NMSC.

Patients taking hydrochlorothiazide should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of hydrochlorothiazide may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

Other:

In patients receiving hydrochlorothiazide, a component of **HYLOKAT**, 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 hydrochlorothiazide, as contained in **HYLOKAT**.

Lactose:

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

4.5 Interaction with other medicines and other forms of interaction

LOSARTAN POTASSIUM

In clinical pharmacokinetic trials no interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbital (see hydrochlorothiazide, alcohol, barbiturates or narcotics below) ketoconazole, and erythromycin. Rifampicin and fluconazole have been reported to reduce levels of the active metabolite of **HYLOKAT**. The clinical consequences of these interactions have not been evaluated.

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

Lithium excretion may be reduced. Therefore, lithium salts should not be given concomitantly (see section 4.3).

Non-steroidal anti-inflammatory medicines (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of **HYLOKAT.**

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 patients with compromised renal function who are being treated with non-steroidal anti-inflammatory medicines (NSAIDs), the co-administration of **HYLOKAT** may result in a further deterioration of renal function.

Dual blockade of the RAAS with ARBs, ACE inhibitors, or aliskiren

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (see section 4.3 and 4.4).

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.

Concomitant use of fluoroquinolones:

Concomitant use of fluoroquinolones and Angiotensin-converting enzyme (ACE) inhibitors/Angiotensin receptor blockers (ARBs) may precipitate acute kidney injury. The mechanism of the possible interaction between the different classes of medicines, over and above different mechanisms of kidney damage, is unknown (see section 4.3).

HYDROCHLOROTHIAZIDE

When administered concurrently the following medication may interact with *thiazide diuretics:* Alcohol, barbiturates, or narcotics: potentiation of orthostatic hypotension may occur.

Antidiabetic medication (oral medicine and insulin): dosage adjustment of the antidiabetic medicine may be required.

Other antihypertensive medication: 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 gastro-intestinal tract by up to 85 and 43

percent, respectively. **HYLOKAT** should therefore be administered one hour before the intake of the resin.

Corticosteroids, ACTH: intensified electrolyte depletion, particularly hypokalaemia.

Pressor amines (e.g. norepinephrine): possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants: response to nondepolarising medicines may be increased.

Lithium: should not be given with **HYLOKAT**. Diuretic medicines reduce the renal clearance of lithium and add a high risk of lithium toxicity.

Non-steroidal anti-inflammatory medication including Cyclooxygenase-2 Inhibitors: the administration of a nonsteroidal anti-inflammatory drug (NSAID) including a selective cyclooxygenase-2 inhibitor can reduce the diuretic, natriuretic, and antihypertensive effects of **HYLOKAT**.

Medicines used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol)
Dosage adjustment of uricosuric medicines 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 medicines (e.g. atropine, biperiden)
Increase of the bioavailability to thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate.

Cytotoxic medicines (e.g. cyclophosphamide, methotrexate)
Thiazides may reduce the renal excretion of cytotoxic medicines 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.

Cyclosporin

Concomitant treatment with cyclosporin 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.

Medicines affected by serum potassium disturbances

Periodic monitoring of serum potassium and ECG is recommended when losartan/hydrochlorothiazide is administered with medicines affected by serum potassium disturbances (e.g. digitalis glycosides and antiarrhythmics) and with the following torsades de pointes (ventricular tachycardia)-inducing medicines (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, halofantrin, 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.

Laboratory Test Interactions

Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function (see section 4.4).

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of **HYLOKAT** in pregnant women is contra-indicated. (see section 4.3). When pregnancy is planned or confirmed **HYLOKAT** should be discontinued. Medicines affecting the renin-angiotensin system, such as **HYLOKAT**, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women. Women of childbearing age should ensure effective contraception. Teratogenicity has been shown in experimental animals.

Thiazides such as **HYLOKAT** cross the placental barrier and appear in cord blood.

Breastfeeding

Safety in breastfeeding has not been established. Thiazides appear in human milk.

4.7 Effects on ability to drive and use machines

No studies on the reactions on the ability to drive and use machines have been performed. However, when driving vehicles or operating machinery it must be borne in mind that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy in particular during initiation of treatment or when the dose is increased.

4.8 Undesirable effects

System Organ Class	Frequency	Undesirable effects
Losartan and hydrochlorothiazide combination		
Nervous system disorders	Frequent	Dizziness
General disorders and administration site conditions	Frequent	Asthenia/fatigue
Losartan		
Infections and infestations	Frequent	Upper respiratory infection
Blood and the lymphatic system disorders	Less frequent	Anaemia, Henoch Schönlein purpura, ecchymosis, haemolysis
	Frequency unknown	Thrombocytopaenia
Immune system disorders	Less frequent	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; in some of these patients angioedema had been reported in the past in connection with the administration of other medicines, including ACE inhibitors
Metabolism and nutrition disorders	Less frequent	Anorexia, gout
Psychiatric disorders	Frequent	Insomnia

System Organ Class	Frequency	Undesirable effects
	Less frequent	Anxiety, anxiety disorder, panic disorder, confusion, depression, abnormal dreams, sleep disorder, somnolence, memory impairment
Nervous system disorders	Frequent	Headache, dizziness
	Less frequent	Nervousness, paraesthesia, peripheral neuropathy, tremor, migraine, syncope
	Frequency unknown	Dysgeusia, restlessness
Eye disorders	Less frequent	Blurred vision, burning/stinging in the eye, conjunctivitis, decrease in visual acuity
Ear and labyrinth disorders	Less frequent	Vertigo, tinnitus
Cardiac disorders	Frequent	Palpitation, tachycardia
	Less frequent	Hypotension, orthostatic hypotension, sternalgia, angina pectoris, grade II-AV block, cerebrovascular event, myocardial infarction, arrhythmias (atrial fibrillations, sinus bradycardia, ventricular tachycardia, ventricular fibrillation)
Vascular disorders	Less frequent	Orthostatic hypotension, vasculitis
Respiratory, thoracic and mediastinal disorders	Frequent	Cough, pharyngitis, nasal congestion, sinus disorder, sinusitis, upper respiratory infection
	Less frequent	Pharyngeal discomfort, laryngitis, dyspnoea, bronchitis, epistaxis, rhinitis, respiratory congestion
Gastro-intestinal disorder	Frequent	Diarrhoea, nausea, abdominal pain, dyspepsia
	Less frequent	Constipation, dental pain, dry mouth, flatulence, gastritis, vomiting, obstipation
	Frequency unknown	Pancreatitis, gastric irritation
Hepatobiliary disorders	Frequency unknown	Liver function abnormalities

System Organ Class	Frequency	Undesirable effects
Skin and subcutaneous tissue disorders	Less frequent	Rash, alopecia, dermatitis, dry skin, erythema, flushing, photosensitivity, pruritus, urticaria sweating
	Frequency unknown	Purpura
Musculoskeletal, connective tissue and bone disorders	Frequent	Back pain, muscle cramps, leg pain, myalgia
	Less frequent	Arm pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, coxalgia, fibromyalgia, muscle weakness
	Frequency unknown	Rhabdomyolysis, muscle spasm
Renal and urinary disorders	Frequent	Renal impairment, renal failure
	Less frequent	Nocturia, urinary frequency, urinary tract infection
Reproductive system and breast disorders	Less frequent	Decreased libido, erectile dysfunction/ impotence
General disorders and administration site conditions	Frequent	Asthenia/fatigue, oedema/swelling, chest pain
	Less frequent	Fever
	Frequency unknown	flu-like symptoms, malaise
Investigations	Frequent	Hyperkalaemia, elevations of ALT, mild reduction of haematocrit and haemoglobin, hypoglycaemia
	Less frequent	Mild increase in urea and creatinine serum levels, increase in hepatic enzymes and bilirubin
	Frequency unknown	Hyponatraemia
Hydrochlorothiazide		
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Frequency unknown	Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma)
Blood and the lymphatic system	Less frequent	Thrombocytopenia, leukopenia, agranulocytosis, haemolytic anaemia,

System Organ Class	Frequency	Undesirable effects
disorders		aplastic anaemia, purpura
Immune system disorders	Frequency unknown	Anaphylactic reaction
Metabolic and nutrition disorders	Less frequent	Anorexia; hyperuricaemia, hyperglycaemia, hypokalaemia, hyponatraemia
Psychiatric disorders	Less frequent	Insomnia
	Frequency unknown	Restlessness
Nervous System Disorders	Less frequent	Paraesthesia; headache
Eye disorders	Less frequent	Transient blurred vision, xanthopsia
Ear and labyrinth disorders	Frequency unknown	Vertigo
Vascular Disorders	Less frequent	Hypotension, (including orthostatic hypotension), necrotizing angiitis (vasculitis, cutaneous vasculitis)
Respiratory, thoracic and mediastinal disorders	Less frequent	Respiratory distress including pneumonitis and pulmonary oedema
Gastro-intestinal Disorders	Less frequent	Nausea; vomiting, diarrhoea; constipation, pancreatitis, sialoadenitis, spasms
	Frequency unknown	Gastric irritation
Hepato-Biliary disorders	Less frequent	Jaundice (intrahepatic cholestatic jaundice), pancreatitis
Skin and subcutaneous tissue disorders	Less frequent	Rash; urticaria, photosensitivity, necrotising angiitis (vasculitis and cutaneous vasculitis), toxic epidermal necrolysis.
	Frequency unknown	Cutaneous lupus erythematosus, purpura
Musculoskeletal, connective tissue disorders	Less frequent	Muscle cramps
Renal and urinary disorders	Less frequent	Glycosuria, interstitial nephritis, renal dysfunction, renal failure
General disorders and	Frequency	Fever, dizziness, weakness

System Organ Class	Frequency	Undesirable effects
administration site conditions	unknown	
Post-marketing experience		
Blood and the lymphatic system disorders	Frequency unknown	Thrombocytopenia
Immune system disorders	Frequency unknown	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 in patients treated with losartan and hydrochlorothiazide a contained in HYLOKAT; some of these patients previously experienced angioedema with other medicines including ACE inhibitors.
Nervous system disorders	Frequency unknown	Dysgeusia (reported with losartan)
Vascular disorders	Frequency unknown	Vasculitis, including Henoch-Schoenlein purpura
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Cough
Gastro-intestinal disorders	Frequency unknown	Diarrhoea, vomiting
Hepato-biliary disorders	Frequency unknown	Hepatitis
Skin and subcutaneous tissue disorders	Frequency unknown	Urticaria, erythroderma has been reported with losartan and Photosensitivity has been reported with losartan and hydrochlorothiazide as contained in HYLOKAT
Musculoskeletal, connective tissue, and bone disorders	Frequency unknown	Arthralgia (reported with losartan)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows

continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

LOSARTAN POTASSIUM

Significant lethality was observed in mice and rats after oral administration of 1000 mg/kg (3000 mg/m²) and 2000 mg/kg (11800 mg/m²) (500 and 1000 times ** the maximum recommended daily human dose), respectively.

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 the active metabolite can be removed by haemodialysis.

HYDROCHLOROTHIAZIDE

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digoxin has also been administered, hypokalaemia may accentuate cardiac dysrhythmias. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 7.1.3. Other hypotensives

Pharmacotherapeutic group: Angiotensin II antagonists and diuretics

ATC code: C09DA01

Losartan potassium is an angiotensin II receptor (type AT_1) antagonist and hydrochlorothiazide is a diuretic.

Mechanism of action:

LOSARTAN POTASSIUM

Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin-angiotensin system, and a major determinant of the pathophysiology of hypertension. 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 cell proliferation.

Losartan is a synthetic, orally active compound which binds selectively to the AT1 receptor. Both losartan and its pharmacologically active carboxylic acid metabolite (E-3174) block the actions of angiotensin II, regardless of the source of synthesis.

HYDROCHLOROTHIAZIDE

The mechanism of the antihypertensive effect of thiazides is unknown.

Hydrochlorothiazide, when used as a diuretic affects the distal renal tubular mechanism of electrolyte reabsorption. Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by loss of potassium, magnesium and bicarbonate.

LOSARTAN POTASSIUM-HYDROCHLOROTHIAZIDE

Losartan and hydrochlorothiazide are additive in their antihypertensive efficacy.

5.2 Pharmacokinetic properties

LOSARTAN POTASSIUM

Absorption:

Following oral administration, losartan 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 losartan was administered with a standardised meal.

Distribution:

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

Biotransformation:

About 14 % of an intravenously- or orally-administered dose of losartan is converted to its active metabolite.

Elimination:

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 potassium 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.

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

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 metabolite can be removed by haemodialysis

HYDROCHLOROTHIAZIDE

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. Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney. At least 61 % of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

LOSARTAN POTASSIUM-HYDROCHLOROTHIAZIDE

In a pharmacokinetic interaction study, hydrochlorothiazide 12,5 mg did not alter the pharmacokinetics of losartan 50 mg and vice versa.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Contains: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinised starch and Opadry yellow 20A52135/ Instacoat universal yellow A05G13052.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months from the date of manufacturing for Blister pack and HDPE 90s

24 months from the date of manufacturing for HDPE 30s pack

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light and moisture.

Keep the blister in the carton until required for use.

Keep the containers tightly closed.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Blister pack:

Tablets are packed in cold form laminate, 25 µm OPA/45 µm aluminum foil/60 µm PVC and plain 25 µm aluminum foil/6-8 gsm HSL as the lidding material.

Pack sizes include 10 and 30 tablets.

HDPE container pack:

Round, white, HDPE container 40 cc or 75 cc with 33 mm or 38 mm neck finish, containing 30 or 90 tablets, closed with child resistant closure, with pulp and heat seal liner 33 mm or 38 mm and packed in a pre-printed unit carton.

Pack sizes include 30 or 90 tablets.

Not all packs and pack sizes are necessarily marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

MACLEODS PHARMACEUTICALS SA (PTY) LTD

Office block 1, Bassonia Estate Office Park (East),

1 Cussonia Drive, Bassonia Rock, Ext. 12,

Alberton, South Africa.

8. REGISTRATION NUMBER(S)

HYLOKAT 50/12.5: 47/7.1.3/0887

HYLOKAT 100/25: 47/7.1.3/0888

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 MAY 2022

10. DATE OF REVISION OF THE TEXT

14 MARCH 2023

PM0047-01

Vanita Rajool

Digitally signed by Vanita Rajool
DN: cn=Vanita Rajool, o=Macleods Pharmaceuticals SA (Pty) Ltd., ou=Responsible Pharmacist, email=vanitar@macleodspharma.com, c=ZA
Date: 2023.06.26 12:05:18 +02'00'