MODULE 1.3.1.1 – Package Insert

Product proprietary name:	***Losaar Plus 50/12,5 & Losaar Plus 100/25***
Dosage form and strength:	***50/12,5 mg & 100/25 mg Losartan-Hydrochlorothiazide per Tablet***
Applicant/PHCR:	***Accord Healthcare (Pty) Ltd***

SCHEDULING STATUS:

S3

PROPRIETARY NAME AND DOSAGE FORM:

LOSAAR PLUS 100 /25 (tablets)

LOSAAR PLUS 50 /12,5 (tablets)

COMPOSITION:

- **Losaar Plus 50/12,5 mg:**

  Each tablet contains: 50 mg losartan potassium and 12,5 mg hydrochlorothiazide

- **Losaar Plus 100/25 mg:**

  Each tablet contains: 100 mg losartan potassium and 25 mg hydrochlorothiazide

Contains lactose monohydrate.

PHARMACOLOGICAL CLASSIFICATION:

A 7.1.3 Other hypotensives

PHARMACOLOGICAL ACTION:

LOSAAR PLUS combines an angiotensin II receptor (type AT_1) antagonist losartan and a diuretic hydrochlorothiazide.

LOSARTAN

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 AT_1 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 AT_1 receptor. Both losartan and its pharmacologically active carboxylic acid metabolite (E-3174) block the actions of angiotensin II regardless of the source of synthesis. Losartan binds selectively to the AT_1 receptor and does not bind to or block other hormone receptors or ion channels important in cardiovascular regulation.

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Initials:

HYDROCHLOROTHIAZIDE

The mechanism of the antihypertensive effect of thiazides is unknown.

Thiazides do not usually affect normal blood pressure. Hydrochlorothiazide is a thiazide diuretic and antihypertensive agent. It affects the distal renal tubular mechanism of electrolyte re-absorption. Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by excretion of potassium, magnesium and bicarbonate. Excretion of calcium is reduced. After oral administration diuresis begins within 2 hours and peaks in about 4 hours and lasts about 6 to 12 hours.

LOSARTAN POTASSIUM-HYDROCHLOROTHIAZIDE

Losartan and hydrochlorothiazide are additive in their antihypertensive efficacy.

Pharmacokinetics

LOSARTAN

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.

No clinically significant effect on the plasma concentration of losartan was observed when losartan was administered with a standardised meal.

Distribution

Both losartan and its active metabolite are 99 % and more bound to plasma proteins, primary albumin. The volume of distribution of losartan is 34 litres.

Metabolism

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

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Initials:

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 poly-exponentially 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 ^{14}C-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 barrier but not the blood-brain barrier.

LOSARTAN POTASSIUM-HYDROCHLOROTHIAZIDE

Hydrochlorothiazide does not alter the pharmacokinetics of losartan and vice versa.

INDICATIONS:

LOSAAR PLUS is indicated for the treatment of hypertension in patients established on identical doses of the individual agents.

CONTRA-INDICATIONS:

LOSAAR PLUS is contra-indicated in patients who are hypersensitive to any component of this product.

Because of the hydrochlorothiazide component, this product is contra-indicated:

- in patients with anuria or hypersensitivity to other sulfonamide-derived medicines.

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Initials:

- Sensitivity to any of the components of LOSAAR PLUS
- 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)
- Moderate to severe renal function impairment (creatinine clearance less than 30 ml/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 with LOSAAR PLUS should not be given to patients with Addison's disease. This therapy is also contra-indicated in patients with severe renal impairment or anuria, and in patients who show hypersensitivity to other sulphonamide-derived medicines
- Lithium therapy: Concomitant administration with LOSAAR PLUS may lead to toxic blood concentrations of lithium
- Pregnancy and lactation (see **WARNINGS AND SPECIAL PRECAUTIONS and PREGNANCY AND LACTATION**).

WARNINGS AND SPECIAL PRECAUTIONS:

"Should a woman become pregnant while receiving LOSAAR PLUS, the treatment should be stopped promptly and switched to a different class of medicine (See CONTRA-INDICATIONS and PREGNANCY AND LACTATION)".

See **CONTRA-INDICATIONS.**

Hepatic and renal impairment

LOSAAR PLUS is not recommended for patients with hepatic impairment or severe renal impairment (see

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Initials:

DOSAGE AND DIRECTIONS FOR USE). 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. Other medications that affect the renin-angiotensin system including LOSAAR PLUS may increase blood urea and serum creatine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney (see **CONTRA-INDICATIONS**). These changes in renal function may be reversible upon discontinuation of therapy.

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 LOSAAR PLUS, or a lower starting dose should be used (see **DOSAGE AND DIRECTIONS FOR USE**).

Periodic determination of serum electrolytes should be performed at appropriate intervals as in patients receiving LOSAAR PLUS.

Metabolic and endocrine effects

Hydrochlorothiazide therapy may impair glucose. Dosage adjustment of antidiabetic agents, including insulin, may be required (see **INTERACTIONS**)**.**

Hydrochlorothiazide may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium.

Marked hypercalcemia may be evidence of hidden hyperparathyroidism. LOSAAR PLUS should be discontinued before carrying out tests for parathyroid function. Increases in cholesterol and triglyceride levels may be associated with hydrochlorothiazide therapy. Hydrochlorothiazide therapy may precipitate hyperuricaemia and/or gout in certain patients.

Other

In patients receiving hydrochlorothiazide, sensitivity 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.

LOSAAR PLUS contains lactose and should not be administered to patients with rare hereditary problems, or a

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Initials:

history of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

Effects on ability to drive and use machines

There is no data to suggest that LOSAAR PLUS affects the ability to drive and use machines.

INTERACTIONS:

LOSARTAN POTASSIUM

The antihypertensive effects of LOSAAR PLUS may be potentiated when taken together with other antihypertensive medicines.

- An additive hyperkaleamic effect is possible with potassium supplements, potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride) and other medicines that can cause hyperkalaemia.
- Rifampicin and fluconazole – reduce levels of the active metabolite.
- Non-steroidal anti-inflammatory agents (NSAIDS) – may attenuate the antihypertensive effect of LOSAAR PLUS.

HYDROCHLOROTHIAZIDE

When administered concurrently the following medication may interact with hydrochlorothiazide:

Alcohol, barbiturates, or narcotics: Potentiation of orthostatic hypotension may occur.

Antidiabetic medication: (oral agents and insulin) dosage adjustment of the antidiabetic medicine may be required, as LOSAAR PLUS may increase blood glucose.

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 gastrointestinal tract by up to 85 and 43 percent, respectively. LOSAAR PLUS 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, nondepolarizing (e.g. **tubocurarine):** possible increased responsiveness to the

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Initials:

muscle relaxant.

Lithium: should not be given with diuretics. Hydrochlorothiazide reduces the renal clearance of lithium and adds a high risk of lithium toxicity (see **CONTRA-INDICATIONS**). Refer to the package insert for lithium preparations before use of such preparations with LOSAAR PLUS.

Non-steroidal anti-inflammatory medication: in some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic and antihypertensive effects of loop, potassium-sparing and thiazide diuretics.

PREGNANCY AND LACTATION:

- Safety in pregnancy and lactation has not been established. When pregnancy is planned or confirmed, LOSAAR PLUS should be discontinued as soon as possible. (See **CONTRA-INDICATIONS** and **WARNINGS AND SPECIAL PRECAUTIONS**).
- Medicines affecting the renin-angiotensin system, such as LOSAAR PLUS, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women.
- Women of childbearing age should ensure adequate contraception.

Pregnancy: When pregnancy is detected, LOSAAR PLUS should be discontinued as soon as possible. Not to be used in pregnancy as teratogenicity has been shown, in experimental animals.

Hydrochlorothiazide crosses the placental barrier and appears in cord blood. Foetal or neonatal jaundice and thrombocytopenia have been reported. Hydrochlorothiazide does not prevent development of toxaemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxaemia.

Women of Childbearing Potential: Women of childbearing age should ensure adequate contraception. Medicines affecting the renin-angiotensin system such as losartan, can cause foetal and neonatal morbidity and mortality when administered to pregnant women.

Lactation: Safety and efficacy has not been established, hence LOSAAR PLUS should not be administered to lactating mothers.

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Initials:

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Dosage form and strength:	***50/12,5 mg & 100/25 mg Losartan-Hydrochlorothiazide per Tablet***
Applicant/PHCR:	***Accord Healthcare (Pty) Ltd***

DOSAGE AND DIRECTIONS FOR USE:

The usual starting and maintenance dose of LOSAAR PLUS 50/12,5 is one tablet once daily. For patients who do not respond adequately to LOSAAR PLUS 50/12,5; the dosage may be changed to one tablet of LOSAAR PLUS 100/25 once daily or two tablets of LOSAAR PLUS 50/12,5 once daily. The maximum dose is one tablet of LOSAAR PLUS 100/25 once daily or two tablets of LOSAAR PLUS 50/12,5 once daily.

The maximum antihypertensive effect is attained within three weeks after initiation of therapy. LOSAAR PLUS should not be initiated in patients who are intravascularly volume-depleted (e.g. those treated with high-dose diuretics).

LOSAAR PLUS is not recommended for patients with severe renal impairment or for patients with hepatic impairment (see **WARNINGS AND SPECIAL PRECAUTIONS**). No initial dosage adjustment is necessary for elderly patients. LOSAAR PLUS may be administered with other antihypertensive agents, particularly calcium channel blockers and beta-blockers.

LOSAAR PLUS may be administered with or without food.

SIDE EFFECTS:

The adverse reactions below are classified where appropriate by system organ class and frequency.

Adverse reactions with losartan /hydrochlorothiazide are the following:

LOSARTAN

Blood and lymphatic system disorders

Less Frequent: Anaemia, Henoch-Schönlein purpura, ecchymosis, haemolysis

Immune system disorders

Less Frequent: Anaphylactic reactions, angioedema, urticarial

Metabolism and nutrition disorders

Less Frequent: Anorexia, gout

Psychiatric disorders

Frequent: Insomnia

Less Frequent: Anxiety, anxiety disorder, panic disorder, confusion,

depression, abnormal dreams, sleep disorder, somnolence, memory impairment

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Initials:

Nervous system disorders

Frequent: Headache, dizziness

Less Frequent: Nervousness, paraesthesia, peripheral neuropathy, tremor, migraine, syncope

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

Less Frequent: Hypotension, orthostatic hypotension, sternalgia, angina pectoris, grade II-AV block, cerebrovascular event, myocardial infarction, palpitation, dysrhythmias (atrial fibrillations, sinus bradycardia, tachycardia, ventricular tachycardia, ventricular fibrillation)

Vascular disorders

Less Frequent: Vasculitis

Respiratory, thoracic and mediastinal disorders

Frequent: Cough, upper respiratory infection, nasal congestion, sinusitis, sinus disorder

Less Frequent: Pharyngeal discomfort, pharyngitis, laryngitis, dyspnoea, bronchitis, epistaxis, rhinitis, respiratory congestion

Gastrointestinal disorders

Frequent: Abdominal pain, nausea, diarrhoea, dyspepsia

Less Frequent: Constipation, dental pain, dry mouth, flatulence, gastritis, vomiting

Hepato-biliary disorders

Less Frequent: Hepatitis

Frequency Unknown: Liver function abnormalities

Skin and subcutaneous tissue disorders

Less Frequent: Alopecia, dermatitis, dry skin, erythema, flushing, photosensitivity, pruritus, rash, urticaria, sweating

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Initials:

Musculoskeletal and connective tissue disorders

Frequent: Muscle cramp, back pain, leg pain, myalgia

Less Frequent: Arm pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, coxalgia, fibromyalgia, muscle weakness

Renal and urinary disorders

Less Frequent: Nocturia, urinary frequency, urinary tract infection

Reproductive system and breast disorders

Less Frequent: Decreased libido, impotence

General disorders and administration site conditions

Frequent: Asthenia, fatigue, chest pain

Less Frequent: Facial oedema, fever

Investigations

Frequent: Hyperkalaemia, mild reduction of haematocrit and haemoglobin

Less Frequent: Mild increase in urea and creatinine serum levels

Increase in hepatic enzymes and bilirubin, ALT elevation.

HYDROCHLOROTHAZIDE

Blood and lymphatic system disorders

Less Frequent: Agranulocytosis, aplastic anaemia, haemolytic anaemia, leukopenia, purpura, thrombocytopenia

Immune system disorders

Less Frequent: Anaphylactic reaction

Metabolism and nutrition disorders

Less Frequent: Anorexia, hyperglycaemia, hyperuricaemia, hypokalaemia, hyponatraemia

Psychiatric disorders

Less Frequent: Insomnia

Nervous system disorders

Frequent: Headache, restlessness, vertigo

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Initials:

Eye disorders

Less Frequent: Transient blurred vision, xanthopsia

Vascular disorders

Frequent: Hypotension, including orthostatic hypotension

Less Frequent: Necrotising angiitis (vasculitis, cutaneous vasculitis)

Respiratory, thoracic and mediastinal disorders

Less Frequent: Respiratory distress including pneumonitis and pulmonary oedema

Gastrointestinal disorders

Less Frequent: Sialoadenitis, spasms, stomach irritation, nausea, vomiting, diarrhoea, constipation

Hepato-biliary disorders

Less Frequent: Icterus (intrahepatic cholestasis), pancreatitis

Skin and subcutaneous tissue disorders

Less Frequent: Photosensitivity, urticaria, toxic epidermal necrolysis, rash, purpura

Musculoskeletal and connective tissue disorders

Less Frequent: Muscle cramps and muscle weakness

Renal and urinary disorders

Less Frequent: Glycosuria, interstitial nephritis, renal dysfunction, renal failure

General disorders and administration site conditions

Less Frequent: Fever, dizziness

KNOWN SYMPTOMS OF OVER DOSAGE AND PARTICULARS OF ITS TREATMENT:

LOSARTAN POTASSIUM

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 digitalis has also been

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Initials:

administered, hypokalaemia may accentuate cardiac dysrhythmias. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

IDENTIFICATION:

LOSAAR PLUS 50/12,5 tablets are yellow, oblong, film-coated tablets, scored on one side.

LOSAAR PLUS 100/25 tablets are yellow, round, film-coated tablets, scored on one side.

PRESENTATION:

LOSAAR PLUS 50/12,5: 10 tablets per white PVC/PE/PVDC blister strip, supplied in a pack size of 30.

LOSAAR PLUS 100/25: 10 tablets per white PVC/PE/PVDC blister strip, supplied in a pack size of 30.

STORAGE INSTRUCTIONS:

Store at or below 25 °C. Keep in outer carton until before use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

LOSAAR PLUS 50/12,5: 42/7.1.3/0325

LOSAAR PLUS 100/25: 42/7.1.3/0326

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Accord Healthcare (Pty) Ltd

Tuscany Office Park

6 Coombe Place

Rivonia

Gauteng

South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT:

18 February 2011

5 February 2015

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Initials: