Professional Information

SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

LOSARTAN MACLEODS 50 mg (Film Coated Tablets)

LOSARTAN MACLEODS 100 mg (Film Coated Tablets)

COMPOSITION

Each film coated tablet contains 50 mg/100 mg losartan potassium. Contains lactose.

Excipients: Lactose monohydrate, dried corn starch, povidone, methylene chloride, silicified microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, film coating consisting of hydroxypropyl cellulose, hypromellose and titanium dioxide.

PHARMACOLOGICAL CLASSIFICATION

A 7.1.3 Other hypotensives

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin-angiotensin system, and a major determinant of the pathophysiology of hypotension. Angiotensin II binds to the AT1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys and 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 block the actions of angiotensin II, regardless of the source or route of synthesis.

Losartan binds selectively to the AT1 receptor and does not bind to or block other hormone receptors or ion channels important in the cardiovascular regulation. Furthermore, losartan doses not inhibit ACE (kininase II), the enzyme that degrades bradykinin.

Pharmacokinetic properties

Absorption:

Following oral administration of losartan it is well absorbed and undergoes substantial first pass metabolism by cytochrome P450 enzymes. It is converted, in part, to an active carboxylic acid metabolite that is responsible for most of the angiotensin II receptor antagonism that follows losartan treatment. In addition to the active metabolite, several inactive metabolites are formed. The systemic bioavailability of losartan tablets is approximately 33 %. Mean peak concentrations of losartan and its active metabolite are reached in 1 hr and in 3 to 4 hrs, respectively.

Effect of food:

Food slows absorption of losartan and decreases its C_{max} but has only minor effects on losartan AUC or on the AUC of the metabolite.

Distribution:

Both losartan and its active metabolite are bound to plasma proteins by 99 % or more 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.

Metabolism:

About 14 % of 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 is administered orally, about 4 % of the dose is excreted unchanged in urine, and about 6 % of the dose is excreted in the urine as the active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan doses up to 200 mg.

Following oral administration in normal volunteers, plasma concentrations of losartan and its metabolite decline polyexponentially with a terminal half-life of about 2 hrs and 6 to 9 hrs, respectively.

Both biliary and urinary excretion contributes 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. Following an intravenous dose of 14C-labelled losartan in man, about 43 % of radioactivity is recovered in the urine and 50 % in the faeces.

Characteristics in patients

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. Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 ml/min. Compared to patients with normal renal function, the AUC for losartan is approximately 2-fold greater in haemodialysis patients. Plasma concentrations of the active metabolite are not altered in patients with renal impairment or in haemodialysis patients. Neither losartan nor the active metabolite can be removed by haemodialysis.

INDICATIONS

LOSARTAN MACLEODS is indicated for the treatment of hypertension.

Renal protection in type 2 diabetic patients with hypertension and proteinuria.

CONTRA-INDICATIONS

- Hypersensitivity to any of the ingredients of **LOSARTAN MACLEODS**.
- 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 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 (see INTERACTIONS).
- Porphyria.
- Lithium therapy: Concomitant administration with **LOSARTAN MACLEODS** may lead to toxic blood concentrations of lithium (see INTERACTIONS).
- Pregnancy and lactation (see HUMAN REPRODUCTION).
- The concomitant use of **LOSARTAN MACLEODS** with aliskiren-containing products is contraindicated. (see WARNINGS & SPECIAL PRECAUTIONS AND INTERACTIONS)[1]
- Concomitant use of fluoroquinolones with ACE inhibitors/Renin-Angiotensin blockers is contraindicated in patients with moderate to severe renal impairment[2].

Paediatric use

Safety and effectiveness in children have not been established.

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[1] PACKAGE INSERTS FOR HUMAN MEDICINES STANDARDISED TEXTS: 2.20_PI_standardised_texts_Jun15_v4 July 2015, page 6 of 29, lines 31 - 32

[2] As per SAHPRA letter reference, PVC83 Item #6.6.5 dated 25 March 2019

WARNINGS AND SPECIAL PRECAUTIONS

Should a woman become pregnant while receiving **LOSARTAN MACLEODS**, the treatment must be stopped promptly and changed to a different class of antihypertensive medicine (see CONTRA-INDICATIONS and HUMAN REPRODUCTION).

Serum potassium levels should be monitored regularly.

Hypotension and electrolyte/fluid imbalance

In patients who are intravascularly volume-depleted (e.g. those treated with high-dose diuretics), symptomatic hypotension can occur. These conditions should be corrected prior to administration of **LOSARTAN MACLEODS**, or a lower starting dose should be used.

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed (see SIDE-EFFECTS).

Liver function impairment

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a dose of 25 mg should be considered for patients with a history of hepatic impairment (see DOSAGE AND DIRECTIONS FOR USE).

Renal function impairment

When impaired renal function is present, changes in renal function as a consequence of inhibiting the renin angiotensin system, including renal failure, have been reported in susceptible individuals; in some patients these changes in renal function may be reversible upon discontinuation of therapy.

In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure), treatment with angiotensin converting

enzyme inhibitors has been associated with oliguria and/or progressive uraemia and with acute renal failure and/or death. Similar outcomes have been reported with **LOSARTAN MACLEODS**.

Medicines 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 MACLEODS** (see CONTRA-INDICATIONS).

Porphyria

Limited information is available regarding the effect of antihypertensive medication in patients with porphyria. Safety of **LOSARTAN MACLEODS** in patients with porphyria has not been fully established (see CONTRA-INDICATIONS).

Use in the elderly

In clinical studies there was no age related difference in efficacy or safety profile of losartan.

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

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers (ARBs) 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 **LOSARTAN MACLEODS** and aliskiren is therefore contraindicated (see CONTRAINDICATIONS). **LOSARTAN MACLEODS** should not be used concomitantly with aliskiren. (see CONTRAINDICATIONS)[3].

[3] PACKAGE INSERTS FOR HUMAN MEDICINES STANDARDISED TEXTS: 2.20_PI_standardised_texts_Jun15_v4 July 2015, page 7 of 29, lines 5 - 11

Concomitant use of ACE inhibitors/renin-angiotensin receptor blockers and fluoroquinolones in renal impairment and elderly patients

Concomitant use of ACE inhibitors/renin-angiotensin receptor blockers including **LOSARTAN MACLEODS** and Fluoroquinolones may precipitate acute kidney injury (AKI) in patients, especially those with moderate to severe renal impairment and elderly patients. (See CONTRAINDICATIONS). Renal function should be assessed before initiating treatment, and monitored during treatment, with **LOSARTAN MACLEODS** or ACE inhibitors/renin-angiotensin receptor blockers[4].

Effects on ability to drive and use machines

LOSARTAN MACLEODS may cause dizziness, somnolence and fatigue. Patients should be cautioned about operating hazardous machinery, including motor vehicles until they are reasonably certain that **LOSARTAN MACLEODS** does not adversely affect them.

Lactose intolerance:

LOSARTAN MACLEODS contains lactose and is unsuitable for patients with known hereditary problems, or a history of galactose intolerance, Lapp-lactase deficiency or glucose-galactose malabsorption.

INTERACTIONS

No interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbital, ketoconazole and erythromycin. Rifampicin and fluconazole have been reported to reduce levels of active metabolite. The clinical consequences of these interactions have not been evaluated.

[4] As per SAHPRA letter reference, PVC83 Item #6.6.5 dated 25 March 2019

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 (see CONTRA-INDICATIONS).

Lithium excretion may be reduced (see CONTRA-INDICATIONS).

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of diuretics and other antihypertensive medicines. Therefore, the antihypertensive effect of angiotensin II receptor antagonists may be attenuated by NSAIDs including selective COX-2 inhibitors.

In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, including selective cyclo-oxygenase-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 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 CONTRAINDICATIONS, WARNINGS AND SPECIAL PRECAUTIONS).[5]

Fluoroquinolones:

Concomitant use of ACE inhibitors/renin-angiotensin receptor blockers including **LOSARTAN MACLEODS** and Fluoroquinolones may precipitate acute kidney injury (see CONTRAINDICATIONS). A potential mechanism for the observed interaction has not been

[5] PACKAGE INSERTS FOR HUMAN MEDICINES STANDARDISED TEXTS: 2.20_PI_standardised_texts_Jun15_v4 July 2015, page 7 of 29, lines 12 – 17

identified. Most of the published reports indicate acute interstitial nephritis as the underlying cause of AKI with fluoroquinolones. Interstitial nephritis or other pathology due to a fluoroquinolone could be a trigger for ACE inhibitor-related AKI or more severe AKI leading to admission[6] .

HUMAN REPRODUCTION[7]Safety in pregnancy and lactation has not been established (see CONTRA-INDICATIONS).

Pregnancy

When pregnancy is planned or confirmed **LOSARTAN MACLEODS** should be discontinued. Medicines affecting the renin-angiotensin system, such as **LOSARTAN MACLEODS**, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women.

Women of childbearing age should ensure effective contraception.

If a woman is contemplating, a different class of medicine should be used.

Breastfeeding[8]It is not known whether losartan is excreted in human milk. Safety of breastfeeding in mothers taking losartan has not been established. However, significant levels of losartan and the active metabolites were shown to be present in rat milk.

DOSAGE AND DIRECTIONS FOR USE

LOSARTAN MACLEODS may be administered with or without food.

LOSARTAN MACLEODS may be administered with other antihypertensive agents.

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[6] Reference 1: Savage R: Ciprofloxacin, Enalapril and Acute Kidney Injury: Strengthening of a Drug Interaction Signal. SIGNAL 2017, Uppsala Monitoring Centre and New Zealand, Page 10, Column 1, line 1 - 14.

[7] PREGNANCY AND LACTATION modified as per Regulation 11, Vol. 626, 25 August 2017, No. 41064.

[8] PREGNANCY AND LACTATION modified as per Regulation 11, Vol. 626, 25 August 2017, No. 41064.

Hypertension

The usual starting and maintenance dose is 50 mg once daily. The maximal anti-hypertensive effect is attained 3 - 6 weeks after initiation of therapy. The dose may be increased to 100 mg once daily.

For patients with intravascular volume-depletion (e.g. those treated with high-dose diuretics), a starting dose of 25 mg once daily should be considered (see WARNINGS AND SPECIAL PRECAUTIONS).

No initial dosage adjustment is necessary for elderly patients or for patients with mild to moderate renal impairment, including patients on dialysis. A lower dose should be considered for patients with a history of hepatic impairment (see WARNINGS AND SPECIAL PRECAUTIONS).

Renal Protection in Type 2 diabetic patients with hypertension and proteinuria

The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily based on blood pressure response. **LOSARTAN MACLEODS** may be administered with other antihypertensive agents (e.g. diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycaemic agents (e.g. sulfonylurea, glitazones and glucosidase inhibitors).

SIDE-EFFECTS

Infections and infestations

Frequent: Upper respiratory tract infection

Psychiatric disorders

Frequent: Insomnia

Nervous system disorders

Frequent: Headache

Less frequent: Dizziness, somnolence, sleep disorders

Ear and labyrinth disorders:

Less frequent: Vertigo

Cardiac disorders

Frequent: Palpitation, tachycardia

Less frequent: Angina pectoris

Vascular disorders

Frequent: Orthostatic hypotension

Respiratory, thoracic and mediastinal disorders

Frequent: Cough, pharyngitis, nasal congestion, sinus disorder

Gastro-intestinal disorders

Frequent: Diarrhoea, nausea, abdominal pain, dyspepsia

Skin and subcutaneous tissue disorders

Less frequent: Rash

Musculoskeletal, connective tissue and bone disorders

Frequent: Back pain, muscle cramps

General disorders and administration site conditions

Frequent: Asthenia/fatigue, oedema/swelling, chest pain

Investigations

Less frequent: Hyperkalaemia, elevations of ALT

The following adverse reactions have been reported in post-marketing experience; they are derived from spontaneous reports for which precise incidences cannot be determined, therefore the frequency is unknown.

Blood and lymphatic system disorders

Anaemia

Immune system disorders

Anaphylactic reactions, angio-oedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue

Nervous system disorders

Migraine, disgeusia

Vascular disorders

Vasculitis, including Henoch-Schönlein purpura

Respiratory, thoracic and mediastinal disorders

Cough

Hepato-biliary disorders

Hepatitis

Skin and subcutaneous tissue disorders

Urticaria, pruritus, erythoderma

Musculoskeletal, connective tissue and bone disorders

Myalgia, arthralgia

Investigations

Liver function abnormalities

Haematological disorders

Thrombocytopenia

Gastro-intestinal disorders

Vomiting

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Signs and symptoms

Limited data are available in regard to overdosage in humans. The most likely manifestations 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.

IDENTIFICATION

For LOSARTAN MACLEODS 50 mg

White to off white oval shaped biconvex film coated tablets having ‘CL14’ debossed on one side and break line on other side.

For LOSARTAN MACLEODS 100 mg

White to off white oval shaped biconvex film coated tablets having ‘CL17’ debossed on one side and break line on other side.

PRESENTATION

HDPE container pack of 30 tablets: The tablets are packed in a white HDPE container with a white, child resistant with pulp and heat seal liner, polypropylene closure.

Cold formed aluminium blister pack of 10 tablets. Pack of 30s.

The HDPE container and blisters are packed in a pre-printed outer carton.

STORAGE INSTRUCTIONS

Store in a dry place at or below 30 °C. Protect from light. Keep container tightly closed. Keep the blister in the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

LOSARTAN MACLEODS 50 mg: 46/7.1.3/0205

LOSARTAN MACLEODS 100 mg: 46/7.1.3/0206

NAME AND BUSINESS ADDRESS OF the holder of the certificate of registration

Macleods Pharmaceuticals SA (Pty)

Office Block 1, Bassonia Estate Office Park (East)1 Cussonia Drive, Bassonia Rock, Ext 12 Alberton, South Africa[9]

DATE OF PUBLICATION OF THE PACKAGE INSERT

Date of registration: 6 August 2015

The date of the most recently revised package insert as approved by SAHPRA:

20 December 2019