Clean amended proposed professional information for LOSARTAN BIOTECH 50

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

LOSARTAN BIOTECH 50 film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LOSARTAN BIOTECH 50: Each film-coated tablet contains 50 mg losartan potassium.

Excipients with known effect:

Contains sugar: Lactose monohydrate.

Each film-coated tablet contains 2,16 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

White, oval, film-coated tablets with one notch on each side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LOSARTAN BIOTECH 50 is indicated for:

- The treatment of hypertension.
- Renal protection in type 2 diabetic patients with hypertension and proteinuria.

4.2 Posology and method of administration

Posology

The usual starting and maintenance dose is 50 mg once daily for most patients. The maximum antihypertensive effect is achieved 3 to 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 section 4.4).

Special populations

No initial dosage adjustment is necessary for elderly patients or for patients with renal impairment, including patients on dialysis. A lower dose should be considered for patients with a history of hepatic impairment (see section 4.4).

Children and adolescents

The safety and efficacy of LOSARTAN BIOTECH 50 have not been established in children (see section 4.3).

Method of administration

LOSARTAN BIOTECH 50 may be administered with other antihypertensive medicines of a different class.

LOSARTAN BIOTECH 50 may be administered with or without food.

4.3 Contraindications

- Hypersensitivity to losartan potassium or any of the excipients listed in section 6.1.
- Pregnancy and lactation (see section 4.6). LOSARTAN BIOTECH 50 should be discontinued as soon as possible when pregnancy is suspected.
- History of angioedema related to previous therapy with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor antagonists, such as LOSARTAN BIOTECH 50: These

patients must never again be given these medicines.

- Hereditary or idiopathic angioedema.
- Hypertrophic obstructive cardiomyopathy.
- LOSARTAN BIOTECH 50 is not recommended for patients with severe renal impairment (creatinine clearance less than 30 mL/min) or for patients with hepatic impairment.
- Aortic stenosis, left ventricular outflow tract obstruction.
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Concomitant therapy with potassium-sparing diuretics, such as spironolactone, triamterene and amiloride (see section 4.5).
- Porphyria.
- Lithium therapy: Concomitant administration with LOSARTAN BIOTECH 50 may lead to toxic blood concentrations of lithium (see section 4.5).
- The concomitant use of LOSARTAN BIOTECH 50 with aliskiren-containing products is contraindicated (see section 4.4).
- The safety and efficacy of LOSARTAN BIOTECH 50 have not been established in children.

4.4 Special warnings and precautions for use

Should a woman become pregnant while taking LOSARTAN BIOTECH 50, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see sections 4.3 and 4.6).

Hypotension and electrolyte/fluid imbalance

Symptomatic hypotension may occur after initiation and after increasing the dose of LOSARTAN BIOTECH 50.

Patients who are volume- and/or sodium-depleted (e.g. those treated with high-dose diuretics, dietary salt restriction, diarrhoea or vomiting) may experience hypotension. These conditions should be corrected prior to administration of LOSARTAN BIOTECH 50 or a lower starting dose

should be used (see section 4.2).

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. Since hyperkalaemia may occur, serum-potassium concentrations as well as creatinine clearance values should be closely monitored, especially in the elderly and patients with heart failure or renal impairment (creatinine clearance 30 – 50 mL/min).
The concomitant use of potassium-sparing diuretics, potassium supplements, potassium-containing salt substitutes, or other medicines that may increase serum potassium (e.g. trimethoprim-containing medicines) with LOSARTAN BIOTECH 50 should be avoided (see sections 4.3 and 4.5).

Hepatic impairment

LOSARTAN BIOTECH 50 must not be administered in patients with hepatic impairment (see sections 4.3 and 5.2).

Renal 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 LOSARTAN BIOTECH 50 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 ACE inhibitors has been associated with oliguria and/or progressive azotaemia and (less frequently) with acute renal failure and/or death. Similar outcomes are likely with LOSARTAN BIOTECH 50 therapy.

Medicines affecting 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 (see section

4.3). These changes in renal function may be reversible upon discontinuation of LOSARTAN BIOTECH 50 therapy.

Porphyria

Limited information is available regarding the effect of antihypertensive medicine in patients with porphyria. The safety of LOSARTAN BIOTECH 50 in patients with porphyria has not been fully established (see section 4.3).

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

There is evidence that the concomitant use of ACE inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreases renal function (including acute renal failure). Dual blockade of RAAS through the combined use of LOSARTAN BIOTECH 50 and aliskiren is therefore contraindicated (see sections 4.3 and 4.5).
LOSARTAN BIOTECH 50 should not be used concomitantly with aliskiren (see section 4.3).

Renal transplantation

There is no experience in patients with recent kidney transplantation.

Primary hyperaldosteronism

Patients with primary aldosteronism will generally not respond to antihypertensive medicines acting through inhibition of the renin-angiotensin system. Therefore, the use of LOSARTAN BIOTECH 50 is not recommended.

Coronary heart disease and cerebrovascular disease

As with any antihypertensive medicine, excessive blood pressure decrease in patients with ischaemic cardiovascular and cerebrovascular disease could result in a myocardial infarction or stroke.

Heart failure

In patients with heart failure, with or without renal impairment, there is, as with other medicines acting on the renin-angiotensin system, a risk of severe arterial hypotension and (often acute) renal impairment.

There is no sufficient therapeutic experience with LOSARTAN BIOTECH 50 in patients with heart failure and concomitant severe renal impairment, in patients with severe heart failure (New York Heart Association class IV) as well as in patients with heart failure and symptomatic life-threatening cardiac arrhythmias. Therefore, LOSARTAN BIOTECH 50 should be used with caution in these patient groups. The combination of LOSARTAN BIOTECH 50 with a beta-blocker should be used with caution (see section 5.1).

Pregnancy

LOSARTAN BIOTECH 50 is contraindicated in pregnancy (see sections 4.3 and 4.6).

Other warnings and precautions

As observed for ACE inhibitors, LOSARTAN BIOTECH 50 and the other angiotensin antagonists are less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low renin states in the black hypertensive population.

Excipient warnings

LOSARTAN BIOTECH 50 contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take LOSARTAN BIOTECH 50.

LOSARTAN BIOTECH 50 contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say it is essentially sodium free.

4.5 Interaction with other medicines and other forms of interaction

As with other medicines that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (e.g. amiloride, triamterene, spironolactone), potassium-containing medicines, medicines which may increase potassium levels (e.g. heparin, trimethoprim-containing medicines), potassium supplements or salt substitutes containing potassium with LOSARTAN BIOTECH 50 may result in hyperkalaemia, since reduction of aldosterone production induced by LOSARTAN BIOTECH 50 may lead to elevation of serum potassium (see sections 4.3 and 4.4).

Dual blockade of the 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 (including acute renal failure) compared to the use of a single RAAS-acting medicine (see sections 4.3 and 4.4).

Other antihypertensive medicines may increase the hypotensive action of LOSARTAN BIOTECH 50. Concomitant use with other medicines which may induce hypotension as an adverse reaction (e.g. tricyclic antidepressants, antipsychotics, baclofen and amifostine) may increase the risk of hypotension.

Losartan, as contained in LOSARTAN BIOTECH 50, is predominately metabolised by cytochrome P450 (CYP) 2C9 to the active carboxylic acid metabolite. Fluconazole (an inhibitor of CYP2C9) decreases the exposure to the active metabolite. Concomitant treatment with losartan and rifampicin (inducer of metabolism enzymes) reduces the plasma concentration of the active metabolite.

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Very rare cases have also been reported with angiotensin II receptor antagonists. Co-administration of lithium and LOSARTAN BIOTECH 50 should be undertaken with caution. If this combination proves essential, monitoring of serum lithium

levels is recommended during concomitant use.

When angiotensin II antagonists are administered simultaneously with anti-inflammatory medicines, nonsteroidal anti-inflammatory drugs (NSAIDs) (i.e. selective cyclooxygenase-2 (COX-2) inhibitors and especially indometacin), acetylsalicylic acid at anti-inflammatory doses and non-selective NSAIDs, attenuation of the antihypertensive effect of LOSARTAN BIOTECH 50 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 pre-existing poor renal function. The combination should be administered with caution, especially in elderly patients. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Concurrent use with sympathomimetics may reduce the antihypertensive effects of LOSARTAN BIOTECH 50.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established (see section 4.3).

When pregnancy is planned or confirmed LOSARTAN BIOTECH 50 should be discontinued. Medicines affecting the renin-angiotensin system, such as LOSARTAN BIOTECH 50, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women.

Women of childbearing age should ensure adequate contraception.

Breastfeeding

The use of LOSARTAN BIOTECH 50 during breastfeeding is contraindicated as the safety has not been established (see section 4.3).

4.7 Effects on ability to drive and use machines

LOSARTAN BIOTECH 50 may cause side effects, such as dizziness and drowsiness, which can affect the ability to drive a vehicle or use machines (see section 4.8). This applies particularly at the start of treatment or when the dose is increased.

4.8 Undesirable effects

List of adverse reactions

Infections and infestations

Frequent: Upper respiratory infection.

Blood and lymphatic system disorders

Frequent: Decreased haemoglobin concentrations.

Less frequent: Symptomatic anaemia.

Metabolism and nutrition disorders

Frequent: Hyperkalaemia.

Less frequent: Hyponatraemia.

Psychiatric disorders

Less frequent: Insomnia.

Nervous system disorders

Frequent: Headache, dizziness.

Less frequent: Somnolence, sleep disorders, migraine.

Ear and labyrinth disorders

Frequent: Vertigo.

Cardiac disorders

Less frequent: Angina pectoris, palpitations.

Vascular disorders

Less frequent: Hypotension*, orthostatic hypotension*.

Respiratory, thoracic and mediastinal disorders

Less frequent: Cough (dry), nasal congestion, pharyngitis, sinus disorder.

Gastrointestinal disorders

Less frequent: Diarrhoea, dyspepsia, nausea, abdominal pain, obstipation.

Hepatobiliary disorders

Less frequent: Raised liver enzymes values, severe acute hepatotoxicity, cholestasis, hepatitis.

Skin and subcutaneous tissue disorders

Less frequent: Urticaria, rash, atypical cutaneous lymphoid infiltrates.

Musculoskeletal and connective tissue disorders

Less frequent: Back pain, muscle cramps, leg pain, rhabdomyolysis, myalgia.

General disorders and administration site conditions

Less frequent: Asthenia/fatigue*, chest pain and oedema/swelling.

Investigations

Frequent: Hypoglycaemia*.

** Reported frequently only in type 2 diabetic patients with hypertension and proteinuria.*

Post-marketing experience

Blood and lymphatic system disorders

Frequency unknown: Neutropenia, thrombocytopenia.

Immune system disorders

Frequency unknown: Hypersensitivity reactions, anaphylactic reactions, angioedema (involving swelling of the larynx, glottis, face, lips, pharynx and/or tongue (causing airway obstruction)) had been reported less frequently in patients treated with LOSARTAN BIOTECH 50; some of these patients previously experienced angioedema with ACE inhibitors and angiotensin receptor blockers.

Psychiatric disorders

Frequency unknown: Depression.

Nervous system disorders

Frequency unknown: Dysgeusia.

Ear and labyrinth disorders

Frequency unknown: Tinnitus.

Cardiac disorders

Frequency unknown: Tachycardia.

Vascular disorders

Frequency unknown: Vasculitis (including Henoch-Schönlein purpura).

Gastrointestinal disorders

Frequency unknown: Complete taste loss, acute pancreatitis.

Hepatobiliary disorders

Frequency unknown: Liver function abnormalities.

Skin and subcutaneous tissue disorders

Frequency unknown: Pruritis, erythroderma, photosensitivity.

Musculoskeletal and connective tissue disorders

Frequency unknown: Arthralgia.

Renal and urinary disorders

Frequency unknown: Impaired renal function.

Reproductive system and breast disorders

Frequency unknown: Erectile dysfunction/impotence.

General disorders and administration site conditions

Frequency unknown: Malaise.

Description of selected adverse reactions

As a consequence of inhibiting the RAAS, changes in renal function have been reported in patients at risk. These changes may be reversible upon discontinuation of LOSARTAN BIOTECH 50

therapy (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of LOSARTAN BIOTECH 50 is important. It allows continued monitoring of the benefit/risk balance of LOSARTAN BIOTECH 50. 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

Symptoms

The symptoms of an overdosage of LOSARTAN BIOTECH 50 would be hypotension and tachycardia. Bradycardia could occur from parasympathetic (vagal) stimulation.

Treatment

If symptomatic hypotension should occur, supportive treatment should be instituted.
Measures are depending on the time of medicine intake as well as the kind and severity of symptoms. Stabilisation of the cardiovascular system should be given priority. After oral intake the administration of a sufficient dose of activated charcoal is indicated. Afterwards, close monitoring of the vital parameters should be performed and corrected, if necessary.
Neither LOSARTAN BIOTECH 50 nor the active metabolite can be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A7.1.3 Other hypotensives.

Pharmacotherapeutic group: Angiotensin II antagonists, plain.

ATC code: C09CA01.

Losartan is a synthetic nonpeptide oral angiotensin II receptor antagonist with high affinity and selectivity for the AT_1 receptor. 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 selectively blocks the AT_1 receptor. *In vitro* and *in vivo* losartan and its pharmacologically active carboxylic acid metabolite E-3174 block all physiologically relevant actions of angiotensin II, regardless of the source or route of its synthesis.

Losartan does not have an agonist effect, nor does it block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore, losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, there is no potentiation of undesirable bradykinin-mediated effects.

During administration of losartan, removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity resulting in a 2- to 3-fold increase in angiotensin II in plasma. However, antihypertensive activity and suppression of plasma aldosterone concentration were apparent, indicating effective angiotensin II receptor blockade. After discontinuation of losartan, plasma renin activity and angiotensin II levels declined.

Both losartan and its principal active metabolite have a far greater affinity for the AT_1 receptor than for the AT_2 receptor. The active metabolite is 10 to 40 times more active than losartan on a weight for weight basis.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism to form an active carboxylic acid metabolite (which has greater pharmacological activity than losartan) and some inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33 %. The mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3 to 4 hours, respectively.

Distribution

Both losartan and carboxylic acid metabolite are greater than, or equal to 99 % bound to plasma proteins, primarily albumin. The distribution volume of losartan is 34 litres.

Biotransformation

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-labelled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and 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. Following oral dosing, about 35 % of the dose is excreted in the urine and about 60 % in the faeces. 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. The terminal half-life of losartan and its active metabolite is 2 hours and 6 to 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.

Special populations

In elderly hypertensive patients the plasma concentrations of losartan and its active metabolite do not differ essentially from those found in young hypertensive patients.

In female hypertensive patients the plasma levels of losartan were up to twice as high as in male hypertensive patients, while the plasma levels of the active metabolite did not differ between men and women.

In patients with mild to moderate alcohol-induced hepatic cirrhosis, the plasma levels of losartan and its active metabolite after oral administration were respectively 5 and 1,7 times higher than in young male volunteers (see sections 4.2 and 4.4).

Plasma concentrations of losartan are not altered in patients with a creatinine clearance above 10 mL/min. Compared to patients with normal renal function, the area under the curve (AUC) for losartan is approximately 2-fold greater in patients on haemodialysis.

The 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Colloidal silicon dioxide

Magnesium stearate

Microcrystalline cellulose

Povidone

Sodium starch glycolate.

Film-coating:

Opadry White (OY-L-28900) (containing hypromellose (E464), lactose monohydrate, macrogol 4000 (E1521) and titanium dioxide (E171)).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blister strips in the carton until required for use.

6.5 Nature and contents of container

LOSARTAN BIOTECH 50 film-coated tablets are available in PVC/PVDC aluminium blister strips and/or HDPE containers with PP screw cap, in a pack size of 30 film-coated tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

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8. REGISTRATION NUMBER

A40/7.1.3/0069

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 November 2007

10. DATE OF REVISION OF THE TEXT

09 March 2023