SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

LOSARTAN COMP BIOTECH 50/12,5 film-coated tablets

LOSARTAN COMP BIOTECH 100/25 film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LOSARTAN COMP BIOTECH 50/12,5: Each film-coated tablet contains 50 mg losartan potassium and 12,5 mg hydrochlorothiazide.

LOSARTAN COMP BIOTECH 100/25: Each film-coated tablet contains 100 mg losartan potassium and 25 mg hydrochlorothiazide.

Excipients with known effect:

Contains sugar: Lactose monohydrate.

LOSARTAN COMP BIOTECH 50/12,5: Each film-coated tablet contains 26,9 mg lactose monohydrate.

LOSARTAN COMP BIOTECH 100/25: Each film-coated tablet contains 53,8 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

LOSARTAN COMP BIOTECH 50/12,5: Light yellow, round, biconvex, film-coated tablets. Diameter: 8,0 - 8,3 mm; thickness: 3,3 - 3,8 mm.

LOSARTAN COMP BIOTECH 100/25: Light yellow, round, biconvex, film-coated tablets. Diameter: 10,0 - 10,2 mm; thickness: 4,5 - 5,1 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

The usual dose is one LOSARTAN COMP BIOTECH 50/12,5 film-coated tablet once daily, with or without food. The maximum dose is one LOSARTAN COMP BIOTECH 100/25 film-coated tablet once daily. The maximum antihypertensive effect is attained within three weeks after initiation of therapy.

Special populations

LOSARTAN COMP BIOTECH should not be initiated in patients with intravascular volume depletion (e.g., those treated with high-dose diuretics) (see section 4.3).

Elderly patients

No initial dosage adjustment is necessary for elderly patients.

Hepatic and renal impairment

LOSARTAN COMP BIOTECH is not recommended for patients with a history of hepatic or severe renal impairment (see sections 4.3 and 4.4).

Paediatric population

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

Method of administration

For oral administration.

LOSARTAN COMP BIOTECH may be administered with other antihypertensive medicines, particularly calcium channel blockers and beta-blockers.

4.3 Contraindications

- Hypersensitivity to losartan potassium, other sulphonamide-derived medicines, due to the hydrochlorothiazide component, or to any of the excipients listed in section 6.1.
- A history of angioedema related to previous therapy with angiotensin converting enzyme (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.
- Severe hepatic impairment, cholestasis and biliary obstructive disorders.
- Therapy resistant hypokalaemia or hypercalcaemia.
- Refractory hyponatraemia.
- Symptomatic hyperuricaemia/gout.
- Aortic stenosis.

- Concomitant therapy with potassium-sparing diuretics, such as spironolactone, triamterene or amiloride.
- Porphyria.
- Thiazide diuretics in combination with losartan, as contained in LOSARTAN COMP BIOTECH, should not be given to patients with Addison's disease.
- Anuria.
- Concomitant administration with lithium therapy may lead to toxic blood concentrations of lithium.
- Concomitant use of aliskiren-containing medicines in patients with diabetes mellitus or renal impairment (glomerular filtration rate (GFR) < 60 mL/min/1,73 m^2) (see section 4.5).
- Pregnancy and lactation (see section 4.6).
- The safety and efficacy of LOSARTAN COMP BIOTECH have not been established in children.
- Patients with a history of previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and lip.

4.4 Special warnings and precautions for use

Losartan potassium

Hypotension and intravascular volume depletion

Symptomatic hypotension, especially after the first dose, may occur in patients who are intravascularly volume- and/or sodium-depleted (e.g., those treated with high-dose diuretics, dietary salt restriction, or experiencing diarrhoea or vomiting). These conditions should be corrected prior to administration of LOSARTAN COMP BIOTECH, or a lower starting dose should be used (see sections 4.2 and 4.3).

Electrolyte imbalances

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. Since hypokalaemia may occur, serum potassium concentrations and creatinine clearance values should be closely monitored, especially in elderly patients 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 COMP BIOTECH should be avoided (see sections 4.3 and 4.5).

Hepatic impairment

LOSARTAN COMP BIOTECH is not recommended for patients with hepatic impairment. There is no therapeutic experience with LOSARTAN COMP BIOTECH in patients with severe hepatic impairment. Therefore, LOSARTAN COMP BIOTECH is contraindicated in patients with severe hepatic impairment (see sections 4.2 and 4.3).

Renal impairment

LOSARTAN COMP BIOTECH should not be used in patients with severe renal impairment (see section 4.3).

Changes in renal function, including renal failure, have been reported due to inhibition of the renin-angiotensin system. 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 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 COMP BIOTECH therapy.

The blood urea and serum creatinine may be increased in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney during treatment with LOSARTAN COMP BIOTECH (see section 4.3). These changes in renal function may be reversible upon discontinuation of therapy.

Renal transplantation

There is no experience in patients with recent kidney transplantation.

Primary hyperaldosteronism

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

Coronary heart disease and cerebrovascular disease

As with any antihypertensive medicines, 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.

Ethnic differences

As observed for ACE inhibitors, LOSARTAN COMP BIOTECH and the other angiotensin antagonists are apparently 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.

Pregnancy

Women of childbearing age should ensure adequate contraception.

Should a woman become pregnant while receiving LOSARTAN COMP BIOTECH, the treatment should be

stopped immediately and switched to a different class of antihypertensive medicine (see sections 4.3 and 4.6).

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 decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.3 and 4.5).

ACE inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Hydrochlorothiazide

Hypotension and electrolyte/fluid imbalance

As with all antihypertensive therapy, symptomatic hypotension may occur in some patients. Patients should be observed for clinical signs of fluid or electrolyte imbalance, e.g., volume depletion, hyponatraemia, hypochloraemic alkalosis, hypomagnesaemia or hypokalaemia, which may occur during intercurrent diarrhoea or vomiting. Periodic determination of serum electrolytes should be performed at appropriate intervals in such patients. Dilutional hyponatraemia may occur in oedematous patients in hot weather.

Metabolic and endocrine effects

Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic medicines, including insulin, may be required (see section 4.5).

Hydrochlorothiazide in LOSARTAN COMP BIOTECH may decrease urinary calcium excretion and may

cause intermittent and slight elevation of serum calcium. Marked hypocalcaemia may be evidence of hidden hyperparathyroidism. LOSARTAN COMP BIOTECH should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with hydrochlorothiazide in LOSARTAN COMP BIOTECH.

LOSARTAN COMP BIOTECH therapy may precipitate hyperuricaemia and/or gout in certain patients.

Eye disorders

Choroidal effusion, acute myopia and secondary angle-closure glaucoma:

Sulphonamide or sulphonamide-derived medicines can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of therapy initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue LOSARTAN COMP BIOTECH intake as soon as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulphonamide or penicillin allergy.

Hepatic impairment

Hydrochlorothiazide, as contained in LOSARTAN COMP BIOTECH, should be used with caution in patients with impaired hepatic function or progressive liver disease, as it may cause intrahepatic cholestasis, and since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

LOSARTAN COMP BIOTECH is contraindicated for patients with severe hepatic impairment (see section 4.3).

Non-melanoma skin cancer

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

Patients taking LOSARTAN COMP BIOTECH 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 or adequate protection in the case of exposure, should be advised to the patients in order to minimise the risk of skin cancer. Suspicious skin lesions should be promptly examined, potentially including histological examinations of biopsies. LOSARTAN COMP BIOTECH should not be used by patients who have had previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and/or lip (see section 4.3).

Other

In patients receiving LOSARTAN COMP BIOTECH, sensitivity reactions to thiazides 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 LOSARTAN COMP BIOTECH.

Excipient warning

LOSARTAN COMP BIOTECH contains lactose monohydrate.

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

4.5 Interaction with other medicines and other forms of interaction

Losartan potassium

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

As with other medicines which affect the excretion of sodium, lithium excretion may be reduced (see section 4.3).

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).

The antihypertensive effects of LOSARTAN COMP BIOTECH may be potentiated by medicines that lower blood pressure (e.g., tricyclic antidepressants, antipsychotics, baclofen, amifostine).

Rifampicin and fluconazole have been reported to reduce the levels of the active metabolite of losartan.

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

Nonsteroidal anti-inflammatory drugs (NSAIDs) may antagonise the antihypertensive effect of LOSARTAN

COMP BIOTECH.

Hydrochlorothiazide

When administered concurrently, the following medicines may interact with thiazide diuretics:

Lithium

Should not be given with diuretics (see section 4.3). Diuretic medicines reduce the renal clearance of lithium and add a high risk of lithium toxicity.

Alcohol, narcotics, barbiturates or antidepressants

Potentiation of orthostatic hypotension may occur.

Antidiabetic medicines (oral medicines and insulin)

Treatment with a thiazide may influence the glucose tolerance. Dosage adjustment of the antidiabetic medicine may be required. Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

Other antihypertensive medicines

May produce additive hypotensive effect.

Cholestyramine and colestipol resins

Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively: LOSARTAN COMP BIOTECH should be taken one hour before the intake of the resin.

Corticosteroids or adrenocorticotropic hormone (ACTH)

Concurrent use may intensify electrolyte depletion, particularly hypokalaemia.

Sympathomimetics, such as noradrenaline (norepinephrine)

May decrease the response to sympathomimetic medicines.

Skeletal muscle relaxants, non-depolarising (e.g., tubocurarine)

Possible increased responsiveness to the muscle relaxant.

NSAIDs

May reduce the diuretic, natriuretic and antihypertensive effects of loop, potassium-sparing and thiazide diuretics.

Medicines used in the treatment of gout (e.g., probenecid, sulfinpyrazone, allopurinol)

Dosage adjustment of uricosuric medicines may be necessary, since hydrochlorothiazide may raise the level of serum uric acid. Increased dosage of probenecid or sulfinpyrazone may be necessary. The hydrochlorothiazide in LOSARTAN COMP BIOTECH may increase the incidence of hypersensitivity reactions to allopurinol.

Anticholinergic medicines (e.g. atropine, biperiden)

Increase of the bioavailability to hydrochlorothiazide, in LOSARTAN COMP BIOTECH, by decreasing gastrointestinal motility and stomach emptying rate.

Cytotoxic medicines (e.g., cyclophosphamide, methotrexate)

Hydrochlorothiazide, in LOSARTAN COMP BIOTECH, may reduce the renal excretion of cytotoxic medicines and potentiate their myelosuppressive effects.

Salicylates

In case of high dosages of salicylates, the hydrochlorothiazide in LOSARTAN COMP BIOTECH may enhance the toxic effect of the salicylates on the central nervous system.

Methyldopa

There have been reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide, as in LOSARTAN COMP BIOTECH, and methyldopa.

Ciclosporin

Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout-type complications.

Digoxin

Thiazide-induced hypokalaemia or hypomagnesaemia may favour the onset of digitalis-induced cardiac arrhythmias.

Medicines affected by serum potassium disturbances (e.g., antiarrhythmic medicines, antipsychotic medicines and others)

Periodic monitoring of serum potassium and electrocardiogram (ECG) is recommended when LOSARTAN COMP BIOTECH is administered with medicines affected by serum potassium disturbances (e.g., digoxin glycosides and antiarrhythmic medicines) and with the following torsades de pointes (ventricular tachycardia)-inducing medicines (including some antiarrhythmic medicines), hypokalaemia being a

predisposing factor to torsades de pointes:

- Class IA antiarrhythmic medicines (e.g., quinidine, hydroquinidine, disopyramide).
- Class III antiarrhythmic medicines (e.g., amiodarone, sotalol, dofetilide, ibutilide).
- Some antipsychotic medicines (e.g., thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol).
- Others (e.g., bepridil, cisapride, diphemanil, erythromycin IV, halofantrine, mizolastine, pentamidine, terfenadine, vincamine IV).

Calcium salts

Hydrochlorothiazide, as in LOSARTAN COMP BIOTECH, may increase serum calcium levels due to decreased excretion. Serum calcium levels should be monitored and calcium dosage should be adjusted accordingly.

Laboratory test interactions

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

Carbamazepine

Risk of symptomatic hyponatraemia; clinical and biochemical monitoring is required.

Iodine contrast media

In case of 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

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

When pregnancy is planned or confirmed, LOSARTAN COMP BIOTECH should be discontinued.

Medicines affecting the renin-angiotensin system, such as LOSARTAN COMP BIOTECH, can cause embryonal toxicity, fetal and neonatal morbidity and mortality when administered to pregnant women.

Women of childbearing age should ensure effective contraception.

Breastfeeding

No information is available regarding the use of LOSARTAN COMP BIOTECH during breastfeeding. Therefore, the safety of LOSARTAN COMP BIOTECH during breastfeeding has not been established (see section 4.3).

Hydrochlorothiazide is excreted in human milk. Therefore, the use of LOSARTAN COMP BIOTECH during breastfeeding is contraindicated (see section 4.3).

4.7 Effects on ability to drive and use machines

There are no data to suggest that LOSARTAN COMP BIOTECH affects the ability to drive or use machines. However, when driving vehicles or operating machines, 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

Tabulated summary of adverse reactions

Losartan potassium and hydrochlorothiazide

The following adverse reactions have been reported with losartan-hydrochlorothiazide combination such as LOSARTAN COMP BIOTECH.

Immune system disorders	
Frequency unknown:	Angioedema (involving swelling of the face, lips, pharynx and/or tongue).
Nervous system disorders	
Frequent:	Dizziness.
Hepatobiliary disorders	
Less frequent:	Hepatitis.
General disorders and administration site conditions	
Frequent:	Asthenia/fatigue.
Investigations	
Less frequent:	Hyperkalaemia, elevation of alanine aminotransferase (ALT).

The following adverse reactions have been reported for losartan in clinical studies and post-marketing experience.

Blood and lymphatic system disorders	
Less frequent:	Symptomatic anaemia, Henoch-Schönlein purpura, ecchymosis, haemolysis.
Frequency unknown:	Decreased haemoglobin concentrations, neutropenia, thrombocytopenia.
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), angioedema.
Endocrine disorders	
Less frequent:	Acute pancreatitis.
Metabolism and nutritional 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.
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, second degree atrioventricular (AV) block, cerebrovascular event, myocardial infarction, palpitations, arrhythmias (atrial fibrillation, sinus bradycardia, tachycardia, ventricular tachycardia, ventricular fibrillation).

Vascular disorders	
Less frequent:	Vasculitis.
Frequency unknown:	Dose-related orthostatic effects.
Respiratory, thoracic and mediastinal disorders	
Frequent:	Cough, nasal congestion, pharyngitis, upper respiratory infection, sinus disorder, sinusitis.
Less frequent: .	Pharyngeal discomfort, laryngitis, dyspnoea, bronchitis, epistaxis, rhinitis, respiratory congestion.
Gastrointestinal disorders	
Frequent:	Abdominal pain, diarrhoea, dyspepsia, nausea.
Less frequent:	Taste disturbances or complete taste loss, constipation, dental pain, dry mouth, flatulence, gastritis, vomiting, obstipation.
Hepatobiliary disorders	
Frequency unknown:	Severe acute hepatotoxicity, cholestasis, liver function abnormalities.
Skin and subcutaneous tissue disorders	
Less frequent:	Urticaria, rash, atypical cutaneous lymphoid infiltrates, alopecia, dermatitis, dry skin, erythema, flushing, photosensitivity, pruritis, sweating.
Musculoskeletal and connective tissue 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.
Renal and urinary disorders	
Frequent:	Impaired renal function, 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.
Less frequent:	Facial oedema, fever.
Frequency unknown:	Flu-like symptoms, malaise.
Investigations	
Frequent:	Hyperkalaemia, 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.

The following adverse reactions have been reported for hydrochlorothiazide in clinical studies and post-marketing experience.

Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Frequency unknown:	Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma).
Blood and lymphatic system disorders	
Less frequent:	Leucopenia, agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, purpura.
Immune system disorders	
Less frequent:	Anaphylactic reactions.
Endocrine disorders	
Less frequent:	Pancreatitis.

Metabolism and nutrition disorders	
Frequent:	Electrolyte imbalance (hyponatraemia), hypochloraemic alkalosis, hypokalaemia.
Less frequent:	Anorexia, hyperuricaemia, hyperglycaemia.
Psychiatric disorders	
Less frequent:	Insomnia.
Nervous system disorders	
Frequent:	Cephalalgia.
Less frequent:	Paraesthesia, headache.
Frequency unknown:	Vertigo.
Eye disorders	
Less frequent:	Transient blurred vision, xanthopsia.
Frequency unknown:	Vision disturbances, choroidal effusion, acute myopia, acute angle-closure glaucoma.
Vascular disorders	
Less frequent:	Necrotising angiitis (vasculitis, cutaneous vasculitis), hypotension (including orthostatic hypotension).
Respiratory, thoracic and mediastinal disorders	
Less frequent:	Respiratory distress including pneumonitis and pulmonary oedema.
Gastrointestinal disorders	
Less frequent:	Spasms, gastric irritation, nausea, vomiting, diarrhoea, constipation, sialadenitis.
Frequency unknown:	Gastric cramps.
Hepatobiliary disorders	
Less frequent:	Icterus (intrahepatic cholestasis), pancreatitis, jaundice (intrahepatic

	cholestatic jaundice).
Skin and subcutaneous tissue disorders	
Less frequent:	Photosensitivity, urticaria, rash, toxic epidermal necrolysis
Frequency unknown:	Cutaneous lupus erythematosus.
Musculoskeletal and connective tissue disorders	
Less frequent:	Muscle cramps.
Frequency unknown:	Muscle pain.
Renal and urinary disorders	
Less frequent:	Renal dysfunction, interstitial nephritis, renal failure, glycosuria.
General disorders and administration site conditions	
Less frequent:	Dizziness, weakness, restlessness, fever.

Description of selected adverse reactions

NMSC: Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide and NMSC has been observed (see sections 4.4 and 5.1).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of LOSARTAN COMP BIOTECH is important. It allows continued monitoring of the benefit/risk balance of LOSARTAN COMP BIOTECH. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Losartan potassium

Symptoms

The most likely manifestation of overdosage would be hypotension and tachycardia. Bradycardia could occur from parasympathetic (vagal) stimulation.

Treatment

If symptomatic hypotension should occur, supportive treatment should be instituted. Neither losartan nor the active metabolite can be removed by haemodialysis.

Hydrochlorothiazide

Symptoms

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 arrhythmias.

Treatment

The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A7.1.3 Other hypotensives.

Pharmacotherapeutic group: Angiotensin II antagonists and diuretics.

ATC code: C09DA01.

LOSARTAN COMP BIOTECH is a combination of losartan potassium (an angiotensin II receptor type AT_1 antagonist) and hydrochlorothiazide (a diuretic).

Losartan potassium and hydrochlorothiazide combination

Losartan and hydrochlorothiazide are additive in their antihypertensive efficacy, reducing blood pressure to a greater degree than either component alone. This effect is thought to be a result of the complementary actions of both components. Further, as a result of its diuretic effect, hydrochlorothiazide increases plasma renin activity, aldosterone secretion and the levels of angiotensin II whilst it decreases serum potassium. Administration of losartan blocks all the physiologically relevant actions of angiotensin II and through inhibition of aldosterone could tend to attenuate the potassium loss associated with the diuretic.

Losartan has been shown to have a mild and transient uricosuric effect. Hydrochlorothiazide has been shown to cause modest increases in uric acid. The combination of losartan and hydrochlorothiazide tends to attenuate the diuretic-induced hyperuricaemia.

The antihypertensive effect of LOSARTAN COMP BIOTECH is sustained for a 24-hour period and maintained with continued therapy. Despite the significant decrease in blood pressure, administration of LOSARTAN COMP BIOTECH has no clinically significant effect on heart rate.

LOSARTAN COMP BIOTECH is effective in reducing blood pressure in males and females, blacks and non-blacks and in younger (< 65 years) and older (≥ 65 years) patients. LOSARTAN COMP BIOTECH is effective in all degrees of hypertension.

Losartan

Losartan is a synthetic, orally active non-peptide 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 an important 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 increase in bradykinin-mediated undesirable effects.

During administration of losartan the 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 are apparent, indicating effective angiotensin II receptor blockade. After discontinuation of losartan, plasma renin activity and angiotensin II levels declined within 3 days to the baseline values.

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 mass for mass basis.

In a study specifically designed to assess the incidence of cough in patients treated with losartan as compared to patients treated with ACE inhibitors, the incidence of cough reported by patients receiving losartan or hydrochlorothiazide was similar and significantly less than in patients treated with an ACE inhibitor. In addition, in an overall analysis of 16 double-blind clinical trials in 4 131 patients, the incidence of spontaneously reported cough in patients treated with losartan was similar (3,1 %) to that of patients treated

with placebo (2,6 %) or hydrochlorothiazide (4,1 %), whereas the incidence with ACE inhibitors was 8,8 %.

In non-diabetic hypertensive patients with proteinuria, the administration of losartan potassium significantly reduces proteinuria, fractional excretion of albumin and immunoglobulin G (IgG). Losartan maintains glomerular filtration rate and reduces filtration fraction. Generally, losartan causes a decrease in serum uric acid (usually < 0,4 mg/dL) which was persistent in chronic therapy.

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

In patients with left ventricular failure, 25 mg and 50 mg doses of losartan produced positive haemodynamic and neurohormonal effects characterised by an increase in cardiac index and decreases in pulmonary capillary wedge pressure, systemic vascular resistance, mean systemic arterial pressure and heart rate and a reduction in circulating levels of aldosterone and norepinephrine, respectively. The occurrence of hypotension was dose-related in these patients.

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic and has antihypertensive properties. The mechanism of the antihypertensive effect of hydrochlorothiazide is not fully known. Hydrochlorothiazide does not usually affect normal blood pressure. It affects the distal renal tubular mechanism of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity and increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II and, therefore, co-administration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with thiazide diuretics. Natriuresis may be accompanied by some loss of potassium, magnesium and bicarbonate.

After oral use, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours. The antihypertensive effect persists for up to 24 hours.

NMSC

Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide and NMSC has been observed. One study included a population comprised of 71 533 cases of BCC and of 8 629 cases of SCC matched to 1 430 833 and 172 462 population controls, respectively. High hydrochlorothiazide use (≥ 50,000 mg cumulative) was associated with an adjusted odds ratio (OR) of 1,29 (95 % confidence interval (CI): 1,23 - 1,35) for BCC and 3,98 (95 % CI: 3,68 - 4,31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to hydrochlorothiazide: 633 cases of lip cancer were matched with 63 067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR of 2,1 (95 % CI: 1,7 - 2,6) increasing to an OR of 3,9 (3,0 - 4,9) for high use (~25,000 mg) and an OR of 7,7 (5,7 - 10,5) for the highest cumulative dose (~100,000 mg) (see section 4.4).

5.2 Pharmacokinetic properties

Losartan potassium and hydrochlorothiazide

Hydrochlorothiazide 12,5 mg does not alter the pharmacokinetics of losartan 50 mg and vice versa.

Special populations

The plasma concentrations of losartan and its active metabolite and the absorption of hydrochlorothiazide in elderly hypertensive patients are not significantly different from those in young hypertensive patients.

Losartan

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 other inactive metabolites. The systemic bioavailability of losartan 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 the medicine was administered with a standardised meal.

Distribution

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

Metabolism

About 14 % of an intravenously or orally administered dose is converted to its active metabolite. Mean peak plasma concentrations of losartan and its active metabolite occur in 1 hour and 3 to 4 hours, respectively, after an oral dose.

Following oral and intravenous administration of ^{14}C-labelled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about one percent of individuals studied.

In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N2 tetrazole glucuronide.

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 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 of up to 200 mg.

Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal elimination half-life of about 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. Following an oral dose of ^{14}C-labelled losartan in man, about 35 % of radioactivity is recovered in the urine and 58 % in the faeces.

Special populations

Renal impairment

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

Hepatic impairment

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 active metabolite can be removed by haemodialysis.

Hydrochlorothiazide

Absorption

Hydrochlorothiazide is rapidly absorbed after oral administration.

Distribution

Hydrochlorothiazide crosses the placenta, but not the blood-brain barrier and is excreted in breast milk.

Biotransformation

Hydrochlorothiazide is not metabolised, but is eliminated rapidly by the kidneys, with only minute quantities eliminated in the bile.

Elimination

The plasma half-life has been observed to vary between 5,6 and 14,8 hours after 24-hour observation. At least 61 % of the oral dose is eliminated unchanged within 24 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Colloidal silicon dioxide

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Pregelatinised starch.

Tablet coating:

Talc

Tabcoat TC 520074 containing: hydroxylpropylcellulose, hypromellose, titanium dioxide, yellow iron oxide non-irradiated.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep blister strips in outer carton until required for use.

6.5 Nature and contents of container

LOSARTAN COMP BIOTECH 50/12,5 and LOSARTAN COMP BIOTECH 100/25 film-coated tablets are packed into silver aluminium/aluminium blisters or blisters comprising of white ACLAR 3000 film and silver aluminium foil.

Each blister strip contains 10 film-coated tablets.

3 blister strips (30 film-coated tablets) are packed into a cardboard carton together with a patient information leaflet.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

Ground Floor, Block K West, Central Park

400 16th Road

Randjespark, Halfway House

Midrand 1685

8. REGISTRATION NUMBERS

LOSARTAN COMP BIOTECH 50/12,5: 43/7.1.3/0863

LOSARTAN COMP BIOTECH 100/25: 43/7.1.3/0864

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 June 2013

10. DATE OF REVISION OF THE TEXT

13 January 2026