Approved Professional Information for Medicines for Human Use:

LOSARTAN CO AUSTELL

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

LOSARTAN CO 50/12,5 AUSTELL 50/12,5 mg film-coated tablets

LOSARTAN CO 100/12,5 AUSTELL 100/12,5 mg film-coated tablets

LOSARTAN CO 100/25 AUSTELL 100/25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LOSARTAN CO 50/12,5 AUSTELL

Each film-coated tablet contains 50 mg losartan potassium and 12,5 mg hydrochlorothiazide.

LOSARTAN CO 100/12,5 AUSTELL

Each film-coated tablet contains 100 mg losartan potassium and 12,5 mg hydrochlorothiazide.

LOSARTAN CO 100/25 AUSTELL

Each-film coated tablet contains 100 mg losartan potassium and 25 mg hydrochlorothiazide.

Contains sugar (lactose monohydrate):

LOSARTAN CO 50/12,5 AUSTELL: each film-coated tablet contains 112,50 mg lactose monohydrate.

LOSARTAN CO 100/12,5 AUSTELL: each film-coated tablet contains 237,50 mg lactose monohydrate.

LOSARTAN CO 100/25 AUSTELL: each film-coated tablet contains 225,00 mg lactose monohydrate.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablets

LOSARTAN CO 50/12,5 AUSTELL

Yellow, oval, biconvex, film coated tablets with ‘C’ debossed on one side and ‘80’ on other side.

LOSARTAN CO 100/12,5 AUSTELL

White circular, biconvex film coated Tablets with ‘C’ debossed on one side and ‘79’ on other side.

LOSARTAN CO 100/25 AUSTELL

Yellow, circular biconvex film coated tablets with ‘C’ debossed on one side and ‘78’ on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LOSARTAN CO AUSTELL 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

Adults:

The usual starting dose of LOSARTAN CO AUSTELL 50/12,5 is one tablet daily.

The maximum dose is one tablet of LOSARTAN CO AUSTELL 100/25 (100 mg losartan potassium and 25 mg hydrochlorothiazide) once daily.

For patients who do not respond adequately to LOSARTAN CO AUSTELL 50/12,5 the dosage may be increased to one LOSARTAN CO AUSTELL 100/25 tablet once daily. LOSARTAN CO AUSTELL 100/12,5 is available for those patients titrated to 100 mg of LOSARTAN who require additional blood pressure control.

No initial dosage adjustment is required in elderly patients.

The maximum antihypertensive effect is attained within three weeks after initiation of therapy.

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

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

Special populations

Elderly population

LOSARTAN CO AUSTELL should not be used as initial therapy in elderly patients.

Renal impairment

LOSARTAN CO AUSTELL is not recommended for patients with severe renal impairment (see sections 4.3 and 4.4).

Hepatic impairment

LOSARTAN CO AUSTELL is not recommended for patients with hepatic impairment (see sections 4.3 and 4.4).

Paediatric population

LOSARTAN CO AUSTELL should not be administered to children and adolescents.

Method of administration

For oral use.

LOSARTAN CO AUSTELL may be administered with or without food.

4.3 Contraindications

- Hypersensitivity to the losartan potassium, hydrochlorothiazide or to any of the excipients listed in section 6.1

- 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
- Porphyria
- Thiazide diuretics in (fixed dose) combination as with LOSARTAN CO AUSTELL, should not be given to patients with Addison's disease. This therapy is also contraindicated in patients with severe renal impairment or anuria, and in patients who show hypersensitivity to other sulphonamide-derived medicine
- Lithium therapy: Concomitant administration with LOSARTAN CO AUSTELL may lead to toxic blood concentrations of lithium
- Pregnancy and lactation (see section 4.6)
- Hepatic impairment
- Therapy resistant hypokalaemia or hypercalcaemia
- Severe hepatic impairment; cholestasis and biliary obstructive disorders
- Refractory hyponatraemia
- Symptomatic hyperuricaemia/gout
- The concomitant use of LOSARTAN CO AUSTELL with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1,73 m^2) (see sections 4.5 and 5.1)

4.4 Special warnings and precautions for use

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

Losartan

Angioedema

Patients with a history of angioedema (swelling of the face, lips, throat, and/or tongue) should be closely monitored (see section 4.8).

Hypotension and Intravascular volume depletion

Symptomatic hypotension, especially after the first dose, may occur in patients who are volume- and/or sodium-depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of LOSARTAN CO AUSTELL tablets (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. Therefore, the plasma concentrations of potassium and creatinine clearance values should be closely monitored; especially patients with heart failure and a creatinine clearance between 30 - 50 mL/min should be closely monitored.

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 products) with losartan/hydrochlorothiazide is not recommended (see section 4.5).

Liver function impairment

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, LOSARTAN CO AUSTELL should be used with caution in patients with a history of mild to moderate hepatic impairment. There is no therapeutic experience with losartan in patients with severe hepatic impairment. Therefore, LOSARTAN CO AUSTELL is contraindicated in patients with severe hepatic impairment (see sections 4.2, 4.3 and 5.2).

Renal function impairment

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function, including renal failure, have been reported (in particular, in patients whose renal function is dependent on the renin-angiotensin-aldosterone system, such as those with severe cardiac insufficiency or pre-existing renal dysfunction).

Increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy. Losartan should be used with caution in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

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 CO AUSTELL tablets 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 a risk of severe arterial hypotension, and (often acute) renal impairment.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

Special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Ethnic differences

As observed for angiotensin converting enzyme inhibitors, losartan 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

Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (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 4.5 and 5.1).
If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. 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, hyperchloremic 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 agents, including insulin, may be required (see section 4.5). Latent diabetes mellitus may become manifest during thiazide therapy.
Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Thiazide therapy may precipitate hyperuricaemia and/or gout in certain patients. Because losartan

decreases uric acid, losartan in combination with hydrochlorothiazide attenuates the diuretic-induced hyperuricemia.

Hepatic impairment

Thiazides 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 CO is contraindicated for patients with severe hepatic impairment (see section 4.3 and 5.2).

Non-melanoma skin cancer

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

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

Concomitant use with lithium

Concomitant administration of lithium with LOSARTAN CO AUSTELL may lead to toxic blood concentrations of lithium (see section 4.5).

Other

In patients receiving thiazides, hypersensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

Excipients: lactose intolerance

LOSARTAN CO AUSTELL contains lactose monohydrate:

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

4.5 Interaction with other medicines and other forms of interaction

Losartan potassium

Rifampicin and fluconazole have been reported to reduce levels of active metabolite. The clinical consequences of these interactions have not been evaluated.

Concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, salt substitutes containing potassium, or other medicines that may increase serum potassium (e.g., trimethoprim-containing products) may lead to increases in serum potassium. Concomitant use is not advisable.

Lithium excretion may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be co-administered with angiotensin II receptor antagonists.

When angiotensin II antagonists are administered simultaneously with NSAIDs (i.e. selective COX-2 inhibitors, acetylsalicylic acid at anti-inflammatory doses and non-selective NSAIDs), attenuation of the antihypertensive effect 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 poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated, and consideration should be given to monitoring renal function after

initiation of concomitant therapy, and periodically thereafter.

In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, including selective cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists may result in a further deterioration of renal function. These effects are usually reversible.

Clinical trial data have 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 (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4, and 5.1).

Other medicines inducing hypotension like tricyclic antidepressants, antipsychotics, baclofen, amifostine: Concomitant use with these drugs that lower blood pressure, as main or side-effect, may increase the risk of hypotension.

Hydrochlorothiazide

When given concurrently, the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, narcotics or antidepressants

Potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral medicines and insulin)

The treatment with a thiazide may influence the glucose tolerance. Dosage adjustment of the antidiabetic drug 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

Additive 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 CO AUSTELL should therefore be administered one hour before the intake of the resin.

Corticosteroids, ACTH

Intensified electrolyte depletion, particularly hypokalaemia.

Pressor amines (e.g. adrenaline)

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 muscle relaxant.

Lithium

Diuretic medicines reduce the renal clearance of lithium and add a high risk of lithium toxicity; concomitant use is not recommended.

Medicines used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol)

Dosage adjustment of uricosuric medicinal products may be necessary since hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Coadministration of a thiazide may increase the incidence of hypersensitivity reactions to allopurinol.

Anticholinergic medicines (e.g. atropine, biperiden)

Increase of the bioavailability to thiazide-type diuretics by decreasing gastrointestinal motility and

stomach emptying rate.

Cytotoxic medicines (e.g. cyclophosphamide, methotrexate)

Thiazides may reduce the renal excretion of cytotoxic medicinal products and potentiate their myelosuppressive effects.

Salicylates

In case of high dosages of salicylates hydrochlorothiazide may enhance the toxic effect of the salicylates on the central nervous system.

Methyldopa

There have been isolated reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

Ciclosporin

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

Digoxin

Thiazide-induced hypokalaemia or hypomagnesaemia may favour the onset of digoxin-induced cardiac dysrhythmias.

Medicinal products affected by serum potassium disturbances

Periodic monitoring of serum potassium and ECG is recommended when losartan/hydrochlorothiazide is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides and antidysrhythmics) and with the following torsades de pointes (ventricular tachycardia)-inducing medicinal products (including some antidysrhythmics), hypokalaemia being a predisposing factor to torsades de pointes (ventricular tachycardia):

• Class Ia antiarrythmics (e.g. quinidine, hydroquinidine, disopyramide).

• Class III antiarrythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide).

• Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol).

• Others (e.g. bepridil, cisapride, diphemanil, erythromycin IV, halofantrin, mizolastin, pentamidine, terfenadine, vincamine IV).

Calcium salts

Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements must be prescribed, serum calcium levels should be monitored, and calcium dosage should be adjusted accordingly.

Laboratory test interactions

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

Carbamazepine

Risk of symptomatic hyponatremia. Clinical and biological monitoring is required.

Iodine contrast media

In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of the iodine product. Patients should be rehydrated before the administration.
Amphotericin B (parenteral), corticosteroids, ACTH, stimulant laxatives, or glycyrrhizin (found in liquorice)
Hydrochlorothiazide may intensify electrolyte imbalance, particularly hypokalaemia.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / contraception in males and females

Women of childbearing age should ensure adequate barrier contraception.

Pregnancy

LOSARTAN CO AUSTELL is contraindicated for use during pregnancy (see section 4.3).

When pregnancy is planned or confirmed, LOSARTAN CO AUSTELL should be discontinued.

Medicines affecting the renin-angiotensin system, such as LOSARTAN CO AUSTELL, can cause foetal and neonatal morbidity and mortality when administered to pregnant women.

Breastfeeding

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. Women taking LOSARTAN CO AUSTELL should not breastfeed their infants (see section 4.3).

Fertility

No data on effects of LOSARTAN CO AUSTELL on fertility has been established.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

b) Tabulated list of adverse reactions

The tables below show all adverse drug reactions (ADRs) observed during clinical trials and post-market spontaneous reports.

Frequency estimate:

Frequent

Less frequent

Not known (cannot be estimated from the available data).

Tabulated list of adverse reactions for LOSARTAN CO AUSTELL

System Organ Class	**Frequency**		
	Frequent	**Less frequent**	**Not known**
Metabolism and nutrition disorders	-	Hyperkalaemia, electrolyte imbalance including hyponatraemia and hypokalaemia	-
Nervous system disorders	Dizziness	-	-
Hepato-biliary disorders	-	Hepatitis	-
General disorders and administrative site conditions	Asthenia, fatigue	-	-
Investigations	-	Elevation of alanine amino transferase (ALT)	-

The adverse reactions that have been seen with one of the individual components and may be potential adverse reactions with losartan potassium / hydrochlorothiazide are the following:

Tabulated list of adverse reactions for losartan potassium

System Organ Class	Frequency		
	Frequent	**Less frequent**	**Not known**
Infections and infestations	Upper respiratory infection	Urinary tract infection, bronchitis	-
Blood and lymphatic system disorders:	Anaemia, haemolysis	Thrombocytopenia	-
Immune system disorders	-	-	Hypersensitivity, anaphylactic reaction
Metabolism and nutrition	Hyperkalaemia, hypoglycaemia	Anorexia, gout, hyponatraemia	-
Psychiatric disorders	Insomnia	Anxiety, anxiety disorder, panic disorder, confusion, depression, abnormal dreams, sleep disorder, somnolence, memory impairment	-
Nervous system disorders	Headache, dizziness	Migraine, nervousness, paraesthesia, peripheral neuropathy, tremor, syncope, vertigo, dysgeusia	-
Eye disorders	-	Blurred vision, burning/stinging in the eye, conjunctivitis, decrease in visual acuity	-
Ear and labyrinth disorders	-	Tinnitus	-

Cardiac disorders	Chest pain, palpitations, tachycardia	Angina pectoris, grade II-AV block, cerebrovascular event, myocardial infarction, dysrhythmias (atrial fibrillations, sinus bradycardia, ventricular tachycardia, ventricular fibrillation)	-
Vascular disorders	-	Orthostatic hypotension (dose-related), oedema, hypotension, vasculitis	-
Respiratory, thoracic and mediastinal disorders	Cough, nasal congestion, sinusitis, sinus disorder, pharyngitis	Pharyngeal discomfort, laryngitis, dyspnoea, epistaxis, rhinitis, respiratory congestion	-
Gastrointestinal disorders	Abdominal pain, diarrhoea, dyspepsia, nausea	Constipation, dental pain, dry mouth, flatulence, gastritis, vomiting, obstipation, pancreatitis	-
Hepato-biliary disorders	-	Liver function abnormalities	-
Skin and subcutaneous tissue disorders	-	Rash, urticaria, Henoch-Schönlein purpura, angioedema (involving swelling larynx and glottis causing airway obstruction, swelling of the face, lips, pharynx and/or tongue;	-

		angioedema had been reported in connection with the administration of other medicines, including ACE inhibitors), alopecia, dermatitis, dry skin, erythema, flushing, photosensitivity, pruritus, sweating, ecchymosis, erythroderma	
Musculoskeletal, connective tissue and bone disorders	Muscle cramps or pain (myalgia), back pain, leg pain, arm pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, coxalgia, fibromyalgia, muscle weakness	Rhabdomyolysis	-
Renal and urinary disorders	Renal impairment, renal failure	Nocturia, urinary frequency	-
Reproductive system and breast disorders	-	Decreased libido, erectile dysfunction/ impotence	-
General disorders and	Asthenia, fatigue, oedema/swelling	Sternalgia, facial oedema, fever, flu-like symptoms, malaise	-

administrative site conditions			
Investigations	Mild reduction of haematocrit and haemoglobin	Elevations of alanine amino transferase (ALT), mild increase in urea and creatinine serum levels, increase in hepatic enzymes and bilirubin	-

Tabulated list of adverse reactions for hydrochlorothiazide

System organ Class	**Frequency**		
	Frequent	**Less frequent**	**Not Known**
Infections and infestations	-	Sialadenitis	-
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	-	Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma)	-
Blood and lymphatic system disorders	-	Agranulocytosis, leukopenia, thrombocytopenia, aplastic anaemia, haemolytic anaemia	-
Immune system disorders	-	Respiratory distress including pneumonitis and pulmonary oedema, anaphylactic reactions	-
Metabolism and nutrition disorders	Electrolyte disturbances,	Hyperuricemia, hyperglycaemia,	-

	hyperkalaemia	anorexia, hypokalaemia, hyponatraemia	
Psychiatric disorders	-	Insomnia, restlessness	-
Nervous system disorders	Cephalalgia	Vertigo, paraesthesias, headache, dizziness	-
Eye disorders	-	Xanthopsia, transient blurred vision	Choroidal effusion
Vascular disorders	-	Hypotension (including orthostatic hypotension), necrotising angiitis (vasculitis, cutaneous vasculitis)	-
Respiratory, thoracic and mediastinal disorders	-	Respiratory distress including pneumonitis and pulmonary oedema	-
Gastrointestinal disorders	-	Gastric irritation, nausea, vomiting, cramping/ spasms, diarrhoea, constipation, pancreatitis	-
Hepato-biliary disorders	-	Cholecystitis, icterus (intrahepatic cholestasis jaundice)	-
Skin and subcutaneous tissue disorders	-	Skin rash, urticaria, purpura, photosensitivity, toxic epidermal necrolysis (TEN), cutaneous lupus erythematosus	-
Musculoskeletal, connective tissue and bone disorders	-	Muscle spasm, muscle cramps	-

Renal and urinary disorders	-	Renal dysfunction, interstitial nephritis, renal failure, glycosuria	-
General disorders and administrative site conditions	-	Fever, weakness	-

c. Description of selected adverse reactions

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

Cases of choroidal effusion with visual field defect have been reported after the use of thiazide and thiazide-like diuretics.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

No specific information is available on the treatment of overdose with LOSARTAN CO AUSTELL. Treatment is symptomatic and supportive. Therapy with LOSARTAN CO AUSTELL should be discontinued and the patient observed closely. Suggested measures include induction of emesis if ingestion is recent, and correction of dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures.

Losartan potassium

Limited data are available in regard to overdose in humans. The most likely manifestation of overdose 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, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalaemia may accentuate cardiac dysrhythmias.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification/ Category and Class: A 7.1.3. Other hypotensives

Pharmacotherapeutic group: Angiotensin II antagonists and diuretics

ATC Code: C09DA01

Losartan potassium is an angiotensin II receptor (type AT1) antagonist and hydrochlorothiazide is a diuretic.

Losartan potassium

Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin-angiotensin system, and a major determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT1 receptor found in many tissues (e.g., vascular smooth muscle, adrenal gland, kidneys, and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth muscle cell proliferation.

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

Hydrochlorothiazide

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

Losartan potassium-hydrochlorothiazide

Losartan and hydrochlorothiazide are additive in their antihypertensive efficacy

5.2 Pharmacokinetic properties

Losartan potassium

Absorption

Following oral administration, losartan undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33 %. Mean peak concentrations of losartan and its active metabolite are

reached in 1 hour and in 3 - 4 hours, respectively. There was no clinically significant effect on the plasma concentration profile of losartan when losartan was administered with a standardised meal.

Distribution

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

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 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 polyexpone initially with a terminal half-life of about 2 hours and 6-9 hours, respectively.
Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites.
Following an oral dose of 14C-labelled losartan in man, about 35 % of radioactivity is recovered in the urine and 58 % in the faeces.

Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-fold and 1,7-fold greater than those seen in young male volunteers.

Neither losartan nor the metabolite can be removed by haemodialysis.

Hydrochlorothiazide

When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5,6 and 14,8 hours. Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney. At least 61 % of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

Losartan potassium-hydrochlorothiazide

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet content:

Lactose monohydrate

Microcrystalline cellulose (Avicel 101)

Pregelatinised starch

Maize starch (UNI-PURE® FL)

Colloidal anhydrous silica

Magnesium stearate

Film-coat content:

Opadry yellow 03F520215 IHT (100/25 mg & 50/12,5 mg strength)

Opadry white 03F58750 IHT (100/12,5 mg strength)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

This medicine does not require any special storage condition.

6.5 Nature and contents of container

LOSARTAN CO AUSTELL is available in white blister packs packed into cardboard cartons in pack sizes of 30's.

LOSARTAN CO AUSTELL is available in HDPE containers with child resistant screw cap in pack sizes of 500's.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

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JOHANNESBURG

2193

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8. REGISTRATION NUMBER(S)

LOSARTAN CO 50/12,5 AUSTELL: 53/7.1.3/0155

LOSARTAN CO 100/12,5 AUSTELL: 53/7.1.3/0156

LOSARTAN CO 100/25 AUSTELL: 53/7.1.3/0157

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 April 2023

10. DATE OF REVISION OF THE TEXT