

Approved Professional Information for Medicines for Human Use:

AUSTELL LISINOPRIL

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

AUSTELL LISINOPRIL 2,5 mg tablets

AUSTELL LISINOPRIL 5 mg tablets

AUSTELL LISINOPRIL 10 mg tablets

AUSTELL LISINOPRIL 20 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AUSTELL LISINOPRIL 2,5 mg tablet:

Each tablet contains lisinopril dihydrate equivalent to 2,5 mg lisinopril.

Sugar free.

Contains excipient: mannitol 18 mg per tablet.

AUSTELL LISINOPRIL 5 mg tablet:

Each tablet contains lisinopril dihydrate equivalent to 5 mg lisinopril.

Sugar free.

Contains excipient: mannitol 18 mg per tablet.

AUSTELL LISINOPRIL 10 mg tablet:

Each tablet contains lisinopril dihydrate equivalent to 10 mg lisinopril.

Sugar free.

Contains excipient: mannitol 36 mg per tablet.

AUSTELL LISINOPRIL 20 mg tablet:

Austell Pharmaceuticals (Pty) Ltd, 370391 / 380033 / 380032 / 370392, Austell Lisinopril 2,5 mg / Austell Lisinopril 5 mg / Austell Lisinopril 10 mg / Austell Lisinopril 20 mg tablets

Each tablet contains lisinopril dihydrate equivalent to 20 mg lisinopril.

Sugar free.

Contains excipient: mannitol 36 mg per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

AUSTELL LISINOPRIL 2,5 mg tablets:

White to almost white circular biconvex uncoated tablets with “2.5” embossing on one side and “BL” embossing on the other side.

AUSTELL LISINOPRIL 5 mg tablets:

Light pink coloured circular biconvex uncoated tablets with “5” embossed and break line on one side, and “BL” embossed on the other side.

AUSTELL LISINOPRIL 10 mg tablets:

Light pink circular biconvex uncoated tablets with “10” embossed on one side and “BL” embossed on the other side.

AUSTELL LISINOPRIL 20 mg tablets:

Pink circular biconvex uncoated tablets with “20” embossed on one side and “BL” embossed on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AUSTELL LISINOPRIL is indicated for the treatment of:

- Mild to moderate hypertension - alone or in combination with other antihypertensives.
- Congestive heart failure - as an adjunctive therapy with diuretics and, where appropriate,

digitalis.

- Acute myocardial infarction – AUSTELL LISINOPRIL administered within 24 hours to haemodynamically stable patients reduces the risk of left ventricular dysfunction or heart failure and improves survival. Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin and beta-blockers.

4.2 Posology and method of administration

Posology

Mild to moderate hypertension:

ADULTS: Initial dose is 10 mg per day given as a single dose. The dose should be adjusted according to the blood pressure response. The usual effective maintenance dose is 20 mg per day given as a single dose with a maximum of 40 mg per day.

The full therapeutic effect may take several weeks. Therefore, if the desired effect has not been achieved within 2 to 4 weeks, the dose may be increased.

Congestive Heart Failure:

ADULTS: Initial dose is 2,5 mg per day as a single dose. Adjustments should be based on clinical response.

This may be increased:

- by increments of no greater than 10 mg
- at intervals of no less than 2 weeks
- to the highest dose tolerated by the patient up to a maximum of 35 mg once daily.

Maintenance dosing range is 5 to 20 mg per day administered as a single dose.

Patients at high risk of symptomatic hypotension, e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy, should have these conditions corrected, prior to therapy with AUSTELL LISINOPRIL. The

effect of the starting dosage of AUSTELL LISINOPRIL on blood pressure should be monitored carefully.

Acute Myocardial Infarction:

ADULTS: 5 mg within 24 hours of the onset of an acute myocardial infarction, followed by 5 mg after 24 hours of the first dose, 10 mg after 48 hours of the first dose and then 10 mg per day for six weeks.

In patients with low systolic blood pressure (less than or equal to 120 mm Hg), an initial dose of 2,5 mg should be used during the first three days after the infarction.

If hypotension occurs (systolic blood pressure less than or equal to 100 mm Hg), a daily maintenance dose of 5 mg may be given with temporary reductions to 2,5 mg if needed. If prolonged hypotension occurs (systolic blood pressure less than 90 mm Hg for more than 1 hour), AUSTELL-LISINOPRIL should be withdrawn.

Dosing should continue for 6 weeks. The benefit appears to be greatest in patients with large myocardial infarctions and evidence of impaired left ventricular function. Patients who develop symptoms of heart failure should continue with AUSTELL LISINOPRIL (see section 4.2 for congestive heart failure AUSTELL LISINOPRIL).

AUSTELL LISINOPRIL is compatible with intravenous or transdermal glyceryl trinitrate.

Special populations

Diuretic-treated patients:

In order to minimise the possibility of sudden and severe hypotension which may occur within the first 1 to 5 hours after the initial dose of AUSTELL-LISINOPRIL, diuretics should be discontinued 2 to 3 days before beginning therapy with AUSTELL LISINOPRIL (see section 4.4). Caution is

recommended in all patients who may be volume- and/or salt-depleted. In patients where diuretic therapy cannot be discontinued, treatment with AUSTELL-LISINOPRIL should be initiated with a 5 mg dose. Subsequent dosage adjustments will depend on the therapeutic response. If required, diuretic therapy may be resumed.

Renal Impairment:

A lower dose is required in the presence of renal impairment, in patients in whom diuretic therapy cannot be discontinued and in patients who are volume- and/or salt-depleted for any reason. If creatinine clearance is 31 – 80 mL/min the starting dose is 5 mg to 10 mg per day.

The dose may be increased as needed according to therapeutic response to a maximum of 20 mg/day.

Renovascular hypertension:

Special care to be exercised in some *patients* with renovascular hypertension because of the possibility of exaggerated response.

Dose should be lowered to 2,5 mg or 5 mg and the patient should be monitored.

Elderly population:

There are no age-related changes in the efficacy or safety profile of the agent. When advanced age is associated with a decrease in renal function, however, the guidelines set out in the dose adjustment table (see *renal impairment* above) should be used to determine the starting dose of AUSTELL LISINOPRIL. Thereafter, the dosage should be adjusted according to the blood pressure response.

Paediatric population

Safety and effectiveness of AUSTELL LISINOPRIL in children has not been established.

Method of administration

AUSTELL LISINOPRIL is for oral use.

AUSTELL LISINOPRIL should be administered as a single daily dose at approximately the same time every day.

AUSTELL LISINOPRIL is not affected by the presence of food and may be taken with/without meals.

4.3 Contraindications

- Hypersensitivity to lisinopril or to any of the excipients listed in section 6.1.
- Patients with a history of angioedema related to previous ACE- inhibitor therapy or angiotensin receptor blocker. These patients must never again be given these medicines.
- Hereditary or idiopathic angioedema (see section 4.4).
- Aortic stenosis.
- Renal artery stenosis in patients with a single kidney.
- Bilateral renal artery stenosis.
- Hypertrophic obstructive cardiomyopathy.
- Severe renal function impairment (creatinine clearance below 30 mL/min).
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5).
- Porphyria.
- Lithium therapy: Concomitant administration with AUSTELL LISINOPRIL may lead to toxic blood concentrations of lithium (see section 4.5).
- Pregnancy and lactation (see section 4.6).
- The concomitant use of AUSTELL LISINOPRIL with aliskiren-containing products is contraindicated (see section 4.4)
- Concomitant use of fluoroquinolones with ACE inhibitors/Renin-Angiotensin blockers is contraindicated in patients with moderate to severe renal impairment (see section 4.5).
- Concomitant use of AUSTELL LISINOPRIL with sacubitril/valsartan therapy. AUSTELL LISINOPRIL must not be initiated earlier than 36 hours after the last dose of

sacubitril/valsartan (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving an ACE-inhibitor, the treatment must be stopped promptly and changed to a different class of antihypertensive medicine. (See section 4.6)

If a woman is contemplating pregnancy, a different class of medicine should be used. (see section 4.6).

Symptomatic hypotension

Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving AUSTELL-LISINOPRIL, hypotension is more likely to occur if the patient has been volume-depleted, e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependent hypertension (see section 4.5 and section 4.8). In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored. Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of 0,9 % saline. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

In some patients with heart failure who have normal or low blood pressure, additional lowering of

systemic blood pressure may occur with lisinopril as in AUSTELL LISINOPRIL. This effect is anticipated and is not usually a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of AUSTELL LISINOPRIL may be necessary.

Hypotension in acute myocardial infarction

Treatment with AUSTELL LISINOPRIL must not be initiated in acute myocardial infarction patients who are at risk of further serious haemodynamic deterioration after treatment with a vasodilator. These include patients with systolic blood pressure of 100 mm Hg or lower or cardiogenic shock. During the first 3 days following the infarction, the dose should be reduced if the systolic blood pressure is 120 mm Hg or lower. Maintenance doses should be reduced to 5 mg or temporarily to 2,5 mg if systolic blood pressure is 100 mm Hg or lower. If hypotension persists (systolic blood pressure less than 90 mm Hg or more than 1 hour) then AUSTELL-LISINOPRIL should be withdrawn.

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 AUSTELL LISINOPRIL and aliskiren is therefore contra-indicated (see section 4.3).

AUSTELL LISINOPRIL should not be used concomitantly with aliskiren (see section 4.3).

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

Renal function impairment

Decreased elimination of AUSTELL LISINOPRIL (creatinine clearance < 80 mL/min), resulting in an increased risk of hyperkalaemia. These patients may require lower doses (see section 4.2).

In patients with heart failure, hypotension following the initiation of therapy with ACE inhibitors may

lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

Renal artery stenosis, bilateral or in one kidney or renal transplant – Increased risk of renal function impairment may increase blood urea and serum creatinine concentrations, which may be reversible upon discontinuation of therapy. There is also an increased risk of agranulocytosis and neutropenia when immunosuppressants are concurrently administered.

In acute myocardial infarction, treatment with AUSTELL LISINOPRIL should not be initiated in patients with evidence of renal dysfunction (serum creatinine concentrations exceeding 177 micromol/L or proteinuria exceeding 500 mg / 24 hours). If renal dysfunction develops during treatment (serum creatinine concentrations exceeding 177 micromol/L or doubling of the pretreatment value) then AUSTELL-LISINOPRIL may need to be withdrawn.

In acute myocardial infarction, patients may develop persistent hypotension and/or impaired renal function.

Increases in blood urea and serum creatinine have been seen in patients with no apparent pre-existing vascular disease, especially when AUSTELL LISINOPRIL has been given concomitantly with a diuretic. Dosage reduction or discontinuation of AUSTELL LISINOPRIL or the diuretic may be required.

Neutropenia/Agranulocytosis

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Neutropenia and agranulocytosis are reversible after discontinuation of the ACE inhibitor.

AUSTELL LISINOPRIL should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If AUSTELL LISINOPRIL is used in such patients, periodic monitoring of white blood cell counts is advised, and patients should be instructed to report any sign of infection.

Bone marrow depression – Increased risk of agranulocytosis and neutropenia.

Diabetic patients

Diabetes mellitus – Increased risk of hyperkalaemia, as well as hypoglycaemia may occur. In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor (see section 4.5)

Hyperkalaemia

AUSTELL LISINOPRIL may cause an increase in serum potassium levels because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. However, in patients with impaired renal function, diabetes mellitus and/or in patients taking concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene and amiloride may lead to hyperkalaemia, which may be severe and lead to cardiac conduction abnormalities, dysarrhythmias and cardiac arrest (see section 4.3).

Renovascular disease

AUSTELL LISINOPRIL should not be used in patients with renovascular disease or suspected renovascular disease but it may be used cautiously in severe resistant hypertension in such patients. In this instance AUSTELL LISINOPRIL should only be used under specialist supervision. The elderly, patients with peripheral vascular diseases or generalised atherosclerosis may have asymptomatic

renovascular disease (see section 4.2).

Hypersensitivity/Angioedema

If angioedema of the face, extremities, lips, tongue, glottis and /or larynx is observed in patients treated with AUSTELL LISINOPRIL, it should be discontinued promptly. These patients should be monitored to ensure complete resolution of symptoms. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with

antihistamines and corticosteroids may not be sufficient.

Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate emergency therapy should be administered. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred. These patients should never receive any AUSTELL-LISINOPRIL again.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3).

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema.

Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of AUSTELL LISINOPRIL.

Treatment with AUSTELL LISINOPRIL must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk of angioedema (e.g. swelling of the

airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin in a patient already taking an ACE inhibitor.

Desensitisation

Anaphylactoid reactions have occurred in patients using ACE-inhibitors during desensitising protocols involving for example, hymenoptera venom. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld but they have reappeared upon inadvertent re-administration of the medicinal product.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

Anaphylactoid reactions have been reported in patients exposed to either high-flux membrane dialysis or low-density lipoprotein apheresis with dextran sulfate adsorption. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Anaphylactoid reactions in haemodialysis patients

Anaphylactoid reactions have been reported in patients dialysed with high flux membranes (e.g. AN 69) and treated concomitantly with an ACE inhibitor. In these patients, consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent.

Hepatic failure

Very rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving lisinopril who develop jaundice or marked elevations of hepatic enzymes should discontinue lisinopril and receive appropriate medical follow-up.

Race

AUSTELL LISINOPRIL causes a higher rate of angioedema in black patients than in non-black patients. As with other ACE inhibitors, AUSTELL LISINOPRIL may be less effective in lowering blood pressure in black patients than in nonblacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Cough

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anaesthesia

In patients undergoing major surgery or during anaesthesia with medicines that produce hypotension, AUSTELL LISINOPRIL may block angiotensin II formation secondary to complementary renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Concomitant use of fluoroquinolones with ACE inhibitors/renin-angiotensin receptor blockers

Concomitant use of fluoroquinolones with ACE inhibitors/renin-angiotensin receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3). Renal function should be assessed before initiating treatment and monitored during concomitant treatment with ACE inhibitors/renin-angiotensin receptor blockers and fluoroquinolones.

Excipient mannitol

Contains mannitol and may have a laxative effect.

Paediatric population

Safety and efficacy in children have not been established.

4.5 Interaction with other medicines and other forms of interaction

Antihypertensive agents

When AUSTELL LISINOPRIL is combined with other antihypertensive agents (e.g. glyceryl trinitrate and other nitrates, or other vasodilators), additive falls in blood pressure may occur.

Dual blockade of the RAAS with ARBs, ACE inhibitors, or aliskiren

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

Medicines increasing the risk of angioedema

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see section 4.3 and 4.4).

Concomitant treatment of ACE inhibitors with mammalian target of rapamycin (mTOR) inhibitors (e.g. temsirolimus, sirolimus, everolimus) or neutral endopeptidase (NEP) inhibitors (e.g. racecadotril), vildagliptin or tissue plasminogen activator may increase the risk of angioedema (see section 4.4).

Diuretics, alcohol and hypotension-producing medications

The antihypertensive effect is additive. Dosage adjustments may be necessary during concurrent use or when one medicine is discontinued.

Loop, thiazide or related diuretics – “First dose hypotension” may occur. The possibility of symptomatic hypotension with AUSTELL LISINOPRIL can be minimised by discontinuing the diuretic prior to initiation of treatment with AUSTELL LISINOPRIL (see section 4.2 and 4.4)

Non-steroidal anti-inflammatory medicinal products (NSAIDs) including acetylsalicylic acid ≥ 3 g/day
Indomethacin reduces the antihypertensive effects of AUSTELL-LISINOPRIL. When ACE inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE inhibitors 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. These effects are usually reversible. 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.

Potassium supplements, potassium sparing diuretics or potassium-containing salt substitutes and other medicines that may increase serum potassium levels

Potassium supplements, potassium-containing salt substitutes or potassium sparing diuretics such as spironolactone, triamterene or amiloride - concurrent administration may result in hyperkalaemia. Care should also be taken when AUSTELL LISINOPRIL is co-administered with other agents that increase serum potassium, such as trimethoprim and co-trimoxazole (trimethoprim/sulfamethoxazole) as trimethoprim is known to act as a potassium- sparing diuretic like amiloride. Therefore, the combination of lisinopril with the above-mentioned medicines is not recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium. If AUSTELL LISINOPRIL is given with a potassium-losing diuretic, diuretic-induced hypokalaemia may be ameliorated.

Ciclosporin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with ciclosporin. Monitoring of serum potassium is recommended.

Heparin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with heparin. Monitoring of serum potassium is recommended.

Lithium

Increases in lithium concentrations have been reported. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased lithium toxicity with ACE inhibitors (see section 4.3).

Fluoroquinolones

Concomitant use of fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers may precipitate acute kidney injury (see section 4.3).

Gold

Nitritoid reactions (symptoms of vasodilatation including flushing, nausea, dizziness and hypotension, which can be very severe) following injectable gold (for example, sodium aurothiomalate) have been reported more frequently in patients receiving ACE inhibitor therapy.

Tricyclic antidepressants / Antipsychotics / Anaesthetics

Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4).

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Antidiabetics

Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood glucose-lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Acetylsalicylic acid, thrombolytic&, beta-blockers, nitrates

AUSTELL LISINOPRIL may be used concomitantly with acetylsalicylic acid (at cardiologic doses}, thrombolytics, beta-blockers and/or nitrates.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of AUSTELL LISINOPRIL is contraindicated during pregnancy. Pregnant women should be informed of the potential hazards to the foetus and must not take AUSTELL LISINOPRIL during pregnancy (see section 4.3). 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 AUSTELL LISINOPRIL should be stopped immediately and if appropriate, alternative therapy should be started.

Foetal exposure to ACE inhibitors during the first trimester of pregnancy has been reported to be associated with an increased risk of malformations of the cardiovascular (atrial and/or ventricular septal defect, pulmonic stenosis, patent ductus arteriosus) and central nervous system (microcephaly spina bifida) and of kidney malformations. AUSTELL LISINOPRIL passes through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms.

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Oligohydramnios as well as hypotension, oliguria and anuria in new-borns, have been reported after administration of AUSTELL LISINOPRIL during the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur (see section 4.3).

Breastfeeding

Safety in lactation has not been established.

4.7 Effects on ability to drive and use machines

Caution when driving or performing tasks requiring alertness because of possible dizziness.

4.8 Undesirable effects

Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with lisinopril.

System Organ Class	Frequency		
	Frequent	Less Frequent	Not known
Blood and lymphatic system disorders		Decreases in white blood cell count, haemoglobin and haematocrit, bone marrow depression, anaemia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis (see section 4.4), haemolytic anaemia, lymphadenopathy, autoimmune disease	
Immune system disorders			Anaphylactic/anaphylactoid reaction
Endocrine disorders		Hyperkalaemia, hyponatraemia, increases in blood urea, increases in serum creatinine, syndrome of inappropriate	

		antidiuretic hormone secretion (SIADH).	
Metabolism and nutrition disorders		Hypoglycaemia	
Nervous system & psychiatric disorders	Dizziness, headache, fatigue	Mood alterations, mental confusion, paraesthesia, vertigo, sleep disturbances, hallucinations, olfactory disturbance	Depressive symptoms, syncope
Cardiac and vascular disorders	Orthostatic effects (including hypotension)	Myocardial infarction, cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see section 4.4), palpitations, tachycardia), Raynaud's phenomenon	
Respiratory, thoracic and mediastinal disorders	Cough	Bronchospasm, rhinitis, sinusitis, allergic alveolitis/eosinophilic pneumonia.	
Gastro-intestinal disorders	Diarrhoea, nausea, vomiting	Abdominal pain, indigestion, dry mouth, pancreatitis, taste disturbances	

<p>Hepatobiliary disorders</p>		<p>Hepatitis (hepatocellular or cholestatic), jaundice, increase in liver enzymes, increases in serum bilirubin, hepatic failure (see section 4.4)</p>	
<p>Skin and subcutaneous tissue disorders</p>		<p>Rash, urticaria, diaphoresis, alopecia, pruritis, psoriasis, sweating, severe skin disorders including pemphigus, toxic epidermal necrolysis, Steven-Johnsons Syndrome, erythema multiforme, cutaneous pseudolymphoma.</p> <p>Hypersensitivity/angioedema reactions: angioneuroticoedema of the face which may be fatal, extremities, lips, tongue, glottis and /or larynx and intestinal angioedema (see section 4.4).</p> <p>A symptom complex has been reported which may include fever, vasculitis, myalgia, arthritis/arthralgia, a positive</p>	

		antinuclear antibody (ANA), elevated erythrocyte sedimentation rate, eosinophilia and leucocytosis. Rash, photosensitivity or other dermatological manifestations may occur.	
Musculoskeletal and connective tissue disorders		Asthenia	
Renal and urinary disorders	Renal dysfunction	Uraemia, oliguria, anuria, acute renal failure	
Reproductive system and breast disorders		Impotence, gynaecomastia	

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. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

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Suspected adverse reactions can also be reported directly to the HCR via medsafety@austell.co.za

4.9 Overdose

Symptoms

Limited data are available for overdose in humans. Symptoms associated with overdosage of ACE inhibitors may include severe hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough.

Treatment

Treatment is symptomatic and supportive. The recommended treatment of overdose is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Activated charcoal may be given in severe overdosage if the patient presents within 1 hour of ingestion. Treatment consists of volume expansion to correct hypotension and treating dehydration and electrolyte imbalances. Vital signs, serum electrolytes and creatinine concentrations should be monitored frequently. AUSTELL-LISINOPRIL is removable by haemodialysis. Pacemaker therapy is indicated for therapy-resistant bradycardia.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 7.1.3 Other hypotensives

Pharmacotherapeutic group: Angiotensin-converting enzyme inhibitors

ATC Code: C09AA03

Mechanism of action

Lisinopril is an orally active ACE inhibitor. Lisinopril inhibits the angiotensin I - converting enzyme (ACE) activity. It inhibits the conversion of the relatively inactive angiotensin I to the active angiotensin II.

Angiotensin II is a potent vasoconstrictor and stimulates the release of aldosterone.

Decreased angiotensin II levels result in a decrease in vasopressor activity and a reduction in

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aldosterone secretion, which may result in small increases in serum potassium. It is also thought that ACE inhibition may inhibit degradation of bradykinin, leading to increased bradykinin levels.

In patients with diabetes mellitus who have microalbuminuria, lisinopril reduces the urinary albumin excretion.

5.2 Pharmacokinetic properties

Absorption

The extent of absorption after oral administration is 25 % with wide variability between patients (6 to 60 %). The plasma half-life is 12 hours, which is increased in renal impairment. The time to achieve peak serum concentrations is 7 hours, although there was a trend to a small delay in time taken to reach peak plasma concentrations in acute myocardial infarction patients.

The absolute bioavailability is reduced approximately 16 % in patients with heart failure. Lisinopril absorption is not affected by the presence of food.

Elimination

Lisinopril is renally eliminated and excreted 100 % unchanged in the urine.

The clearance of lisinopril in healthy subjects is approximately 50 mL/min.

Upon multiple dosing, lisinopril exhibits an effective half-life of accumulation of 12,6 hours.

Declining serum concentrations exhibit a prolonged terminal phase which does not contribute to medicine accumulation. This terminal phase probably represents saturable binding to ACE and is not proportional to dose.

Hepatic impairment:

Impairment of hepatic function in cirrhotic patients resulted in a decrease in lisinopril absorption (about 30 % as determined by urinary recovery) but an increase in exposure (approximately 50 %) compared to healthy subjects due to decreased clearance.

Renal impairment:

Impaired renal function decreases elimination of lisinopril, which is excreted via the kidneys, but this decrease becomes clinically important only when the glomerular filtration is below 30 mL/min.

Pharmacokinetic parameters of lisinopril to different groups of renal patients after administration of a multiple 5 mg dose.

Renal function measured by creatinine clearance	n	C _{max} (ng/mL)	T _{max} (hr)	AUC (0 – 24 hours) (ng/hr/mL)	t _{1/2} (hr)
> 80 mL/min	6	40,3	6	492 ± 172	6,0 ± 1,1
30 - 80 mL/min	6	36,6	8	555 ± 364	11,8 ± 1,9
5 - 30 mL/min	6	106,7	8	2 228 ± 938	19,5 ± 5,2

Lisinopril can be removed by dialysis.

During 4 hours of haemodialysis, plasma lisinopril concentrations decreased on average by 60 %, with a dialysis clearance between 40 and 55 mL/min.

Heart failure:

Patients with heart failure have a greater exposure of lisinopril when compared to healthy subjects (an increase in AUC on average of 125 %), but based on the urinary recovery of lisinopril, there is reduced absorption of approximately 16 % compared to healthy subjects.

Elderly:

Older patients have higher blood levels and higher values for the area under the plasma concentration time curve (increased approximately 60 %) compared with younger subjects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Austell Pharmaceuticals (Pty) Ltd, 370391 / 380033 / 380032 / 370392, Austell Lisinopril 2,5 mg / Austell Lisinopril 5 mg / Austell Lisinopril 10 mg / Austell Lisinopril 20 mg tablets

Calcium hydrogen phosphate

Mannitol

Maize starch

Maize starch (paste)

Maize starch (dried)

Magnesium stearate

5 mg, 10 mg and 20 mg:

Ferric oxide (EEC. No. 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

Keep the blister packs in the outer carton until required for use.

Keep the HDPE container well closed.

6.5 Nature and contents of container

AUSTELL LISINOPRIL 2,5 mg:

Blister packs (Clear PVC film, Printed Aluminium foil) of 2 x 14 and 3 x 10 tablets.

Bulk packs (HDPE jars) of 30 and 60 tablets.

AUSTELL LISINOPRIL 5 mg:

Austell Pharmaceuticals (Pty) Ltd, 370391 / 380033 / 380032 / 370392, Austell Lisinopril 2,5 mg / Austell Lisinopril 5 mg / Austell Lisinopril 10 mg / Austell Lisinopril 20 mg tablets

Blister packs (Clear PVC film, Printed Aluminium foil) of 2 x 14 and 3 x 10 tablets.

Bulk packs (HDPE jars) of 30 and 60 tablets.

AUSTELL LISINOPRIL 10 mg:

Blister pack (Clear PVC film, Printed Aluminium foil) of 2 x 14 and 3 x 10 tablets.

Bulk pack (HDPE jars) of 30 and 60 tablets.

AUSTELL LISINOPRIL 20 mg:

Blister pack (Clear PVC film, Printed Aluminium foil) of 2 x 14 and 3 x 10 tablets.

Bulk pack (HDPE jars) of 30 and 60 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Parktown

Johannesburg, 2193

Tel: +27 11 611 1400 or +27 860 287 835

8. REGISTRATION NUMBERS

AUSTELL LISINOPRIL 2,5 mg: 37/7.1.3/0391

AUSTELL LISINOPRIL 5 mg: 38/7.1.3/0033

AUSTELL LISINOPRIL 10 mg: 38/7.1.3/0032

Austell Pharmaceuticals (Pty) Ltd, 370391 / 380033 / 380032 / 370392, Austell Lisinopril 2,5 mg / Austell Lisinopril 5 mg / Austell Lisinopril 10 mg / Austell Lisinopril 20 mg tablets

AUSTELL LISINOPRIL 20 mg: 37/7.1.3/0392

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

AUSTELL LISINOPRIL 2,5 mg: 23 July 2004

AUSTELL LISINOPRIL 5 mg: 18 April 2008

AUSTELL LISINOPRIL 10 mg: 18 April 2008

AUSTELL LISINOPRIL 20 mg: 23 July 2004

10. DATE OF REVISION OF THE TEXT

16 May 2025