Austell Pharmaceuticals (Pty) Ltd, 370391-91; 380031-32 Austell Lisinopril Tablets 2,5, 5, 10, 20 mg

Professional Information for Medicines for Human Use:

SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

AUSTELL-LISINOPRIL 2.5 mg TABLETS

AUSTELL-LISINOPRIL 5 mg TABLETS

AUSTELL-LISINOPRIL 10 mg TABLETS

AUSTELL-LISINOPRIL 20 mg TABLETS

COMPOSITION

AUSTELL-LISINOPRIL 2.5 mg:

Each tablet contains lisinopril dihydrate equivalent to lisinopril 2.5 mg.

AUSTELL-LISINOPRIL 5 mg:

Each tablet contains lisinopril dihydrate equivalent to lisinopril 5 mg.

AUSTELL-LISINOPRIL 10 mg:

Each tablet contains lisinopril dihydrate equivalent to lisinopril 10 mg.

AUSTELL-LISINOPRIL 20 mg:

Each tablet contains lisinopril dihydrate equivalent to lisinopril 20 mg.

PHARMACOLOGICAL CLASSIFICATION

A 7.1.3 Other Hypotensives.

PHARMACOLOGICAL ACTION

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 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.

Pharmacokinetics:

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

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.

CONTRA-INDICATIONS

- Sensitivity to any of the components of **AUSTELL-LISINOPRIL.**
- Patients with a history of angioedema related to previous ACE- inhibitor therapy or angiotensin receptor blocker.
- Hereditary or idiopathic angioedema.
- Aortic stenosis.
- Hypertrophic obstructive cardiomyopathy.
- Severe renal function impairment (creatinine clearance below 30 ml/min).
- Renal artery stenosis in patients with a single kidney.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride.
- Porphyria.
- Concomitant use of **AUSTELL ENALAPRIL** with fluoroquinolones in patients with moderate to severe renal impairment.

WARNINGS

Should a woman become pregnant while receiving an ACE-inhibitor, the treatment must be stopped promptly and changed to a different medicine. (SEE PREGNANCY AND LACTATION)

If a woman is contemplating pregnancy, a different class of medicine should be used. (see PREGNANCY AND LACTATION).

AUSTELL-LISINOPRIL should be used with caution in the following conditions:

- Cerebrovascular disease or ischaemic heart disease. Reduction in blood pressure could aggravate these conditions and may result in myocardial infarction and cerebrovascular accidents.
- Volume depleted patients (e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting). Although it may occur in normo volemic patients, hypotension is more likely in volume depleted patients. A sudden reduction in angiotensin II may result in sudden and severe hypotension. There is also an increased risk of **AUSTELL-LISINOPRIL** induced renal failure, especially in those with congestive heart failure.
- Patients at a high risk of symptomatic hypotension e.g. patients with salt or volume depletion with or without hyponatremia should have these conditions corrected before therapy with **AUSTELL-LISINOPRIL.** Monitoring is required after initiating therapy.
- Severe autoimmune disease, especially systemic lupus erythematosus, other collagen vascular disease or scleroderma increase the risk for development of neutropenia or agranulocytosis.
- 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.
- 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 systol blood pressure of 13.33 KPa or lower or cardiogenic shock. During the first 3 days following the infarction, the dose should be reduced if the systolic blood pressure is 15.99 KPa or lower. Maintenance doses should be reduced to 5 mg or temporarily to 2.5 mg if systolic blood pressure is 13.33 Kpa or lower. If hypotension persists (systolic blood pressure less than 11.99 KPa or more than 1 hour) then **AUSTELL-LISINOPRIL** should be withdrawn.
- Bone marrow depression – Increased risk of agranulocytosis and neutropenia.
- Diabetes mellitus – Increased risk of hyperkalaemia, as well as hypoglycaemia may occur.
- Hyperkalaemia - **AUSTELL-LISINOPRIL** may cause an increase in serum potassium levels.
- 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 artherosclerosis may have asymptomatic renovascular disease. (SEE DOSAGE AND DIRECTIONS)

- 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.
- Renal function impairment – Decreased elimination of **AUSTELL-LISINOPRIL** resulting in an increased risk of hyperkalaemia. These patients may require lower doses.
- Anaphylactoid reactions have occurred in patients using ACE-inhibitors during desensitising protocols involving for example, hymenoptera venom.
- Anaphylactoid reactions have been reported in patients exposed to either high-flux membrane dialysis or low-density lipoprotein apheresis with dextran sulfate absorption.
- 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.
- Angoioedema 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**.

- **AUSTELL-LISINOPRIL** causes a higher rate of angioedema in black patients than in non-black patients.
- Porphyria: Use with caution.
- Safety and efficacy in children has not been established.

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, dysarrythmias and cardiac arrest.

Concomitant use of fluoroquinolones with ACE inhibitors, such as **AUSTELL ENALAPRIL**, may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see **CONTRAINDICATIONS**). Renal function should be assessed before initiating treatment, and monitored during concomitant treatment with **AUSTELL ENALAPRIL** and fluoroquinolones.

INTERACTIONS

Concomitant use of **AUSTELL-LISINOPRIL** with:

- 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. (SEE DOSAGE AND DIRECTIONS FOR USE)
- Indomethacin and non-steroidal anti-inflammatory medicines (NSAIDs) - reduce the antihypertensive effects of AUSTELL-LISINOPRIL. Blood pressure monitoring should be increased when any NSAID is added or discontinued in a patient treated with **AUSTELL-LISINOPRIL**.
- Potassium supplements or potassium sparing diuretics such as spironolactone, triamterene or amiloride. Concurrent administration may result in hyperkalaemia.

Lithium – Increases in lithium concentrations have been reported. Frequent monitoring of serum lithium concentrations is recommended.

Fluoroquinolones

Concomitant use of fluoroquinolones and ACE inhibitors, such as **AUSTELL ENALAPRIL**, may precipitate acute kidney injury (see **CONTRAINDICATIONS**).

PREGNANCY AND LACTATION

Use of **AUSTELL-LISINOPRIL** limited to the first trimester does not appear to present significant risk to the foetus, but foetal exposure after this time has been associated with teratogenicity and severe toxicity in the foetus and newborn, including death. **AUSTELL-LISINOPRIL** crosses the placenta. Foetal exposure to ACE-inhibitors during the second and third trimester can cause hypotension, renal failure, anuria, skull hypoplasia, hyperkalaemia

and oliguria.

Oligohydramnios may occur resulting in pulmonary hypoplasia, limb contractures and craniofacial deformation.

Infants who have been exposed in utero to **AUSTELL-LISINOPRIL** should be closely monitored.

Peritioneal dialysis may be of some benefit in the clearance of **AUSTELL-LISINOPRIL** from the neonatal circulation. Safety in lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE

AUSTELL-LISINOPRIL tablets may be taken with/without meals, preferably at the same time each day.

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.

This may be increased at intervals of 4 weeks until the therapeutic effect is reached. Adjustments should be based on clinical response. Maintenance dosing range is 5 to 20 mg per day administered as a single dose.

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 mmHg for more than 1 hour), **AUSTELL-LISINOPRIL** should be withdrawn.

Dosing in high-risk individuals:

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** . 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. If creatinine clearance is 31 – 70 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:

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

AUSTELL-LISINOPRIL is not affected by the presence of food.

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

SIDE EFFECTS AND SPECIAL PRECAUTIONS

Side-effects:

Haematological

Less frequent: Decreases in white blood cell count, haemoglobin and haematocrit, bone marrow depression, anaemia, thrombocytopenia, agranulocytosis, haemolytic anaemia.

Cardiovascular

*Less frequent***:** Orthostatic effects (including hypotension, myocardial infarction, cerebrovascular accident, palpitations, tachycardia).

Neurological

- *More frequent***:** Dizziness, headache, fatigue.
- *Less frequent***:** Mood alterations, mental confusion, paraesthesia, vertigo, sleep disturbances.

Endocrine/Metabolic

Less frequent: Hyperkalaemia, hyponatraemia, increases in blood urea, increases in serum creatinine.

Gastro-intestinal

- *More frequent:* Diarrhoea, nausea.
- *Less frequent:* Abdominal pain, indigestion, dry mouth, pancreatitis, vomiting, taste disturbances.

Kidney/Genito-urinary

Less frequent: Uraemia, oliguria, anuria, renal dysfunction, acute renal failure, impotence.

Liver/Hepatic

Less frequent: Hepatitis (hepatocellular or cholestatic), jaundice, increase in liver enzymes, increases in serum bilirubin.

Musculoskeletal

Less frequent: Asthenia.

Respiratory

- *More frequent:* Cough.
- *Less frequent:* Bronchospasm, rhinitis, sinusitis.

Skin

Less frequent: Rash, urticaria, diaphoresis, alopecia, pruritis, psoriasis, severe skin disorders including pemphigus, toxic epidermal necrolysis, Steven-Johnsons Syndrome and erythema multiforme.

Other

Less frequent: Hypersensitivity/angioedema reactions: angioedema of the face, which may be fatal, extremities, lips, tongue, glottis and /or larynx and intestinal angioedema. A symptom complex has been reported which may include :fever, vasculitis, myalgia, arthritis/arthralgia, a positive antinuclear antibodies (ANA) , elevated erythrocyte sedimentation rate, eosinophilia and leucocytosis. Rash, photosensitivity or other dermatological manifestations may occur.

Special precautions

- Myocardial infarction and cerebrovascular accidents may be due to severe falls in blood pressure in high-risk patients e.g. those with ischaemic heart disease or cerebrovascular disease.
- In volume-depleted patients or patients with ischaemic heart disease or cerebrovascular disease, therapy should be monitored especially when the dose of **AUSTELL-LISINOPRIL** or diuretic is adjusted.
- If hypotension occurs, the patient should be placed in the supine position and if necessary receive an intravenous infusion of 0.9% saline.
- 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.

- Signs of facial or extremity swelling or difficulty in swallowing or breathing, requires immediate medical attention, because of the risk of angioedema.
- Caution when driving or performing tasks requiring alertness because of possible dizziness.
- In patients undergoing major surgery or during anesthesia with agents 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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

(SEE SIDE EFFECTS AND SPECIAL PRECAUTIONS)

Symptoms of overdosage: Severe hypotension, electrolyte disturbances and renal failure.

Treatment of overdosage: Treatment is symptomatic and supportive. 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. **AUSTELL-LISINOPRIL** is removable by haemodialysis.

IDENTIFICATION

AUSTELL–LISINOPRIL 2.5 mg:

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:

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

AUSTELL-LISINOPRIL 10 mg:

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

AUSTELL –LISINOPRIL 20 mg:

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

PRESENTATION

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:

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.

STORAGE INSTRUCTIONS

Store below 25 °C. Protect from light.

Keep blister packs in carton until required for use.

Keep the HDPE container well closed.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

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-LISINOPRIL 20 mg: 37/7.1.3/0392

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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