Professional Information: AUSTELL LOSARTAN CO

SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

AUSTELL LOSARTAN CO tablets

COMPOSITION

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

Excipients

Colloidal anhydrous silica, lactose monohydrate, magnesium stearate, maize starch, microcrystalline cellulose, pregelatinized starch.

Film coating

Hydroxypropyl methylcellulose, macrogol, purified talc, titanium dioxide, purified talc.

Contains sugar (lactose monohydrate: 111,50 mg per capsule).

CATEGORY AND CLASS

A 7.1.3: Other hypotensives.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

AUSTELL LOSARTAN CO contains an Angiotensin II receptor antagonist, losartan and a diuretic, hydrochlorothiazide.

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 AT_1 receptor found in many tissues (vascular smooth muscles, 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 AT_1 receptor. Both losartan and its pharmacologically active carboxylic acid metabolite (E-3174) blocks the actions of angiotensin II, regardless of the source of synthesis. Losartan binds selectively to the AT_1 receptor and does not bind to or block other hormone receptors or ion channels important in cardiovascular regulation. Losartan does not inhibit ACE (Kininase II), the enzyme that degrades bradykinin.

Hydrochlorothiazide

The mechanism of the anti-hypertensive effect of thiazides is unknown. Thiazides do not usually affect normal blood pressure. Hydrochlorothiazide is a diuretic and anti-hypertensive agent. It affects the distal renal tubular mechanism of electrolyte re-absorption. Hydrochlorothiazide increases the excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium, magnesium and bicarbonate. After oral use, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

Losartan potassium and hydrochlorothiazide are additive in their anti-hypertensive efficacy.

Pharmacokinetic properties [L] losartan [P]potassium

Losartan is readily absorbed from the gastro-intestinal tract following oral administration, and undergoes substantial first pass metabolism resulting in a systemic bioavailability of about 33 %. It is metabolized to an active carboxylic acid metabolite E-3174 (EXP-3174), which has greater pharmacological activity than losartan; some inactive metabolites are also formed. Metabolism is primarily by cytochrome P450, isoenzymes CYP2C9 and CYP3A4. Peak plasma concentrations of losartan and [E-3174] its active metabolite are reached in 1 hour and in 3 to 4 hours, respectively, after an oral dose. Both losartan and its active metabolite are more than

98 % bound to plasma proteins. Losartan is excreted in the urine, and in the faeces via bile, as unchanged drug and metabolite. Following oral dosing about 4 % of the dose is excreted unchanged in urine and about 6 % is excreted in urine as the active metabolite. The terminal elimination half- lives of losartan and its active metabolite are about 1,5 to 2,5 hours and 3 to 9 hours, respectively. There was no clinically significant effect on the plasma concentration profile of losartan when the drug was administered with a standardized meal.

Hydrochlorothiazide:

Hydrochlorothiazide is fairly rapidly absorbed from the gastro-intestinal tract. It is reported to have a bioavailability of about 65-70 %. It has been estimated to have a plasma half-life of between about 5 and 15 hours and appears to be preferentially bound to red blood cells. It is excreted mainly unchanged in the urine. Hydrochlorothiazide crosses the placental barrier and is distributed into breast milk.

INDICATIONS

AUSTELL LOSARTAN CO is indicated for the treatment of hypertension in patients established on identical doses of the individual agents.

CONTRAINDICATIONS

AUSTELL LOSARTAN CO is contraindicated in the following circumstances:

- In patients who are hypersensitive to any of the ingredients of **AUSTELL LOSARTAN CO**
- In pregnancy and lactation (see HUMAN REPRODUCTION)
- Therapy resistant hypokalaemia or hypercalcaemia
- Severe hepatic impairment; cholestatis and biliary obstructive disorders
- Refractory hyponatraemia
- Symptomatic hyperuricaemia/gout
- Severe renal impairment (creatinine clearance <30 ml/min)

- Anuria
- The concomitant use of **AUSTELL LOSARTAN CO** with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1,73 m^2)
- Concomitant use of fluoroquinolones in patients with moderate to severe renal impairment.

WARNINGS AND SPECIAL PRECAUTIONS

- **AUSTELL LOSARTAN CO** should be used with caution in patients with renal artery stenosis.
- Patients with volume depletion may experience hypotension. Therefore volume depletion should be corrected before starting the therapy.
- Hydrochlorothiazide should not be given to patients with Addison's disease.
- All patients should be observed carefully for signs of fluid and electrolyte imbalance.
- Blood glucose concentrations should be monitored in patients taking anti-diabetics, since requirements may change.
- There is an increased risk in non-melanoma skin cancer (NMSC) (basal cell carcinoma, squamous cell carcinoma) with exposure to increasing cumulative doses of hydrochlorothiazide.
- Patients taking **AUSTELL LOSARTAN CO** should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions as well as changes to existing ones, and to report any suspicious skin lesions, which should be examined.
- Exposure to sunlight and ultra violet (UV) rays should be limited.
- The use of **AUSTELL LOSARTAN CO** may also need to be carefully reconsidered in patients who have had previous skin cancer.
- Concomitant use of fluoroquinolones with ACE inhibitors, such as **AUSTELL LOSARTAN CO** , 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 treatment with **AUSTELL LOSARTAN CO** .

Special precautions:

AUSTELL LOSARTAN CO is not recommended for patients with hepatic or severe renal impairment (see CONTRAINDICATIONS).

As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported. These changes in renal function may be reversible upon discontinuation of therapy.

Other medication that affect the rennin-angiotensin system including **AUSTELL LOSARTAN CO** may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. Similar effects have been reported with losartan; these changes in renal function may be reversible upon discontinuation of therapy.

Hypotension and electrolyte/fluid imbalance

In patients who are intravascularly volume-depleted (e.g. those treated with high-dose diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of **AUSTELL LOSARTAN CO** , or a lower starting dose should be used (see DOSAGE AND DIRECTIONS FOR USE). Periodic determination of serum electrolyte should be performed at appropriate intervals as in any patient receiving diuretics.

Metabolic and endocrine effects

Thiazide therapy may impair glucose tolerance. Dosage adjustment of anti-diabetic agents, including insulin, may be required (see INTERACTIONS).

Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcaemia may be evidence of hidden

hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increase 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 hyperuricaemia.

Other

In patients receiving thiazides, sensitivity 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.

Thiazides cross the placenta and there have been reports of neonatal jaundice and thrombocytopenia

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.

Porphyria

Hydrochlorothiazide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

AUSTELL LOSARTAN CO contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take **AUSTELL LOSARTAN CO .**

Contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

INTERACTIONS

- Concomitant use with other drugs which lower the blood pressure, should be avoided.
- **AUSTELL LOSARTAN CO** should not generally be given with potassium sparing diuretics such as spironolactone, triamterene and amiloride as it leads to additive effect of hyperkalaemia (see CONTRAINDICATIONS)
- May interact with drugs which affect cytochrome P450 isoenzymes
- Hypokalaemia caused by hydrochlorothiazide may enhance the toxicity of digitalis glycosides and may also increase the risk of arrhythmias with drugs that prolong the QT intervals such as astemizole, terfenadine, halofantrine, pimozide and sotalol.
- Thiazides may enhance the neuromuscular blocking action of competitive neuromuscular blockers, such as atracurium, probably by their hypokalaemic effects.
- The potassium depleting effect of diuretics may be enhanced by corticosteroids, carticotropin, beta^2 agonist such as salbutamol, carbenoxolone, amphotericin B or reboxetine.
- Orthostati[~~s~~]t hypotension associated with diuretics may be enhanced by alcohol, barbiturates or opioids.
- Lithium therapy: Concomitant administration with **AUSTELL LOSARTAN CO** may lead to toxic blood concentrations of lithium (see CONTRAINDICATIONS)
- The concomitant use of **AUSTELL LOSARTAN CO** with aliskiren- containing products is contraindicated (see CONTRAINDICATIONS)
- Concomitant use of fluoroquinolones and ACE inhibitors, such as **AUSTELL ENALAPRIL**, may precipitate acute kidney injury (see **CONTRAINDICATIONS**).

HUMAN REPRODUCTION

Pregnancy

Safety in pregnant and lactation has not been established.

When pregnancy is detected, AUSTELL LOSARTAN CO should be discontinued as soon as possible.

DOSAGE AND DIRECTIONS FOR USE

The usual starting dose and maintenance dose of **AUSTELL LOSARTAN CO** is one tablet once daily. For patients who do not respond adequately to **AUSTELL LOSARTAN CO** , the dosage may be changed to two tablets of **AUSTELL LOSARTAN CO** once daily.

The maximum dose is two tablets of **AUSTELL LOSARTAN CO** once daily. The maximum anti-hypertensive effect is attained within three weeks after initiation of therapy.

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

No initial dosage adjustment is necessary for elderly patients.

AUSTELL LOSARTAN CO may be administered with or without food.

SIDE-EFFECTS

The side-effects below are classified by system organ class and frequency according to the following convention:

very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000); unknown.

The following side effects have been reported for losartan

System organ class
Side-effect
Frequency
Blood and lymphatic system disorders
Anaemia, Henoch-Schönlein purpura, ecchymosis, haemolysis
uncommon

thrombocytopenia
unknown
Cardiac disorders
Hypotension, orthostatic hypotension, sternalgia, angina pectoris, grade II-AV block, cerebrovascular event, myocardial infarction, palpitation, arrhythmias (atrial fibrillations, sinus bradycardia, tachycardia, ventricular fibrillation)
uncommon
Ear and labyrinth disorders
Vertigo, tinnitus

uncommon
Eye disorders
Blurred vision, burning/stinging in the eye, conjunctivitis, decrease in visual acuity
uncommon
Gastrointestinal disorders
Abdominal pain, nausea, diarrhoea, dyspepsia
common

Constipation, dental pain, dry mouth, flatulence, gastritis, vomiting, obstipation
uncommon

pancreatitis
unknown
General disorders and administration site conditions
Asthenia, fatigue, chest pain
common

facial oedema, oedema, fever
uncommon

flu-like symptoms, malaise
unknown
Hepatobiliary disorders
Liver function abnormalities
unknown
Immune system disorders
Hypersensitivity: anaphylactic reactions, angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue; in some of these patients angioedema had been reported in the past in connection with the administration of the other medicines, including ACE inhibitors
rare
Metabolism and nutrition disorders
Anorexia, gout
uncommon
Musculoskeletal and connective tissue disorders
Muscle cramps, back pain, leg pain, myalgia
common

Arm pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, coxalgia, fibromyalgia, muscle weakness
uncommon

Rhabdomyolysis
unknown
Nervous system disorders
Headache, dizziness
common

Nervousness, paraesthesia, peripheral neuropathy, tremor, migraine, syncope
uncommon

Dysgeusia
unknown
Psychiatric disorders
Insomnia
common

Anxiety, anxiety disorder, panic disorder, confusion, depression, abnormal dreams, sleep disorder, somnolence, memory impairment
uncommon
Renal and urinary disorders
Renal impairment, renal failure
common

Nocturia, urinary frequency, urinary tract infection
uncommon
Reproductive system and breast disorders
Decreased libido, erectile dysfunction/impotence
uncommon
Respiratory, thoracic and mediastinal disorders
Cough, upper respiratory infection, nasal congestion, sinusitis, sinus disorder
common

Pharyngeal discomfort, pharyngitis, laryngitis, dyspnoea, bronchitis, epistaxis, rhinitis, respiratory congestion
uncommon
Skin and subcutaneous tissue disorders
Alopecia, dermatitis, dry skin, erythema, flushing, photosensitivity, pruritus, rash, urticaria, sweating
uncommon
Vascular disorders
Vasculitis
uncommon

Dose-related orthostatic effects
unknown
Investigations
Hyperkalaemia, mild reduction of haematocrit and haemoglobin, hypoglycaemia
common

Mild increase in urea and creatinine serum levels
uncommon

Increase in hepatic enzymes and bilirubin
very rare

Hyponatraemia
unknown

The following side effects have been reported for hydrochlorothiazide

System organ class
Side effect
Frequency
Blood and lymphatic system disorders
Agranulocytosis, aplastic anaemia, haemolytic anaemia, leukopenia, purpura, thrombocytopenia
uncommon
Immune system disorders
Anaphylactic reaction
rare
Metabolism and nutrition disorders
Anorexia, hyperglycaemia, hyperuricaemia, hypokalaemia, hyponatraemia
uncommon
Psychiatric disorders
Insomnia
uncommon
Nervous system disorders
Cephalalgia
common
Eye disorders
Transient blurred vision, xanthopia
uncommon
Vascular disorders
Sialoadenitis, spasms, stomach irritation, nausea, vomiting, diarrhoea, constipation
uncommon
Respiratory, thoracic and mediastinal disorders

Respiratory distress including pneumonitis and pulmonary oedema
uncommon
Gastrointestinal disorders
Sialoadenitis, spasms, stomach irritation, nausea, vomiting, diarrhoea, constipation
uncommon
Hepato-biliary disorders
Icterus (intrahepatic cholestatis), pancreatitis
uncommon
Skin and subcutaneous tissue disorders
Photosensitivity, urticaria, toxic epidermal necrolysis
uncommon

cutaneous lupus erythematosus
unknown
Musculoskeletal and connective tissue disorders
Muscle cramps
uncommon
Renal and urinary disorders
Glycosuria, interstitial nephritis, renal dysfunction, renal failure
uncommon
General disorders and administration site conditions
Fever, dizziness
uncommon

KNOWN SYMPTOMS OF OVER-DOSAGE AND PARTICULARS OF ITS TREATMENTS

Losartan potassium

Limited data is available with regards to over-dosage in humans. The most likely manifestation of over-dosage would be hypotension and tachycardia. Bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan not the active metabolite can be removed by haemodialysis.

Hydrochlorothiazide

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalaemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

IDENTIFICATION

AUSTELL LOSARTAN CO is a yellow coloured, oval, biconvex, film-coated tablet.

PRESENTATION

White - Opaque Aluminium/PVDC coated PVC blister packs of 3 x 10 tablets.

Not all pack sizes may be marketed.

STORAGE INSTRUCTIONS

Store in a dry place at or below 25 °C. Protect from light.

Keep blister packs in the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

AUSTELL LOSARTAN CO TABLETS: 42/7.1.3/0027

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