Approved Package Insert for Medicines for Human use:

AUSTELL CO-AMOXICLAV ES 600

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

AUSTELL CO-AMOXICLAV ES 600 600

(Powder for suspension)

COMPOSITION:

AUSTELL CO-AMOXICLAV ES 600 600

(Powder for suspension):

When reconstituted, each 5 ml suspension contains amoxicillin trihydrate equivalent to 600 mg amoxicillin and potassium clavulanate equivalent to clavulanic acid 42,9 mg.

The excipients are: carmellose sodium (Avicel CL 611), hydrated (Syloid AL-1-FP), microcrystalline cellulose, tutti frutti flavour (51880), artificial sweetener - saccharin sodium, silica colloidal anhydrous (Aerosil 200), silica colloidal, succinic acid, xanthan gum and vanilla flavour (054286).

Contains Saccharin sodium.

AUSTELL CO-AMOXICLAV ES 600 is sugar free.

PHARMACOLOGICAL CLASSIFICATION:

A 20.1.2 Penicillins.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Amoxiclav is the group name for the formulations containing 14 parts of a broad spectrum penicillin, amoxicillin and 1 part of potassium clavulanate. Potassium clavulanate has been shown *in vitro* to be an irreversible inhibitor of beta-lactamases produced by certain bacteria.

Potassium clavulanate does not inactivate the chromosomally mediated (Sykes Type 1 Cephalosporinase) beta-lactamases produced by *Acinetobacter* species, *Citrobacter* species, *Enterobacter*, Indole positive *Proteus, Providencia* species and *Serratia marcescens*. *In vitro* the amoxiclav formulation shows synergism against amoxicillin-resistant organisms, with no evidence of antagonism and the activity was not reduced in the presence of serum. (*In vitro* activity does not necessarily imply *in vivo* efficacy.)

Bactericidal action - The amoxicillin component of the formulations exert a bactericidal action against many strains of Gram-positive and Gram-negative organisms. The clavulanic acid component has very little bactericidal action. It does however, by inactivation of susceptible beta-lactamases, protect amoxicillin from degradation by a large number of beta-lactamase enzymes produced by penicillin resistant strains of organisms.

Organisms inherently resistant against the amoxicillin and clavulanic acid combination may include:

Aerobic Gram-negative micro-organisms

Acinetobacter sp.

Citrobacter freundii

Enterobacter sp.

Legionella pneumophila

Morganella morganii

Providencia spp.

Pseudomonas sp.

Serratia sp.

Stenotrophomonas maltophilia

Other micro-organisms

Chlamydophila pneumoniae

Chlamydophila psittaci

Coxiella burnetti

Mycoplasma pneumoniae

Pharmacokinetic properties:

Absorption:

Both components, amoxicillin and clavulanic acid are fully dissociated in aqueous solution at physiological pH and are well absorbed when taken orally. Absorption is optimised when taken at the start of a meal.

Amoxicillin is stable in the presence of acidic gastric secretions. Peak blood levels are achieved 1-2 hours after administration.

The pharmacokinetics of amoxicillin and clavulanic acid are closely allied and neither is adversely affected by the presence of food in the stomach.

Distribution:

Approximately 17 - 20 % of the total plasma amoxicillin content is protein bound. Amoxicillin diffuses readily into most body tissues with the exception of the brain and spinal fluid. Inflammation generally increases the permeability of the meninges to penicillins and this may apply to amoxicillin.

Excretion:

The major route of elimination is via the kidneys for amoxicillin whilst for clavulanic acid it is by both renal and non-renal mechanisms. Approximately 60 – 70 % of amoxicillin and 40 – 65 % of clavulanic acid are excreted unchanged in the urine in the first 6 hours after an oral dose. Amoxicillin is partly excreted in the urine as the inactive metabolite penicilloic acid. Clavulanic acid is extensively metabolised and the metabolites are eliminated via urine and faeces. Co-

administration of probenecid delays amoxicillin excretion, but has little effect on the excretion of the clavulanic acid component of the formulation.

Small amounts of amoxicillin are also excreted in the faeces and bile. The elimination pharmacokinetics seen in adults also apply to children with mature kidney function.

INDICATIONS:

AUSTELL CO-AMOXICLAV ES 600 is indicated for the short-term treatment of acute bacterial otitis media infections when caused by the following amoxiclav sensitive organisms: *Haemophilus influenzae, Streptococcus pneumonia* (penicillin MIC ≤ 4 µg/ml) and *Moxarella catarrhalis.*

CONTRA- INDICATIONS:

- Hypersensitivity to amoxicillin, other penicillins, beta-lactams, cephalosporins or any ingredient of **AUSTELL CO-AMOXICLAV ES 600**. Cross-sensitivity between penicillins and cephalosporins is well documented.
- **AUSTELL CO-AMOXICLAV ES 600** is contra-indicated in patients with a previous history of amoxicillin/clavulanic-associated jaundice/hepatic dysfunction.
- Safety in children under 2 months of age has not been established. There is no clinical data in children under 3 months of age.

WARNINGS AND SPECIAL PRECAUTIONS:

- Serious and occasionally fatal hypersensitivity reactions such as anaphylaxis have been reported in patients on penicillin therapy. Before initiating therapy with **AUSTELL CO-AMOXICLAV ES 600**, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillin. These reactions are more likely to occur in individuals with a history

of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity, who have experienced severe reactions when treated with cephalosporins. If an allergic reaction occurs, **AUSTELL CO-AMOXICLAV ES 600** should be discontinued and the appropriate therapy instituted. Serious anaphylactic reactions may require immediate emergency treatment with epinephrine (adrenaline). Oxygen, intravenous steroids and airway management, including intubation may also be required.

- During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria.
- Prolonged use may result in overgrowth of non-susceptible organisms such as *Clostridium difficile* and *Candida*.
- Pseudomembranous enterocolitis may occur.
- Abnormal prolongation of prothrombin time (increased INR) has been reported in patients receiving amoxicillin-clavulanic acid and oral anticoagulants, e.g. warfarin. Appropriate monitoring should be undertaken with concurrent prescriptions. Adjustments in the dosage of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see **INTERACTIONS**).
- Use of **AUSTELL CO-AMOXICLAV ES 600** may lead to the selection of resistant strains of organisms and sensitivity testing should be carried out whenever possible.
- **AUSTELL CO-AMOXICLAV ES 600** contains amoxicillin, an aminopenicillin, it is not the treatment of choice in patients presenting with sore throat or pharyngitis because of the possibility that the underlying cause is infectious mononucleosis, in the presence of which there is a high incidence of rash if amoxicillin is used.
- **AUSTELL CO-AMOXICLAV ES 600** should be given with caution to patients with lymphatic leukaemia since they are especially susceptible to amoxicillin induced skin rashes.

- The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Aerobacter, Pseudomonas or Candida*), **AUSTELL CO-AMOXICLAV ES 600** should be discontinued and/or appropriate therapy instituted.
- Caution is needed when administering **AUSTELL CO-AMOXICLAV ES 600** to patients with syphilis as Jarisch Herxheimer reaction may occur in these patients.
- Periodic assessment of organ function, including renal, hepatic and haematopoietic functions, is advisable during prolonged therapy.

***Impaired hepatic function*:**

Transient hepatitis, cholestatic jaundice and changes in liver function may occur.

AUSTELL CO-AMOXICLAV ES 600 should be used with care in patients with evidence of severe hepatic dysfunction. Hepatic function should be monitored regularly (see **DOSAGE AND DIRECTIONS FOR USE**).

***Impaired renal function*:**

In patients with moderate or severe renal impairment **AUSTELL CO-AMOXICLAV ES 600** dosage should be adjusted (see **DOSAGE AND DIRECTIONS FOR USE**).

Interactions with laboratory tests:

During treatment with **AUSTELL CO-AMOXICLAV ES 600** false positive readings are possible with chemical methods to test for glucose in the urine (see **INTERACTIONS**).

Effects on the ability to drive and use machines:

There is no evidence of the effects on the ability to drive and use machines, but the patient should be cautioned not to drive or operate machinery until their individual susceptibility is known.

INTERACTIONS:

- Concurrent use of **AUSTELL CO-AMOXICLAV ES 600** with probenecid is not recommended since probenecid decreases the renal tubular secretion of amoxicillin, but does not affect clavulanic acid excretion resulting in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.
- **AUSTELL CO-AMOXICLAV ES 600** may reduce the efficacy of oral contraceptives. Patients should be warned accordingly.
- The concomitant administration of allopurinol and ampicillin substantially increases the incidence of skin rashes in patients receiving both **AUSTELL CO-AMOXICLAV ES 600** as compared to patients receiving ampicillin alone.
- Tetracyclines and other bacteriostatic medicines may interfere with the bactericidal effects of amoxicillin.
- The ingestion of alcohol and **AUSTELL CO-AMOXICLAV ES 600** can precipitate a disulfiram- like reaction. Therefore, the ingestion of alcohol should be avoided during and for several days after treatment with **AUSTELL CO-AMOXICLAV ES 600.**
- Oral anticoagulants taken with **AUSTELL CO-AMOXICLAV ES 600** may increase prothrombin time. If co-administration is necessary, patients should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary (see **WARNINGS AND SPECIAL PRECAUTIONS**)**.**
- During treatment with **AUSTELL CO-AMOXICLAV ES 600** false positive readings are possible with chemical methods to test for glucose in the urine. (see **WARNINGS AND SPECIAL PRECAUTIONS**)**.**

PREGNANCY AND LACTATION:

Pregnancy:

- The safety of **AUSTELL CO-AMOXICLAV ES 600** in pregnancy has not been established.
- Prophylactic treatment with **AUSTELL CO-AMOXICLAV ES 600** may be associated with an increased risk of necrotising enterocolitis in neonates.

Lactation:

- Amoxicillin is distributed into breast milk. Although significant problems in humans have not been documented, the use of **AUSTELL CO-AMOXICLAV ES 600** by nursing mothers may lead to sensitisation, diarrhoea, candidiasis and skin rash in the infant.

DOSAGE AND DIRECTIONS FOR USE:

- **AUSTELL CO-AMOXICLAV ES 600** should be taken immediately before a meal.
- The duration of treatment should be appropriate to the indication and should not exceed 14 days without review.
- **AUSTELL CO-AMOXICLAV ES 600 reconstitution (100 ml):** 90 ml of water is required for reconstitution. Method for reconstitution: tap the bottle until the powder flows freely. Add 2/3 of the total amount of water for reconstitution (60 ml) and shake vigorously to suspend the powder. Add the remainder of the water (1/3) to the marked line on the bottle and shake vigorously again.
- **AUSTELL CO-AMOXICLAV ES 600 reconstitution (50 ml):** 44 ml of water is required for reconstitution. Method for reconstitution: tap the bottle until the powder flows freely. Add 2/3 of the total amount of water for reconstitution (30 ml) and shake vigorously to suspend the powder. Add the remainder of the water (1/3) to the marked line on the bottle and shake vigorously again.

Dosages:

AUSTELL CO-AMOXICLAV ES 600 should be dosed at 90/6,4 mg/kg/day in two divided doses at 12 hourly intervals for 10 days in children aged 3 months and older.

There is no experience in patients weighing > 40 kg or in adults. There are is no clinical data for children under 3 months of age.

Body weight (kg)	Volume of **AUSTELL CO-AMOXICLAV ES 600** providing 90/6,4 mg/kg/day
8	3,0 ml twice daily
12	4,5 ml twice daily
16	6,0 ml twice daily
20	7,5 ml twice daily
24	9,0 ml twice daily
28	10,5 ml twice daily
32	12,0 ml twice daily
36	13,5 ml twice daily

Renal Impairment: There are no dosing recommendations in patients with renal impairment.

Hepatic Impairment: There is no sufficient data on which to base a recommendation.

SIDE EFFECTS

The incidence and severity of adverse effects, particularly nausea and diarrhoea, can be minimised by administering **AUSTELL CO-AMOXICLAV ES 600** at the start of a meal.

The following adverse reactions may occur with **AUSTELL CO-AMOXICLAV ES 600.**

Infections and infestations:

Frequent: Mucocutaneous candidiasis (including vaginitis).

Blood and lymphatic system disorders:

Less frequent: Haemolytic anaemia, reversible thrombocytopenia, reversible leukopenia (including neutropenia), reversible agranulocytosis and prolongation of prothrombin and bleeding time (see **WARNINGS AND SPECIAL PRECAUTIONS**). Monitor appropriately when anticoagulants are concomitantly prescribed.

Immune system disorders:

Less frequent: Angioedema, anaphylaxis, serum sickness-like syndrome, hypersensitivity vasculitis.

Nervous system disorders:

Less frequent: Dizziness, headache, reversible hyperactivity and convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Gastrointestinal disorders:

Frequent: Diarrhoea, nausea, vomiting. Nausea is more common with higher oral doses.

Less frequent: Indigestion, abdominal pain and abnormal taste, gastritis, stomatitis, glossitis, black “hairy” tongue, tiredness and hot flushes, enterocolitis, and antibiotic-associated colitis and diarrhoea (AAD) (including pseudomembranous colitis and haemorrhagic colitis). Superficial tooth discolouration can occur which can be removed by brushing.

If gastrointestinal reactions are evident, they may be reduced by taking **AUSTELL CO-AMOXICLAV ES 600** at the start of a meal.

Hepato-biliary disorders:

Less frequent: Hepatitis and cholestatic jaundice, a moderate rise in AST and/or ALT.

Hepatic events may occur predominantly in males and elderly patients and may be associated with prolonged treatment. Signs and symptoms may occur shortly after treatment and may also become apparent several weeks after treatment has ceased. These are usually reversible.

Hepatic events may be severe and death may occur.

Skin and subcutaneous tissue disorders:

Less frequent: Skin rashes, pruritus and urticaria, erythema multiforme, Stevens-Johnson syndrome, hypersensitivity, bullous exfoliative dermatitis,

acute generalised exanthematous pustulosis (AGEP) and toxic epidermal necrolysis.

Whenever such reactions occur, **AUSTELL CO-AMOXICLAV ES 600** should be discontinued. Serious and occasional fatal hypersensitivity (anaphylactic) reactions and angioedema can occur with oral penicillin (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Renal and urinary disorders:

Less frequent: Interstitial nephritis, crystalluria.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS:

Gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident and symptoms of water and electrolyte imbalance should be treated symptomatically.

- **AUSTELL CO-AMOXICLAV ES 600** may be removed from circulation by haemodialysis.
- Adequate fluid intake and urinary output must be maintained to minimise the possibility of crystalluria which in some cases can lead to renal failure.

IDENTIFICATION:

AUSTELL CO-AMOXICLAV ES 600:

Before reconstitution: White to creamy white coloured tutti frutti, vanilla odoured, homogeneous powder mixture.

After reconstitution: White to creamy white coloured, aromatic odoured (tutti frutti-vanilla) homogeneous suspension.

PRESENTATION:

- **AUSTELL CO-AMOXICLAV ES 600** (Powder for suspension) 100 ml: is packed in a 150 ml, Type III, amber coloured glass bottle; with gravure line at 100 ml and is closed with a child resistant, white opaque, polypropylene cap. It is accompanied by a 5 ml

polypropylene spoon in a cardboard box.

- (**AUSTELL CO-AMOXICLAV ES 600** Powder for suspension) 50 ml: is packed in a 100 ml, Type III, amber coloured glass bottle; with gravure line at 50 ml and is closed with a child resistant, white opaque, polypropylene cap. It is accompanied by a 5 ml polypropylene spoon in a cardboard box.

STORAGE INSTRUCTIONS:

Store at or below 30°C.

Keep tightly closed.

After reconstitution, store the suspension in a refrigerator between 2 °C and 8 °C and use within 10 days. Do not freeze.

Store in the original packaging until required for use.

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBER:

AUSTELL CO-AMOXICLAV ES 600 600: 48/20.1.2/1123

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

Austell Pharmaceuticals (Pty) Ltd.

1 Sherborne Road

Parktown,

Johannesburg, 2193

South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT:

Date on the registration certificate: 18 February 2016