APPROVED PACKAGE INSERT: AUSTELL CO-AMOXICLAV 375/625 mg Tablets

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

AUSTELL CO- AMOXICLAV 375 mg TABLETS

AUSTELL CO-AMOXICLAV 625 mg TABLETS

COMPOSITION

AUSTELL CO-AMOXICLAV 375 mg TABLETS:

Each tablet contains amoxicillin trihydrate equivalent to 250 mg amoxicillin and potassium clavulanate equivalent to 125 mg clavulanic acid.

AUSTELL CO-AMOXICLAV 625 mg tablets:

Each tablet contains amoxicillin trihydrate equivalent to 500 mg amoxicillin and potassium clavulanate equivalent to 125 mg clavulanic acid.

PHARMACOLOGICAL CLASSIFICATION

A.20.1.2 Penicillins.

PHARMACOLOGICAL ACTION

AUSTELL CO- AMOXICLAV tablets is a combination of amoxicillin and clavulanic acid.

Amoxicillin is a semisynthetic beta-lactamase–susceptible penicillin, which has *in vitro* bactericidal activity against broad spectrum of non beta-lactamase-producing Gram positive and Gram negative organisms. The spectrum of activity does not include those organisms that produce beta-lactamases, namely resistant staphylococci, and all strains of *Pseudomonas, Klebsiella* and *Enterobacter.*

Clavulanic acid has been shown *in vitro* to be an irreversible inhibitor of beta-lactamases produced by: *Staphylococcus aureus*, *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Proteus vulgaris, Haemophilus influenzae, Neisseria gonorrhoea* and *Bacteroides fragilis*. Clavulanic acid 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 formulation showed 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.) The clavulanic acid component has very little bactericidal action.

Pharmacokinetics:

Absorption**:**

Amoxicillin is stable in the presence of acidic gastric secretions. Peak blood levels are achieved 1-2 hours after administration. There is a linear dose response in peak serum levels.

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

Distribution:

Approximately 18 % 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 elimination half –life of amoxicillin is approximately 1 hour. Co-administration of probenecid 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.

INDICATIONS

AUSTELL CO-AMOXICLAV tablets are indicated for the treatment of infections caused by amoxicillin resistant organisms producing beta-lactamases sensitive to clavulanic acid:

Upper respiratory tract infections, such as sinusitis, recurrent otitis media, tonsillitis. Lower respiratory tract infections, such as bronchitis and bronchopneumonia. Genito-urinary tract infections, such as cystitis, urethritis, pyelonephritis. Skin and soft tissue infections.

AUSTELL CO-AMOXICLAV will also be effective in the treatment of infections caused by amoxicillin sensitive organisms at the appropriate amoxicillin dosage since in this situation the clavulanic acid component does not contribute to the therapeutic effect.

CONTRA-INDICATIONS

Hypersensitivity to penicillins or to cephalosporins. Cross- sensitivity between penicillins and cephalosporins is well documented.

AUSTELL CO-AMOXICLAV is contra-indicated in patients with a previous history of amoxicillin/clavulanic –associated jaundice/hepatic dysfunction.

WARNINGS

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. Before initiating therapy with

AUSTELL CO-AMOXICLAV careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. Although anaphaylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. 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** should be discontinued and the appropriate therapy instituted. Serious anaphylactic reactions may require immediate emergency treatment with adrenaline. Oxygen, intravenous steroids and airway management, including intubation may also be required.

AUSTELL CO-AMOXICLAV should be avoided if infectious mononucleosis is suspected since the occurrence of morbilliform rash has been associated with this condition following the use of amoxicillin.

Prolonged use may result in overgrowth of non-susceptible organisms. Pseudomembranous enterocolitis has been reported.

Prolongation of prothrombin time has been reported rarely in patients receiving **AUSTELL CO-AMOXICLAV**. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently.

Periodic assessment of organ function, including renal, hepatic and haematopoietic functions, is advisable during prolonged therapy.

Transient hepatitis and cholestatic jaundice has been reported. **AUSTELL CO-AMOXICLAV** should be used with caution in patients with evidence of hepatic dysfunction.

INTERACTIONS

Probenecid decreases the renal tubular secretion of amoxicillin, but does not affect clavulanic acid excretion. Concurrent use with **AUSTELL CO-AMOXICLAV** may result in increased and prolonged blood levels of amoxicillin, but not of clavulanic acid.

AUSTELL CO-AMOXICLAV may reduce the efficacy of oral contraceptives and the patients should be warned accordingly.

The concomitant administration of allopurinol and ampicillin substantially increases the incidence of skin rashes in patients receiving both agents as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricaemia present in these patients.

Tetracyclines and other bacteriostatic drugs may interfere with the bactericidal effects of amoxicillin.

Interaction with Laboratory tests:

It is recommended that when testing for the presence of glucose in urine during **AUSTELL CO-AMOXICLAV** treatment, enzymatic glucose oxidase methods should be used. Due to the high urinary concentrations of amoxicillin, false positive readings are common with chemical methods.

PREGNANCY AND LACTATION

Use in pregnancy:

The safety of **AUSTELL CO-AMOXICLAV** in pregnancy has not been established.

Use in lactation:

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

DOSAGE AND DIRECTIONS FOR USE

Tablets should be taken immediately before a meal.

Dosages:

General Information: For infections caused by amoxicillin sensitive organisms the dosage is that approved for amoxicillin as the clavulanic acid component does not contribute to the therapeutic effect.

Adult:

The adult dose for **AUSTELL CO- AMOXICLAV** is one

AUSTELL CO-AMOXICLAV 375 mg tablet every eight hours at the start of a meal. For more severe infections and infection of the respiratory tract, the dose should be one **AUSTELL CO-AMOXICLAV 625 mg** tablet every eight hours at the start of a meal.

Since **AUSTELL CO-AMOXICLAV 375 mg and 625 mg** tablets contain the same amount of clavulanic acid (125 mg as the potassium salt), two

AUSTELL CO-AMOXICLAV 375 mg tablets are not equivalent to one

AUSTELL CO-AMOXICLAV 625 mg tablet**.**

Therefore two **AUSTELL CO-AMOXICLAV** 375 mg tablets should not be substituted for one **AUSTELL CO-AMOXICLAV** 625 mg tablet.

Impaired renal function:

Both amoxicillin and clavulanic acid are excreted by the kidneys and the serum half-life of each increases in patients with renal failure. Therefore, the dose may need to be reduced or the interval extended. Dosage adjustments are based on the maximum recommended level of amoxicillin.

The following schedule is proposed:

AUSTELL CO-AMOXICLAV 375 mg and 625 mg Tablets:

Mild impairment (creatinine clearance greater than 30 ml/minute): no change in dosage.

Moderate impairment (creatinine clearance 10 to 30 ml/minute): 1 tablet every twelve hours.

Severe impairment (creatinine clearance less than 10 ml/minute): half a tablet every twelve hours.

Haemodialysis decreases serum concentrations of both amoxicillin and clavulanic acid and an additional dose should be administered at the end of dialysis.

Dosage Guide:

Amoxicillin-Sensitive Organisms

Product	**Upper Respiratory Tract Infection**	**Lower Respiratory Tract Infection**	**Urinary Tract infection**	**Skin and soft Tissue Infections**
Austell-Co Amoxiclav 375 mg Tablets	1 tablet 8 hourly	-	1 tablet 8 hourly	1 tablet 8 hourly
Austell-Co Amoxiclav 625 mg Tablets	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly

Amoxicillin-Resistant Organisms

Product	**Upper Respiratory Tract Infection (otitis media)**	**Lower Respiratory Tract Infection (bronchitis)**	**Urinary Tract infection**	**Skin and soft Tissue Infections**
Austell-Co Amoxiclav 375 mg Tablets	-	-	1 tablet 8 hourly	1 tablet 8 hourly
Austell-Co Amoxiclav	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly

625 mg Tablets				

Children: The dose of **AUSTELL CO-AMOXICLAV** in children is 25-50 mg/kg/day of the 4 parts amoxicillin, 1 part clavulanic acid preparations (which corresponds to a daily dosage of the equivalent of 20-40 mg/kg of amoxicillin and 5–10 mg/kg of clavulanic acid) to be taken in divided doses every eight hours, at the start of a meal.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

The most frequently reported adverse effects are diarrhoea, nausea, vomiting, indigestion, abdominal pain, skin rashes, urticaria and erythema multiforme, vaginitis, abnormal taste, headache, dizziness, tiredness and hot flushes.

The incidence and severity of adverse effects, particularly nausea and diarrhoea, increased with the higher recommended dose and can be minimised by administering **AUSTELL CO-AMOXICLAV** at the start of a meal. In addition, as these symptoms are especially related to the potassium clavulanate component, where these gastro-intestinal symptoms occur and a higher concentration of amoxicillin is required, consideration should be given to administering the additional amoxicillin separately.

The following adverse reactions have been reported for and may occur with

AUSTELL CO-AMOXICLAV.

Hypersensitivity reactions

Less frequent:

Skin rashes, pruritus and urticaria, serum sickness-like syndrome, erythema multiforme, bullous exfoliative dermatitis and toxic epidermal necrolysis have been reported. Whenever such reactions occur, **AUSTELL CO-AMOXICLAV** should be discontinued. Serious and occasional fatal hypersensitivity (anaphylactic) reactions and angioneurotic oedema can occur with oral penicillin (see Warnings).

Less frequent:

Interstitial nephritis, Stevens-Johnson syndrome, hypersensitivity vasculitis.

Gastro-intestinal reactions

Less frequent:

Nausea, vomiting, diarrhoea**,** gastritis, stomatitis, glossitis, black 'hairy' tongue, enterocolitis, mucocutaneous candidiasis and antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis). If gastro-intestinal reactions are evident, they may be reduced by taking **AUSTELL CO-AMOXICLAV** at the start of a meal.

Hepatic effects

Less frequent:

Hepatitis and cholestatic jaundice have been reported. The events may be severe, and occur predominantly in adult or elderly patients. Signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until several weeks after treatment has ceased. **The hepatic events are usually reversible. However, in extremely rare circumstances, death has been reported. These have almost always been cases associated with serious underlying disease or concomitant medication.**

A moderate raise in Aspartate transaminase (AST) and/or Alanine transaminase (ALT) has been noted in patients treated with **AUSTELL CO-AMOXICLAV,** but the significance of these findings is unknown.

Renal effects

Less frequent:

Crystalluria has been reported.

Haematological effects

Less frequent:

Haemolytic anaemia, reversible thrombocytopenia, thrombocytopenic purpura, eosinophilia, reversible leucopenia and agranulocytosis have been reported. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1 % of the patients treated with **AUSTELL CO-AMOXICLAV**. Prolongation of bleeding time and prothrombin time have also been reported. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly.

CNS effects

Less Frequent:

Reversible hyperactivity, dizziness, headache and convulsions. Convulsions may occur with impaired renal function or in those receiving high doses.

Miscellaneous

Less Frequent:

Superficial tooth discolouration has been reported. It can usually be removed by brushing.

Special precautions:

Caution is needed when administering amoxicillin to patients with syphilis, as the Jarisch-Herxheimer reaction may occur in these patients.

When high doses are administered, adequate fluid intake and urinary output must be maintained. The sodium content must be taken into account in patients on a sodium-restricted diet if the administration of high doses is necessary.

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function, is advisable during prolonged therapy. Since

AUSTELL CO-AMOXICLAV 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 should be given with caution to patients with lymphatic leukemia 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*), the agent should be discontinued and/or appropriate therapy instituted.

Impaired hepatic function:

Changes in liver function tests have been observed in some patients receiving **AUSTELL CO- AMOXICLAV**. It should be used with care in patients with evidence of severe hepatic dysfunction.

Impaired renal function:

In patients with moderate or severe renal impairment **AUSTELL CO- AMOXICLAV** dosage should be adjusted. (See Dosage and administration.)

Use in lactation:

Amoxicillin is excreted in the milk; there is no data on the excretion of clavulanic acid in human milk. Therefore, caution should be exercised when **AUSTELL CO-AMOXICLAV** is administered to a nursing woman.

The use of **AUSTELL CO-AMOXICLAV** may lead to the selection of resistant strains of organisms and sensitivity testing should, therefore, be carried out whenever possible, to demonstrate the appropriateness of therapy.

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KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Overdosage with amoxicillin is usually asymptomatic. However, gastro-intestinal effects such as nausea, vomiting and diarrhoea may be evident and symptoms of water and electrolyte imbalance should be treated symptomatically.

Adequate fluid intake and urinary output must be maintained to minimise the possibility of crystalluria.

Amoxicillin may be removed from circulation by haemodialysis. The molecular weight, degree of protein binding and pharmacokinetic profile of clavulanic acid together with information from a single patient with renal insufficiency all suggest that this compound may also be removed by haemodialysis.

IDENTIFICATION

AUSTELL CO-AMOXICLAV 375 mg TABLETS:

White to off-white oval shaped film coated tablets with ‘R375’ embossing on one side.

AUSTELL CO-AMOXICLAV 625 mg TABLETS:

White to off-white oval shaped film coated tablets with ‘R625’ embossing on one side.

PRESENTATION

AUSTELL CO-AMOXICLAV 375 mg TABLETS:

Aluminium strip pack of 5X3’s.

AUSTELL CO-AMOXICLAV 625 mg TABLETS:

Aluminium strip pack of 5X3’s.

STORAGE INSTRUCTIONS

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

Keep strip packs in carton until required for use.

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER

AUSTELL CO-AMOXICLAV 375 mg: A39/20.1.2/0488

AUSTELL CO-AMOXICLAV 625 mg: A39/20.1.2/0489

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