Professional Information for Medicines for Human Use: CO-AMOXYCLAV BD AUSTELL

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CO-AMOXYCLAV BD AUSTELL FILM-COATED TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each CO-AMOXYCLAV BD AUSTELL film-coated tablet contains amoxicillin trihydrate equivalent to 875 mg amoxicillin and potassium clavulanate equivalent to 125 mg of clavulanic acid.

Sugar free

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

CO-AMOXYCLAV BD AUSTELL film-coated tablets

White to off-white, capsule-shaped, biconvex, film-coated scored tablets debossed with „875" on one side and D score line V on the other side. The score line at 875/125 mg strength is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CO-AMOXYCLAV BD AUSTELL formulations are indicated for the treatment of infections caused by amoxicillin-resistant organisms producing β-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.
- CO-AMOXYCLAV BD AUSTELL formulations 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.

4.2 Posology and method of administration

Posology

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.

Adults

For severe infections and infection of the respiratory tract, the dose should be one CO-AMOXYCLAV BD AUSTELL tablet every 12 hours at the start of a meal.

Dosage guide: Adults

AMOXICILLIN-SENSITIVE ORGANISMS

UPPER RESPIRATORY TRACT INFECTIONS	LOWER RESPIRATORY TRACT INFECTIONS	URINARY TRACT INFECTIONS	SKIN & SOFT TISSUE INFECTIONS
1 tablet 12-hourly	1 tablet 12-hourly	1 tablet 12-hourly	1 tablet 12-hourly

AMOXICILLIN-RESISTANT ORGANISMS

UPPER RESPIRATORY TRACT INFECTIONS	LOWER RESPIRATORY TRACT INFECTIONS	URINARY TRACT INFECTIONS	SKIN & SOFT TISSUE INFECTIONS

(otitis media) *H. influenzae,* *H. parainfluenzae*	(bronchitis) *H. influenzae,* *H. parainfluenzae*	*E.coli,* *Klebsiella pneumonia*	*Staphylococcus aureus*
1 tablet 12-hourly	1 tablet 12-hourly	1 tablet 12-hourly	1 tablet 12-hourly

Special populations

Elderly population

No dose adjustment is considered necessary.

Renal impairment

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.

CO-AMOXYCLAV BD AUSTELL should not be used in patients with a glomerular filtration rate of less than 30 mL/minute.

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

Hepatic impairment

Dose with caution and monitor hepatic function at regular intervals (see sections 4.3 and 4.4).

Method of administration

CO-AMOXYCLAV BD AUSTELL is for oral use.

Tablets should be taken immediately before a meal.

During the administration of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output to prevent any possibility of amoxicillin crystalluria.

4.3 Contraindications

- Hypersensitivity to amoxicillin, clavulanic acid or to any of the penicillins or to any of the excipients listed in section 6.1.
- History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam medicine (e.g. a cephalosporin, carbapenem or monobactam).
- History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid (see section 4.8).

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Before initiating therapy with amoxicillin/clavulanic acid, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam medicines (see sections 4.3 and 4.8).

Anaphylactic reactions can occur when taking CO-AMOXYCLAV BD AUSTELL which may be serious and occasionally fatal at times.
Hypersensitivity / anaphylactic reactions (including anaphylactoid and severe cutaneous adverse events) have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. If an allergic reaction occurs, amoxicillin/clavulanic acid therapy must be discontinued, and appropriate alternative therapy instituted.

Non-susceptible microorganisms

In the case that an infection is proven to be due to an amoxicillin-susceptible organisms(s) then consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance.

This presentation of CO-AMOXYCLAV BD AUSTELL is not suitable for use when there is a high risk that the presumptive pathogens have resistance to beta-lactam agents that is not mediated by beta-lactamases susceptible to inhibition by clavulanic acid. This presentation should not be used to treat penicillin-resistant *S. pneumoniae*.

Jarisch-Herxheimer reaction

The Jarisch-Herxheimer reaction has been seen following amoxicillin treatment of Lyme disease (see section 4.8). It results directly from the bactericidal activity of amoxicillin on the causative bacteria of Lyme disease, the spirochaete *Borrelia burgdorferi*. Patients should be reassured that this is a common and usually self-limiting consequence of antibiotic treatment of Lyme disease.

Convulsions

Convulsions may occur in patients with impaired renal function or in those receiving high doses (see section 4.8).

Skin reactions

Amoxicillin/clavulanic acid should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.

Patients with lymphatic leukaemia and possibly with HIV infection are particularly prone to developing erythematous rashes with amoxicillin. Amoxicillin should be discontinued if a skin rash occurs.

Overgrowth of non-susceptible microorganisms

Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

Acute generalised exanthemous pustulosis (AGEP)

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (AGEP) (see section 4.8). This reaction requires CO-AMOXYCLAV BD AUSTELL discontinuation and contraindicates any subsequent administration of amoxicillin.

Hepatic Impairment

Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment (see sections 4.2, 4.3 and 4.8).

Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been reported in children. In all populations, 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. These are usually reversible.

Hepatic events may be severe, and in extremely circumstances, deaths have been reported. These have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have the potential for hepatic effects (see section 4.8).

Antibiotic-associated colitis

Antibiotic-associated colitis has been reported with nearly all antibacterial medicines including amoxicillin and may range in severity from mild to life threatening (see section 4.8).
Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Should antibiotic-associated colitis occur, amoxicillin/clavulanic acid should immediately be discontinued, a medical practitioner be consulted, and an appropriate therapy initiated. Anti-peristaltic medicine are contraindicated in this situation.

Periodic assessment of organ system functions

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

Prothrombin time

Prolongation of prothrombin time has been reported in patients receiving amoxicillin/clavulanic acid. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see sections 4.5 and 4.8).

Renal Impairment

In patients with renal impairment, the dose should be adjusted according to the degree of impairment (see section 4.2).
CO-AMOXYCLAV BD AUSTELL should not be used in patients with glomerular filtration rate less than 30 mL/min.
In patients with reduced urine output, crystalluria has been observed, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to

maintain adequate fluid intake and urinary output to reduce the possibility of amoxicillin crystalluria.

In patients with bladder catheters, a regular check of patency should be maintained (see section 4.9).

4.5 Interaction with other medicines and other forms of interaction

Oral contraceptives

Amoxicillin may decrease the efficacy of combined oral contraceptives. It is advisable for patients to use a barrier method of contraception during antibiotic therapy and for seven days after. If the course of antibiotics runs into the seven-daybreak from pill taking then the patient should start the next pack immediately and skip the pill free break. The patient should again use a barrier method of contraception during antibiotic therapy and for seven days after completing the course of antibiotics.

Oral anticoagulants

Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are cases of increased international normalised ratio in patients maintained on warfarin and prescribed a course of amoxicillin. If coadministration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary (see sections 4.4 and 4.8).

Methotrexate

Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

Probenecid

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.

Mycophenolate mofetil

In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid (MPA) of approximately 50 % has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure. Therefore, a change in the dose of mycophenolate mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

Tetracyclines

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 CO-AMOXYCLAV BD AUSTELL treatment, enzymatic glucose oxidase methods should be used. Due to high urinary concentrations of amoxicillin, false positive readings are common with chemical methods.

The presence of clavulanic acid in CO-AMOXYCLAV BD AUSTELL may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test. There have been reports of positive test results using the Bio-Rad Laboratories Platelia *Aspergillus* EIA test in patients receiving amoxicillin/clavulanic acid who were subsequently

found to be free of *Aspergillus* infection. Cross-reactions with non-*Aspergillus* polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia *Aspergillus* EIA test have been reported. Therefore, positive test results in patients receiving amoxicillin/clavulanic acid should be interpreted cautiously and confirmed by other diagnostic methods.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety CO-AMOXYCLAV BD AUSTELL in pregnancy has not been established.

Breastfeeding

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

The most frequently reported adverse drug reactions (ADRs) are diarrhoea, nausea and vomiting. The ADRs indicated in the table below are derived from clinical studies and post-marketing surveillance with CO-AMOXYCLAV BD AUSTELL, sorted by MedDRA System Organ Class.

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and post-market spontaneous reports with amoxicillin trihydrate/clavulanic acid.

System Organ	**Frequency**

Class	Frequent	Less Frequent	Not known
Infections and infestations	Mucocutaneous candidiasis		Overgrowth of non-susceptible organisms
Blood and lymphatic system disorders		Reversible leucopenia (including neutropenia), Thrombocytopenia	Reversible agranulocytosis, Haemolytic anaemia, Prolongation of bleeding time and prothrombin time[1]
Immune system disorders[10]			Angioedema, Anaphylaxis, Serum sickness-like syndrome, Hypersensitivity vasculitis
Nervous system disorders		Dizziness, Headache	Reversible hyperactivity, Convulsions[2], Aseptic meningitis
Gastrointestinal disorders	Diarrhoea, Nausea[3], Vomiting	Indigestion	Antibiotic-associated colitis[4], Black hairy tongue
Hepatobiliary disorders		Rises in AST and/or ALT[5]	Hepatitis[6], Cholestatic jaundice[6]

Skin and subcutaneous tissue disorders[7]		Skin rash, Pruritus, Urticaria, Erythema multiforme	Stevens-Johnson syndrome, Toxic epidermal necrolysis, Bullous exfoliative-dermatitis, Acute generalised exanthemous pustulosis (AGEP)[9], Drug reaction with eosinophilia and systemic symptoms (DRESS)
Renal and urinary disorders			Interstitial nephritis, Crystalluria[8]

[1] See section 4.4

[2] See section 4.4

[3] Nausea is more often associated with higher oral doses. If gastrointestinal reactions are evident, they may be reduced by taking amoxicillin/clavulanic acid with a meal.

[4] Including pseudomembranous colitis and haemorrhagic colitis (see section 4.4)

[5] A moderate rise in AST and/or ALT has been noted in patients treated with beta-lactam class antibiotics, but the significance of these findings is unknown.

[6] These events have been noted with other penicillins and cephalosporins (see section 4.4).

[7] If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see section 4.4).

[8] See section 4.9

[9] See section 4.4

[10] See sections 4.3 and 4.4

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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Signs and symptoms of overdose

Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident.

Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see section 4.4).

Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Treatment of intoxication

Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance.

Amoxicillin/clavulanic acid can be removed from the circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification/ Category and Class:

A 20.1.2 Penicillins

Pharmacotherapeutic group:

Combinations of penicillins, incl. beta-lactamase inhibitors; ATC Code: J01CR02

Mechanism of action

Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.

Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

Pharmacokinetic/pharmacodynamic relationship

The time above the minimum inhibitory concentration (T > MIC) is considered to be the major determinant of efficacy for amoxicillin.

Mechanisms of resistance

The two main mechanisms of resistance to amoxicillin/clavulanic acid are:

- Inactivation by those bacterial beta-lactamases that are not themselves inhibited by clavulanic acid, including class B, C and D.
- Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target.

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance, particularly in Gram-negative bacteria.

Species for which acquired resistance may be a problem

Aerobic Gram-positive micro-organisms

Enterococcus faecium[1]

Aerobic Gram-negative micro-organisms

Escherichia coli

Klebsiella oxytoca

Klebsiella pneumoniae

Proteus mirabilis

Proteus vulgaris

Inherently resistant organisms

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

[1] Natural intermediate susceptibility in the absence of acquired mechanism of resistance.

5.2 Pharmacokinetic properties

Absorption

Amoxicillin and clavulanic acid are fully dissociated in aqueous solution at physiological pH. Both components are absorbed by the oral route of administration. Following oral administration, amoxicillin and clavulanic acid are approximately 70 % bioavailable. The plasma profiles of both components are similar and the time to peak plasma concentration (T_{max}) in each case is approximately one hour.

Distribution

About 25 % of total plasma clavulanic acid and 18 % of total plasma amoxicillin is bound to protein. The apparent volume of distribution is around 0,3 - 0,4 L/kg for amoxicillin and around 0,2 L/kg for clavulanic acid.

Following intravenous administration, both amoxicillin and clavulanic acid have been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid.

From animal studies there is no evidence for significant tissue retention of medicine-derived material for either component. Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanic acid can also be detected in breast milk (see section 4.6).
Both amoxicillin and clavulanic acid have been shown to cross the placental barrier (see section 4.6).

Biotransformation

Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10 to 25 % of the initial dose. Clavulanic acid is extensively metabolized in man and eliminated in urine and faeces and as carbon dioxide in expired air.

Elimination

The major route of elimination for amoxicillin is via the kidney, whereas for clavulanic acid it is by both renal and non-renal mechanisms.

Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 L/h in healthy subjects. Approximately 60 to 70 % of the amoxicillin and approximately 40 to 65 % of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of a single dose CO-AMOXYCLAV BD AUSTELL 250 mg/125 mg or 500 mg/125 mg tablets. Various studies have found the urinary excretion to be 50 - 85 % for amoxicillin and between 27 - 60 % for clavulanic acid over a 24 hour period. In the case of clavulanic acid, the largest amount of medicine is excreted during the first 2 hours after administration.

Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid (see section 4.5).

Age

The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and older children and adults. For very young children (including preterm newborns) in the first week of life the interval of administration should not exceed twice daily administration due to immaturity of the renal pathway of elimination. Because elderly patients are more likely to have

decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Gender

Following oral administration of amoxicillin/clavulanic acid to healthy males and female subjects, gender has no significant impact on the pharmacokinetics of either amoxicillin or clavulanic acid.

Renal impairment

The total serum clearance of amoxicillin/clavulanic acid decreases proportionately with decreasing renal function. The reduction in medicine clearance is more pronounced for amoxicillin than for clavulanic acid, as a higher proportion of amoxicillin is excreted via the renal route. Doses in renal impairment must therefore prevent undue accumulation of amoxicillin while maintaining adequate levels of clavulanic acid (see section 4.2).

Hepatic impairment

Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Colloidal Anhydrous Silica

Crosscarmellose Sodium

Magnesium Stearate

Microcrystalline Cellulose

Tablet film-coat

Copovidone

Hypromellose 2910

Macrogol 3350

Polydextrose

Titanium dioxide (E171)

Triglycerides

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

Tablets in desiccated pouch packs should be used within 30 days of opening.

6.4 Special precautions for storage

Store in the original package to protect from moisture.

Do not store above 25 °C.

6.5 Nature and contents of container

PVC/Aluminium/Polyamide laminate with aluminium lidding foil referred to as a cold formed aluminium blister (CFB) containing 2, 4, 10, 12, 14, 16, 20, 24, 30, 100 or 500 tablets.

Aluminium PVC/PVdC blister enclosed within an aluminium laminate pouch containing a desiccant sachet, referred to as a desiccated pouch pack (DPP) containing 14 tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER(S)

CO-AMOXYCLAV BD AUSTELL film-coated tablets: 53/20.1.2/0464

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 February 2021

10. DATE OF REVISION OF THE TEXT