PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

PROPRIETARY NAME:

SANDOZ CO-AMOXYCLAV 625 DISP TABLET (Dispersible tablets)

SANDOZ CO-AMOXYCLAV 1000 DISP TABLET (Dispersible tablets)

COMPOSITION:

Each Sandoz Co-Amoxyclav 625 Disp Tablet contains:

Amoxicillin trihydrate equivalent to 500 mg amoxicillin and potassium clavulanate equivalent to 125 mg clavulanic acid.

Each Sandoz Co-Amoxyclav 1000 Disp Tablet contains:

Amoxicillin trihydrate equivalent to 875 mg amoxicillin and potassium clavulanate equivalent to 125 mg clavulanic acid.

Inactive ingredients:

Crospovidone Type A, Silicon Dioxide, Iron oxide yellow (E172), Sweet orange flavour (powdered), Sucralose, Magnesium stearate, Silicified microcrystalline cellulose (Type 50) – dried.

Contains artificial sweetener (sucralose).

Each Sandoz Co-Amoxyclav 625 Disp Tablet contains sweetener (sucralose 5.500 mg per tablet).

Each Sandoz Co-Amoxyclav 1000 Disp Tablet contains sweetener (sucralose 8.208 mg per tablet).

PHARMACOLOGICAL CLASSIFICATION:

A 20.1.2 Penicillins

PHARMACOLOGICAL ACTION:

SANDOZ CO-AMOXYCLAV DISP TABLET 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 gonorrhoeae* 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.

Pharmacokinetic properties:

Absorption:

Amoxicillin is stable in the presence of acidic gastric secretions. Peak blood levels are achieved 1 to 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 is 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:

SANDOZ CO-AMOXYCLAV DISP 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 caused by β -lactamase–producing strains of *H. influenzae* and *M. catarrhalis*.
- Lower respiratory tract infections, such as bronchitis, bronchopneumonia caused by β lactamase–producing strains of *H. influenzae* and *M. catarrhalis*.
- Genito-urinary tract infections, such as cystitis, urethritis, pyelonephritis caused by β -lactamase–producing strains of *E. coli*, *Klebsiella* spp.and *Enterobacter* spp.
- Skin and soft tissue infections caused by β lactamase–producing strains of *S. aureus*, *E.coli*, and *Klebsiella* spp.

SANDOZ CO-AMOXYCLAV DISP TABLETS 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.

CONTRAINDICATIONS:

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

SANDOZ CO-AMOXYCLAV DISP TABLETS is contra-indicated in patients with a previous history of amoxicillin/clavulanic-associated jaundice or hepatic dysfunction.

WARNINGS AND SPECIAL PRECAUTIONS:

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. Before initiating therapy with SANDOZ CO-AMOXYCLAV DISP TABLETS 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 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.

SANDOZ CO-AMOXYCLAV 625 DISP TABLETS should not be used in patients with a glomerular filtration rate of less than 10mℓ /min.

If an allergic reaction occurs, SANDOZ CO-AMOXYCLAV DISP TABLETS 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.

SANDOZ CO-AMOXYCLAV DISP TABLETS 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.

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

Prolongation of prothrombin time has been reported less frequent in patients receiving SANDOZ CO-AMOXYCLAV DISP TABLETS. 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 have been reported. SANDOZ CO-AMOXYCLAV DISP TABLET should be used with caution in patients with evidence of hepatic dysfunction.
SANDOZ CO-AMOXYCLAV 1000 DISP TABLET should not be used in patients with a glomerular filtration rate of less than 30 ml/minute.

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 SANDOZ CO-AMOXYCLAV DISP TABLET 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. SANDOZ CO-AMOXYCLAV DISP TABLET 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*), 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 SANDOZ CO-AMOXYCLAV DISP TABLET. 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 SANDOZ CO-AMOXYCLAV DISP TABLET dosage should be adjusted (see “Dosage and directions for use”).

The use of SANDOZ CO-AMOXYCLAV DISP TABLET 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.

Effects on ability to drive and use machines:

Patients should be advised to take special care when operating hazardous machinery or driving motor vehicles until they know how SANDOZ CO-AMOXYCLAV DISP TABLETS will affect them.

INTERACTIONS:

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

SANDOZ CO-AMOXYCLAV DISP TABLETS may reduce the efficacy of oral contraceptives and patients should be warned accordingly.

The concomitant administration of allopurinol and amoxicillin substantially increases the incidence of skin rashes in patients receiving both agents as compared to patients receiving amoxicillin alone. It is not known

whether this potentiation of amoxicillin rashes is due to allopurinol or the hyperuricaemia present in these patients.

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

Interaction with laboratory test:

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

PREGANANCY AND LACTATION:

Use in pregnancy:

The safety of SANDOZ CO-AMOXYCLAV DISP TABLETS in pregnancy has not been established.

Use in lactation:

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

Amoxicillin is excreted in breast milk; there is no data on the excretion of clavulanic acid in human milk. Therefore, caution should be exercised when SANDOZ CO-AMOXYCLAV DISP TABLETS is administered to a breastfeeding mother.

DOSAGE AND DIRECTIONS FOR USE:

Tablets should be taken immediately before a meal. The tablet should be dispersed in half a glass of water or in the mouth before swallowing.

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 SANDOZ CO-AMOXYCLAV DISP TABLETS for more severe infections and infections of the respiratory tract should be one SANDOZ CO-AMOXYCLAV 625 DISP TABLET every eight hours at the start of a meal, or one SANDOZ CO-AMOXYCLAV 1000 DISP TABLET every 12 hours at the start of a meal.

Since SANDOZ CO-AMOXYCLAV 625 and 1000 DISP TABLET contain the same amount of clavulanic acid (125 mg as the potassium salt), two SANDOZ CO-AMOXYCLAV 625 DISP TABLETS are not equivalent to one SANDOZ CO-AMOXYCLAV 1000 DISP TABLET. Therefore, two SANDOZ CO-AMOXYCLAV 625 DISP TABLETS should not be substituted for one SANDOZ CO-AMOXYCLAV 1000 DISP TABLET for the treatment of more severe infections.

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:

SANDOZ CO-AMOXYCLAV 625 DISP TABLET:

- Mild impairment (creatinine clearance 50 to 80 mℓ /min): no change in dosage.
- Moderate impairment (creatinine clearance 30 to 50 mℓ /min): 1 tablet every 12 hours.
- SANDOZ CO-AMOXYCLAV 625 DISP TABLETS should not be used in patients with a glomerular filtration rate of less than 10mℓ /min.

SANDOZ CO-AMOXYCLAV 1000 DISP TABLET should not be used in patients with glomerular filtration rate of less than 30 mℓ/min.

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 & Soft Tissue Infections***
SANDOZ CO-AMOXYCLAV 625 DISP TABLET	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly
SANDOZ CO-AMOXYCLAV 1000 DISP TABLET	1 tablet 12 hourly	1 tablet 12 hourly	1 tablet 12 hourly	1 tablet 12 hourly

Amoxicillin-Resistant Organisms:				
Product	***Upper Respiratory Tract Infection (otitis media)***	***Lower Respiratory Tract Infection (bronchitis)***	***Urinary Tract Infection***	***Skin & Soft Tissue Infections***
SANDOZ CO-AMOXYCLAV 625 DISP TABLET	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly

SANDOZ CO-AMOXYCLAV 1000 DISP TABLET	1 tablet 12 hourly	1 tablet 12 hourly	1 tablet 12 hourly	1 tablet 12 hourly

The SANDOZ CO-AMOXYCLAV 625 and 1000 DISP TABLETS are not suitable for use in children.

SIDE EFFECTS:

The following adverse reactions have been reported and may occur with SANDOZ CO-AMOXYCLAV DISP TABLET:

Blood and the lymphatic system disorders:

Less frequent: Haemolytic anaemia, reversible thrombocytopenia, thrombocytopenic purpura, eosinophilia, reversible leucopoenia, agranulocytosis (these reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena), epistaxis.

A slight thrombocytosis was noted in less than 1 % of the patients treated with SANDOZ CO-AMOXYCLAV DISP TABLETS. Prolongation of bleeding time and prothrombin time has also been reported. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly.

Immune system disorders:

Frequent: Skin rashes, urticaria

Less frequent: Pruritus, serum sickness-like syndrome, Stevens-Johnson syndrome, hypersensitivity vasculitis, bullous exfoliative dermatitis and toxic epidermal necrolysis, erythema multiforme.

Serious and occasional fatal hypersensitivity (anaphylactic) reactions and angioedema can occur with oral penicillins (see “Warnings”). Whenever such reactions occur, SANDOZ CO-AMOXYCLAV DISP TABLETS should be discontinued.

Psychiatric disorders:

Less frequent: Reversible hyperactivity and convulsions, seizures. Convulsions may occur with impaired renal function or in those receiving high doses.

Nervous system disorders:

Frequent: Dizziness, tiredness, headache.

Gastrointestinal disorders:

Frequent: Diarrhoea, nausea, vomiting, indigestion, gastritis.

Less frequent: Stomatitis, glossitis, black 'hairy' tongue, enterocolitis, mucocutaneous candidiasis and antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis), oral candidiasis, *Clostridium difficile* colitis.

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

Hepato-biliary disorders:

Less frequent: Hepatitis, hepatic dysfunction including cholestatic jaundice.

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 effects 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 SANDOZ CO-AMOXYCLAV DISP TABLETS, but the significance of these findings is unknown.

Renal and urinary disorders:

Less frequent: Crystalluria, dysuria, urinary retention, proteinuria or pyuria.

Frequency unknown: Interstitial nephritis.

Reproductive system and breast disorders:

Less frequent: Vaginal candidiasis.

Frequency unknown: Vaginal itching, soreness and discharge.

General disorders and administrative site conditions:

Less frequent: Superficial tooth discolouration has been reported especially with the suspension and chewable tablet formulations (it can usually be removed by brushing), chest pain, chills, fatigue, malaise.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Overdosage with amoxicillin is usually asymptomatic. However, gastrointestinal 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 the 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:

Sandoz Co-Amoxyclav 625 Disp Tablet: Yellow brown mottled octagonal tablet, with aromatic odour.

Sandoz Co-Amoxyclav 1000 Disp Tablet: Yellow brown mottled octagonal tablet, with aromatic odour.

PRESENTATION:

Sandoz Co-Amoxyclav 625 Disp Tablet: 10, 14 or 16 tablets in aluminium foil blisters.

Sandoz Co-Amoxyclav 1000 Disp tablet: 10, 14 or 16 tablets in aluminium foil blisters.

STORAGE INSTRUCTIONS:

Do not store above 25°C.

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBER:

Sandoz Co-Amoxyclav 625 Disp tablet: 41/20.1.2/0102

Sandoz Co-Amoxyclav 1000 Disp tablet: 41/20.1.2/0103

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

Sandoz SA (Pty) Ltd1

Magwa Crescent West

Waterfall City

Jukskei View

Midrand

2090

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

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Additional country registration details:

Country	*Product name*	*Scheduling status (or Category of distribution)*	*Registration number*
Namibia	Sandoz Co-Amoxyclav 1000 Disp Tablet	NS2	13/20.1.2/0270

ATC code: J01CR02 – Beta Lactam Antibacterials, Penicillins

Name and address of manufacturer:
Sandoz GmbH
Biochemiestraβe 10
A-6250 Kundl
Austria

[1] Company Reg. No.: 1990/001979/07