SCHEDULING STATUS: S4

PROPRIETARY NAMES AND DOSAGE FORMS:

SANDOZ CO-AMOXYCLAV 375 (film-coated tablets)

SANDOZ CO-AMOXYCLAV 625 (film-coated tablets)

SANDOZ CO-AMOXYCLAV 1000 (film-coated tablets)

COMPOSITION:

Each Sandoz Co-Amoxyclav 375 film-coated tablet contains amoxicillin trihydrate equivalent to amoxicillin 250 mg and potassium clavulanate equivalent to clavulanic acid 125 mg.

Each Sandoz Co-Amoxyclav 625 film-coated tablet contains amoxicillin trihydrate equivalent to amoxicillin 500 mg and potassium clavulanate equivalent to clavulanic acid 125 mg.

Each Sandoz Co-Amoxyclav 1000 film-coated tablet contains amoxicillin trihydrate equivalent to amoxicillin 875 mg and potassium clavulanate equivalent to clavulanic acid 125 mg.

Excipients:

Sandoz Co-Amoxyclav 375 and 625 film-coated tablets: Croscarmellose sodium, ethylcellulose aqueous dispersion (ethyl cellulose, sodium lauryl sulphate, cetyl alcohol), hypromellose, magnesium stearate, microcrystalline cellulose, povidone (K 25), talc, titanium dioxide and triethyl citrate.

Sandoz Co-Amoxyclav 1000 film-coated tablets: Colloidal silicone dioxide, croscarmellose sodium, ethylcellulose aqueous dispersion (ethyl cellulose, sodium lauryl sulphate, cetyl alcohol), hypromellose, magnesium stearate, microcrystalline cellulose, povidone (K 25), talc, titanium dioxide and triethyl citrate.

Sugar free.

PHARMACOLOGICAL CLASSIFICATION:

A 20.1.2 Penicillins

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Amoxicillin is a semisynthetic beta-lactamase-susceptible penicillin, which has bactericidal activity against 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 was 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 combination of amoxicillin and clavulanic acid showed synergism against amoxicillin-resistant organisms and activity was not reduced in the presence of serum. The clavulanic acid component has very little bactericidal action.

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

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. Small amounts of amoxicillin are also excreted in the faeces and bile.

INDICATIONS:

SANDOZ CO-AMOXYCLAV is 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 and 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 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.

In the treatment of infections caused by *Pseudomonas aeruginosa*, an aminoglycoside should be administered concomitantly.

CONTRAINDICATIONS:

Hypersensitivity to amoxicillin and clavulanic acid, to any of the penicillins or to any of the excipients of SANDOZ CO-AMOXYCLAV.

History of a hypersensitivity to another beta-lactam agent (e.g. a cephalosporin, carbapenem or monobactam).

History of jaundice/hepatic impairment due to amoxicillin and clavulanic acid medicines (see SIDE EFFECTS).

WARNINGS AND SPECIAL PRECAUTIONS:

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy. Before initiating therapy with SANDOZ CO-AMOXYCLAV careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens beta-lactam medicines (see CONTRAINDICATIONS and SIDE EFFECTS). 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.

If an allergic reaction occurs, SANDOZ CO-AMOXYCLAV should be discontinued and the appropriate therapy instituted. Serious anaphylactic reactions may require immediate emergency treatment with adrenaline (epinephrine). Oxygen, intravenous steroids and airway management, including intubation may also be required.

Convulsions may occur especially in patients with impaired renal function or in those receiving high doses (see SIDE EFFECTS).

SANDOZ CO-AMOXYCLAV 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.

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

The presence of clavulanic acid in SANDOZ CO-AMOXYCLAV may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

Antibiotic-associated colitis: although other organisms including *Candida* spp., has been implicated in

antibiotic- associated diarrhoea, colonisation of the colon with *Clostridium difficile,* a toxin-producing Gram-positive anaerobe, is the most identifiable cause of antibiotic-associated colitis and pseudomembranous colitis been reported with SANDOZ CO-AMOXYCLAV and may range in severity from mild to life threatening (see SIDE EFFECTS). Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of SANDOZ CO- AMOXYCLAV. Should SANDOZ CO-AMOXYCLAV-associated colitis occur, SANDOZ CO-AMOXYCLAV should immediately be discontinued and appropriate therapy initiated.

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

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

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

In patients with reduced urine output, crystalluria has been observed; adequate fluid intake and urinary output must be maintained in order to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained.

Since SANDOZ CO-AMOXYCLAV 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 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*), SANDOZ CO-AMOXYCLAV 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. SANDOZ CO-AMOXYCLAV 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 dosage should be adjusted. (See DOSAGE AND DIRECTIONS FOR USE).

Effects on ability to drive and use machines:

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

INTERACTIONS:

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

The concomitant administration of allopurinol and ampicillin substantially increases the incidence of skin rashes in patients receiving both medicines 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 medicines may interfere with the bactericidal effects of amoxicillin.

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.

SANDOZ CO-AMOXYCLAV may reduce the excretion of methotrexate causing potential increase in toxicity.

Abnormal prolongation of prothrombin time (increased international normalised ratio (INR)) has been reported in patients receiving SANDOZ CO-AMOXYCLAV. Appropriate monitoring should be undertaken when coumarin anticoagulants such as warfarin are prescribed concurrently. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see INTERACTIONS and SIDE EFFECTS).

In patients receiving mycophenoloate mofetil, reduction in concentration of the active metabolite mycophenolic acid (MPA) of approximately 50 % was reported following commencement of oral SANDOZ CO-AMOXYCLAV. Close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

Interaction with laboratory tests:

It is recommended that when testing for the presence of glucose in urine during SANDOZ CO-AMOXYCLAV 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:

Pregnancy:

The safety of SANDOZ CO-AMOXYCLAV in pregnancy has not been established. In a single study, in women with preterm premature rupture of the foetal membrane it was reported that prophylactic treatment with SANDOZ CO-AMOXYCLAV may be associated with an increased risk of necrotising enterocolitis in neonates.

Women of Childbearing Potential:

SANDOZ CO-AMOXYCLAV may reduce the efficacy of oral contraceptives and women of childbearing potential taking the oral contraceptive should be warned accordingly (see INTERACTIONS).

Lactation:

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.

DOSAGE AND DIRECTIONS FOR USE:

SANDOZ CO-AMOXYCLAV film-coated tablets are for oral use. SANDOZ CO-AMOXYCLAV film-coated tablets should be taken at the start of a meal to minimise potential gastrointestinal intolerance.

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 is one SANDOZ CO-AMOXYCLAV 375 film-coated tablet every 8 hours at the start of a meal. For more severe infections and infections of the respiratory tract, the dose should be one SANDOZ CO-AMOXYCLAV 625 film-coated tablet every 8 hours at the start of a meal, or one SANDOZ CO-AMOXYCLAV 1000 film-coated tablet every 12 hours at the start of a meal.

Since SANDOZ CO-AMOXYCLAV 375, 625 and 1000 film-coated tablets contain the same amount of clavulanic acid (125 mg as the potassium salt), two SANDOZ CO-AMOXYCLAV 375 film-coated tablets are not equivalent to one SANDOZ CO-AMOXYCLAV 625 film-coated tablet, and two SANDOZ CO-AMOXYCLAV 625 film-coated tablets are not equivalent to one SANDOZ CO-AMOXYCLAV 1000.
Therefore, two SANDOZ CO-AMOXYCLAV 375 film-coated tablets should not be substituted for one SANDOZ CO-AMOXYCLAV 625 film-coated tablet or two SANDOZ CO-AMOXYCLAV 625 film-coated

tablets for one SANDOZ CO-AMOXYCLAV 1000 film-coated 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 375, 625:

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

Moderate impairment (creatinine clearance 10 to 30 mℓ /min): one tablet every 12 hours.

Severe impairment (creatinine clearance less than 10 mℓ /min): half a tablet every 12 hours.

SANDOZ CO-AMOXYCLAV 1000 should not be used in patients with a 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 375	1 tablet 8 hourly	-	1 tablet 8 hourly	1 tablet 8 hourly

SANDOZ CO-AMOXYCLAV 625	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly
SANDOZ CO-AMOXYCLAV 1000	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 375	-	-	1 tablet 8 hourly	1 tablet 8 hourly
SANDOZ CO-AMOXYCLAV 625	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly
SANDOZ CO-AMOXYCLAV 1000	1 tablet 12 hourly	1 tablet 12 hourly	1 tablet 12 hourly	1 tablet 12 hourly

SIDE EFFECTS:

The following adverse reactions with SANDOZ CO-AMOXYCLAV FILM-COATED TABLETS are listed below:

Infections and infestations:

Frequent: Mucocutaneous candidosis, oral candidiasis, vaginal candidiasis.

Frequency unknown: Overgrowth of non-susceptible organisms.

Blood and lymphatic system disorders:

Less frequent: Reversible leucopenia (including neutropenia), thrombocytopenia.

Frequency unknown: Reversible agranulocytosis, haemolytic anaemia, prolongation of bleeding time and prothrombin time (see WARNINGS AND SPECIAL PRECAUTIONS).

Immune system disorders:

Frequency unknown: Angioedema, anaphylaxis, serum sickness-like syndrome, hypersensitivity vasculitis (see CONTRAINDICATIONS and WARNINGS AND SPECIAL PRECAUTIONS).

Nervous system disorders:

Less frequent: Dizziness, headache.

Frequency unknown: Reversible hyperactivity, convulsions, aseptic meningitis.

Gastrointestinal disorders:

Frequent: Diarrhoea, nausea, vomiting, nausea is more often associated with higher oral doses. If gastrointestinal reactions are evident, they must be reduced by taking SANDOZ CO-AMOXYCLAV at the start of a meal.

Less frequent: Indigestion, glossitis, *clostridium difficile colitis.*

Frequency unknown: Black ‘hairy’ tongue, antibiotic-associated colitis.

Hepato-biliary disorders:

Less frequent: Rises in AST and/or ALT.

A moderate raise in aspartate transaminase (AST) and/ or alanine transaminase (ALT) has been noted in patients treated with SANDOZ CO-AMOXYCLAV, but the significance of these findings is unknown, elevated liver function tests.

Frequency unknown: Hepatitis, cholestatic jaundice (see WARNINGS AND SPECIAL PRECAUTIONS).

Skin and subcutaneous tissue disorders:

Less frequent: Skin rash, pruritus, urticarial, erythema multiforme.

Frequency unknown: Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative-dermatitis, acute generalised exanthemous pustulosis (AGEP) (see WARNINGS AND SPECIAL PRECAUTIONS).

Renal and urinary disorders:

Less frequent: Proteinuria, dysuria.

Frequency unknown: Interstitial nephritis, crystalluria (see KNOWN SYMPTOMS FOR OVERDOSAGE AND PARTICULARS OF ITS TREATMENT).

KNOWN SYMPTOMS FOR 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.

SANDOZ CO-AMOXYCLAV can be removed from the circulation by haemodialysis.

IDENTIFICATION:

Sandoz Co-Amoxyclav 375: Off-white, oblong, biconvex, film-coated tablet, scored on both sides.
Sandoz Co-Amoxyclav 625: Off-white, oval, biconvex, film-coated tablet, scored on both sides.
Sandoz Co-Amoxyclav 1000: White to pale yellow, oblong, film-coated tablet, scored on both sides.

PRESENTATIONS:

Sandoz Co-Amoxyclav 375: 15, 100, 300 or 500 film-coated tablets in aluminium foil blisters.

Sandoz Co-Amoxyclav 625: 15, 100, 300 or 500 film-coated tablets in aluminium foil blisters.

Sandoz Co-Amoxyclav 1000: 10 film-coated tablets in aluminium foil blisters.

STORAGE INSTRUCTIONS:

Store at or below 25 °C. Protect from light and moisture.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

SANDOZ CO-AMOXYCLAV 375: 35/20.1.2/0318

SANDOZ CO-AMOXYCLAV 625: 34/20.1.2/0275

SANDOZ CO-AMOXYCLAV 1000:36/20.1.2/0180

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

Sandoz SA (Pty) Ltd[1]

72 Steel Road

Spartan

Kempton Park

1619

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DATE OF PUBLICATION OF THIS PACKAGE INSERT:

Dates of registration:

SANDOZ CO-AMOXYCLAV 375: 22 May 2002

SANDOZ CO-AMOXYCLAV 625: 20 May 2002

SANDOZ CO-AMOXYCLAV 1000: 28 May 2004

Date of most recent approval of professional information: 22 August 2019

Additional countries registration details:

Country	*Product name*	*Scheduling status (or Category of distribution)*	*Registration number*
Botswana	Sandoz® Co-amoxyclav 375 (15 tabs)	S2	BOT1302466A
	Sandoz® Co-amoxyclav 375 (100 tabs)	S2	BOT1302466B
	Sandoz® Co-amoxyclav 375 (300 tabs)	S2	BOT1302466C
	Sandoz® Co-amoxyclav 375 (500 tabs)	S2	BOT1302466D
	Sandoz® Co-amoxyclav 625 (15 tabs)	S2	BOT1302468A
	Sandoz® Co-amoxyclav 625 (100 tabs)	S2	BOT1302468B
	Sandoz® Co-amoxyclav 625 (300 tabs)	S2	BOT1302468C
	Sandoz® Co-amoxyclav 625 (500 tabs)	S2	BOT1302468D
	Sandoz® Co-amoxyclav 1000	S2	BOT0801392
Namibia	Sandoz® Co-amoxyclav 375	NS2	05/20.1.2/0324
	Sandoz® Co-amoxyclav 625	NS2	05/20.1.2/0325
	Sandoz® Co-amoxyclav 1000	NS2	04/20.1.2/1256
Zambia	Sandoz® Co-amoxyclav 375	POM	039/010
	Sandoz® Co-amoxyclav 625	POM	039/011
	Sandoz® Co-amoxyclav 1000	POM	039/012

ATC code: J01CR02 – Combinations of penicillins, incl. beta-lactamase inhibitors

Name and address of manufacturer:

Sandoz GmbH

Biochemiestraße 10

A-6250 Kundl

Austria

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