SANDOZ CO-AMOXYCLAV BD SUSPENSION PACKAGE INSERT

SCHEDULING STATUS: S4

PROPRIETARY NAMES AND DOSAGE FORMS:

SANDOZ CO-AMOXYCLAV BD SUSPENSION (powder for suspension)

COMPOSITION:

- Each 5 mℓ of reconstituted suspension contains: amoxycillin trihydrate equivalent to 400 mg amoxycillin and potassium clavulanate equivalent to 57 mg clavulanic acid.
- Each 2,5 mℓ of reconstituted suspension contains: amoxycillin trihydrate equivalent to 200 mg amoxycillin and potassium clavulanate equivalent to 28,5 mg clavulanic acid.
- Each 1 mℓ of reconstituted suspension contains: amoxycillin trihydrate equivalent to 80 mg amoxycillin and potassium clavulanate equivalent to 11,4 mg clavulanic acid.

Excipients:

SANDOZ CO-AMOXYCLAV BD SUSPENSION contains: Aspartame, citric acid anhydrous, guar, lemon flavouring powdered, peach-apricot flavouring powdered, orange flavouring, powdered, silicon dioxide, talc and trisodium citrate anhydrous.

Contains sugar (guar, 25,0 mg per 5 mℓ).

Contains artificial sweetener (8,5 mg aspartame per 5 mℓ).

PHARMACOLOGICAL CLASSIFICATION:

A 20.1.2 Penicillins

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Amoxycillin 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 amoxycillin and clavulanic acid showed synergism against amoxycillin-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:

Amoxycillin 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 amoxycillin 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 amoxycillin content is protein bound. Amoxycillin 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 amoxycillin.

Excretion:

The elimination half-life of amoxycillin is approximately 1 hour. Small amounts of amoxycillin are also excreted in the faeces and bile.

INDICATIONS:

SANDOZ CO-AMOXYCLAV BD SUSPENSION is indicated for the treatment of infections caused by amoxycillin resistant organisms producing beta-lactamases sensitive to clavulanic acid:

Upper respiratory tract infections, such as sinusitis, recurrent otitis media, tonsillitis caused by beta-lactamase–producing strains of *H. influenzae* and *M. catarrhalis*.

Lower respiratory tract infections, such as bronchitis and bronchopneumonia caused by beta-lactamase–producing strains of *H. influenzae* and *M. catarrhalis*.

Genito-urinary tract infections, such as cystitis, urethritis, pyelonephritis caused by beta-lactamase–producing strains of *E. coli*, *Klebsiella* spp. and *Enterobacter* spp.

Skin and soft tissue infections caused by beta-lactamase–producing strains of *S. aureus*, *E.coli*, and *Klebsiella* spp.

SANDOZ CO-AMOXYCLAV BD SUSPENSION formulation will also be effective in the treatment of infections caused by amoxycillin sensitive organisms at the appropriate amoxycillin 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 amoxycillin and clavulanic acid, to any of the penicillins or to any of the excipients in SANDOZ CO-AMOXYCLAV BD SUSPENSION.

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

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

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 BD SUSPENSION careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other 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 BD SUSPENSION 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.

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

SANDOZ CO-AMOXYCLAV BD SUSPENSION 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 amoxycillin.

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 BD SUSPENSION discontinuation and contraindicates any subsequent administration of amoxycillin.

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

Impaired hepatic function:

SANDOZ CO-AMOXYCLAV BD SUSPENSION should be used with caution in patients with evidence of hepatic dysfunction (see “CONTRAINDICATIONS” and “SIDE EFFECTS”).

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 BD SUSPENSION 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 BD SUSPENSION. Should SANDOZ CO-AMOXYCLAV BD SUSPENSION -associated colitis occur, SANDOZ CO-AMOXYCLAV BD SUSPENSION should immediately be discontinued and appropriate therapy initiated.

Impaired renal function:

SANDOZ CO-AMOXYCLAV BD SUSPENSION should not be used in patients with a glomerular filtration rate of less than 30 mℓ/min.

In patients with renal impairment, the dose should be adjusted according to the degree of impairment (see “DOSAGE AND DIRECTIONS FOR USE”).

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 amoxycillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained.

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

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

Since SANDOZ CO-AMOXYCLAV BD SUSPENSION contains amoxycillin, 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 amoxycillin is used. SANDOZ CO-AMOXYCLAV BD SUSPENSION should be given with caution to patients with lymphatic leukaemia since they are especially susceptible to amoxycillin 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 BD SUSPENSION should be discontinued and/or appropriate therapy instituted.

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”).

Excipients

SANDOZ CO-AMOXYCLAV BD SUSPENSION contains aspartame. Caution is advised in patients with phenylketonuria.

SANDOZ CO-AMOXYCLAV BD SUSPENSION contains guar, a type of galactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, or glucose-galactose malabsorption, should not take SANDOZ CO-AMOXYCLAV BD SUSPENSION.

SANDOZ CO-AMOXYCLAV BD SUSPENSION may have an effect on the glycaemic control of patients with diabetes mellitus.

INTERACTIONS:

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxycillin. Concurrent use with SANDOZ CO-AMOXYCLAV BD SUSPENSION may result in increased and prolonged blood levels of amoxycillin, but not of clavulanic acid.

SANDOZ CO-AMOXYCLAV BD SUSPENSION 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.

Concomitant use of allopurinol during treatment with SANDOZ CO-AMOXYCLAV BD SUSPENSION can increase the likelihood of allergic skin reactions.

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

Interaction with laboratory test:

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

During treatment with amoxycillin, enzymatic glucose oxidase methods should be used whenever testing for the presence of glucose in urine because false positive results may occur with non-enzymatic methods.

SANDOZ CO-AMOXYCLAV BD SUSPENSION 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 BD SUSPENSION. 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 see 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 BD SUSPENSION. Close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

PREGNANCY AND LACTATION:

Pregnancy:

The safety of SANDOZ CO-AMOXYCLAV BD SUSPENSION 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 BD SUSPENSION may be associated with an increased risk of necrotising enterocolitis in neonates.

Women of Childbearing Potential:

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

Lactation:

Mothers should not breastfeed their baby while taking SANDOZ CO-AMOXYCLAV BD SUSPENSION.

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

DOSAGE AND DIRECTIONS FOR USE:

Directions for reconstituting into suspension:

After opening the bottle remove the membrane carefully and completely and discard before reconstituting the medicine.

Shake the bottle well before every use. Each presentation when prepared as directed will result in suspension containing 400 mg amoxycillin and clavulanic acid 57 mg per 5 mℓ.

Preparation for 35 mℓ SANDOZ CO-AMOXYCLAV BD SUSPENSION:

Add 32 mℓ of previously boiled and cooled water to the powder up to the arrow on the label to obtain 35 mℓ reconstituted suspension.

Preparation of 70 mℓ SANDOZ CO-AMOXYCLAV BD SUSPENSION:

Add 64 mℓ of previously boiled and cooled water to the powder up to the arrow on the label to obtain 70 mℓ reconstituted suspension.

Dosages:

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

Impaired renal function:

Both amoxycillin 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 amoxycillin. The following schedule is proposed:

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

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

Dosage guide:

The tables below give guidance for children.

There is insufficient experience with SANDOZ CO-AMOXYCLAV BD SUSPENSION to make dosage recommendations for children under 2 months old.

The dosage should be taken at the start of a meal.

The recommended dose for children aged 2 months to 2 years is as follows:

Mass (kg)	***25/3,6 mg/kg per day [1)] (mℓ twice per day)***	***45/6,4 mg/kg per day [1)] (mℓ twice per day)***
	mild to moderate infections (upper respiratory tract infections, lower respiratory tract infections, skin and soft tissue infections)	**more severe infections (upper respiratory infections, lower respiratory tract infections and genito-urinary tract infections)**
2	0,3	0,6
3	0,5	0,8
4	0,6	1,1
5	0,8	1,4
6	0,9	1,7
7	1,1	2,0

8	1,3	2,3
9	1,4	2,5
10	1,6	2,8
11	1,7	3,1
12	1,9	3,4
13	2,0	3,7
14	2,2	3,9
15	2,3	4,2

[1)] the first quantity pertains to the amoxycillin and the second one to the clavulanic acid

Children over 2 years:

Indications	***Age/ (mass in kg)***	***Dosage***
mild to moderate infections (Upper respiratory tract infections, lower respiratory infections, skin and soft tissue infections) ***25/3,6 mg/kg per day [1)]***	2 to 6 years (13 to 21 kg)	2,5 mℓ SANDOZ CO-AMOXYCLAV BD SUSPENSION twice per day
	7 to 12 years (22 to 40 kg)	5,0 mℓ SANDOZ CO-AMOXYCLAV BD SUSPENSION twice per day
more severe infections (Upper respiratory infections, lower respiratory tract	2 to 6 years (13 to 21 kg)	5,0 mℓ SANDOZ CO-AMOXYCLAV BD

infections and Genito-urinary tract infections)		SUSPENSION twice per day
45/6,4 mg/kg per day [1)]	7 to 12 years (22 to 40 kg)	10,0 mℓ SANDOZ CO-AMOXYCLAV BD SUSPENSION twice per day

[1)] the first quantity pertains to the amoxycillin and the second one to the clavulanic acid

SIDE EFFECTS:

The following adverse reactions with SANDOZ CO-AMOXYCLAV BD SUSPENSION 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 see “WARNINGS AND SPECIAL PRECAUTIONS”).

Nervous system disorders:

Less frequent: Dizziness, headache.

Frequency unknown: Reversible hyperactivity, convulsions, aseptic meningitis.

Gastrointestinal disorders:

Frequent: Diarrhoea, nausea, vomiting. If gastrointestinal reactions are evident, they must be reduced by taking SANDOZ CO-AMOXYCLAV BD SUSPENSION 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 raise in aspartate transaminase (AST) and/ or alanine transaminase (ALT), elevated liver function tests.

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

Skin and subcutaneous tissue disorders:

Less frequent: Skin rash, pruritus, urticaria, 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 amoxycillin 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.

SANDOZ CO-AMOXYCLAV BD SUSPENSION 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 BD suspension: White to off-white powder, and white to off-white ready-to-use suspension (reconstituted suspension) with a fruity odour, characteristic of the active ingredient.

PRESENTATIONS:

Sandoz Co-amoxyclav BD suspension 35 mℓ: 60 mℓ amber glass bottle with white plastic child resistant screw cap and sealing membrane containing powder for reconstitution to 35 mℓ packed with a 5 mℓ plastic graduated syringe.

Sandoz Co-amoxyclav BD suspension 70 mℓ: 120 mℓ amber glass bottle with white plastic child resistant screw cap and sealing membrane containing powder for reconstitution to 70 mℓ packed with a 5 mℓ plastic measuring spoon.

STORAGE INSTRUCTIONS:

Dry Powder: Store at or below 25 °C in a cool dry place. Keep in the original container. Keep the container tightly closed.

Reconstituted suspension: Store in a refrigerator (2 to 8 °C) and use within 7 days.

Discard any unused portion after 7 days.

The product will only retain its stability if stored in the refrigerator.

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBER:

A 39/20.1.2/0071

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

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SANDOZ CO-AMOXYCLAV BD SUSPENSION PACKAGE INSERT

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Additional countries registration details:

Country	*Product name*	*Scheduling status (or Category of distribution)*	*Registration number*
Namibia	Sandoz Co-Amoxyclav BD	NS2	12/20.1.2/0166
Botswana	Sandoz Co-Amoxyclav BD	S2	BOT0801393
Zambia	Sandoz Co-Amoxyclav BD	POM	039/013

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

Name and address of manufacturer:

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