PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

Co-Amoxyclav ES Sandoz® 600 mg + 42,9 mg/5 mL (Powder for Oral Suspension Extra Strength)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL of reconstituted oral suspension contains: amoxicillin trihydrate equivalent to 600 mg amoxicillin and potassium clavulanate equivalent to 42,9 mg clavulanic acid. The ratio is 14:1.

Sugar free

Contains artificial sweetener (5,0 mg saccharin sodium per 5 mL).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for Oral Suspension Extra Strength

Co-Amoxyclav ES Sandoz powder for oral suspension is a white to light-yellow powder. After reconstitution the suspension is a white to light-yellow, homogeneous suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CO-AMOXYCLAV ES SANDOZ is indicated for short-term treatment of acute bacterial otitis media infections when caused by the following CO-AMOXYCLAV ES SANDOZ sensitive organisms: *Haemophilus influenzae*, *Streptococcus pneumoniae* (penicillin MIC ≤ 4 µg/mL) and *Moraxella*

catarrhalis.

4.2 Posology and method of administration

Posology

CO-AMOXYCLAV ES SANDOZ is recommended for dosing at 90/6,4 mg/kg/day in two divided doses at 12 hourly intervals for 10 days, in children aged 3 months and older. There is no experience in paediatric patients weighing > 40 kg or in adults. There are no clinical data in children under 3 months of age.

Body Weight (kg)	**Volume CO-AMOXYCLAV ES SANDOZ providing 90/6,4 mg/kg/day**
8	3,0 mL twice daily
12	4,5 mL twice daily
16	6,0 mL twice daily
20	7,5 mL twice daily
24	9,0 mL twice daily
28	10,5 mL twice daily
32	12,0 mL twice daily
36	13,5 mL twice daily

CO-AMOXYCLAV ES SANDOZ does not contain the same amount of clavulanic acid (as the potassium salt) as any of the other SANDOZ CO-AMOXYCLAV suspensions, therefore these suspensions should not be substituted for CO-AMOXYCLAV ES SANDOZ, as they are not interchangeable.

Hepatic impairment:

There are insufficient data on which to base a dosage recommendation.

Renal impairment:

There are no dosing recommendations for CO-AMOXYCLAV ES SANDOZ in patients with renal impairment.

Method of administration

CO-AMOXYCLAV ES SANDOZ is for oral use.

CO-AMOXYCLAV ES SANDOZ should be taken immediately before a meal.

For instructions on reconstitution of the medicine before administration, see section 6.6.

Duration of treatment

Duration of therapy should be appropriate to the indication and should not exceed 14 days without review.

4.3 Contraindications

In patients with a history of hypersensitivity to beta-lactams e.g., penicillins and cephalosporins.

CO-AMOXYCLAV ES SANDOZ is contra-indicated in patients with a previous history of Co-Amoxyclav-associated jaundice/hepatic dysfunction.

Safety in children under 2 months of age has not been established.

CO-AMOXYCLAV ES SANDOZ: There are no clinical data in children under 3 months of age.

4.4 Special warnings and precautions for use

Prescribers must adhere to the principles of antibiotic stewardship.

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. 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. Before initiating therapy with CO-AMOXYCLAV ES SANDOZ, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. If an allergic reaction occurs, CO-AMOXYCLAV ES SANDOZ should be discontinued, and the appropriate therapy instituted. Serious anaphylactoid reactions require emergency treatment with adrenaline. Oxygen, intravenous steroids and airway management, including intubation may also be required.

Since CO-AMOXYCLAV ES SANDOZ 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. CO-AMOXYCLAV ES SANDOZ should be avoided if infectious mononucleosis is suspected.

Changes in liver function tests have been observed in some patients receiving CO-AMOXYCLAV ES SANDOZ. Hepatic function should be monitored at regular intervals, see section 4.2. Transient hepatitis and cholestatic jaundice have been reported. CO-AMOXYCLAV ES SANDOZ should be used with caution in patients with evidence of hepatic dysfunction.

In patients with moderate or severe renal impairment CO-AMOXYCLAV ES SANDOZ dosage should be adjusted according to the degree of impairment.

Prolonged use may also occasionally result in overgrowth of non-susceptible organisms. 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*), CO-AMOXYCLAV ES SANDOZ should be discontinued and/or appropriate therapy instituted.

The use of CO-AMOXYCLAV ES SANDOZ 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. Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function, is advisable during prolonged therapy.

Antibiotic-associated colitis, pseudomembranous colitis and *Clostridium difficile* has been reported with 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 CO-AMOXYCLAV ES SANDOZ. Should antibiotic-associated colitis occur, CO-AMOXYCLAV ES SANDOZ should immediately be discontinued, a medical practitioner be consulted, and an appropriate therapy initiated. Anti-peristaltic medicines are contraindicated in this situation.

CO-AMOXYCLAV ES SANDOZ should be given with caution to patients with lymphatic leukaemia since they are especially susceptible to amoxicillin induced skin rashes.

CO-AMOXYCLAV ES SANDOZ contains saccharin sodium and should be used with caution in patients with phenylketonuria.

Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported in patients taking beta-lactam antibiotics. When SCAR is suspected, beta-lactam antibiotics should be discontinued.

4.5 Interaction with other medicines and other forms of interaction

Probenecid

Concomitant use of probenecid is not recommended.

Probenecid decreases the renal tubular secretion of amoxicillin but does not affect clavulanic acid

excretion. Concomitant use with CO-AMOXYCLAV ES SANDOZ may result in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.

Allopurinol

The concomitant administration of allopurinol and ampicillin could substantially increase 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.

There is no data on CO-AMOXYCLAV ES SANDOZ and allopurinol administered concomitantly.

Alcohol

No information is available about the concurrent use of CO-AMOXYCLAV ES SANDOZ and alcohol. However, the ingestion of alcohol whilst being treated with some other beta-lactam antibiotics has precipitated a disulfiram (Antabuse) like reaction in some patients. Therefore, the ingestion of alcohol should be avoided during and for several days after treatment with CO-AMOXYCLAV ES SANDOZ.

Oral contraceptives

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Women of Childbearing Potential/ Contraception in males and females

CO-AMOXYCLAV ES SANDOZ may reduce the efficacy of oral contraceptives and women of childbearing potential taking the oral contraceptive should be warned accordingly (see section 4.5).

Breastfeeding

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

Fertility

There is no information on the effects of CO-AMOXYCLAV ES SANDOZ on human fertility.

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. 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

Data from large clinical trials was used to determine the frequency of frequent to less frequent undesirable effects.

Infections and infestations:

Frequent: Mucocutaneous candidiasis (including vaginitis).

Blood and lymphatic system disorders:

Less frequent: Reversible leucopenia (including neutropenia), thrombocytopenia, reversible agranulocytosis, haemolytic anaemia, prolongation of bleeding time and prothrombin time (see section 4.4).

Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly.

Immune system disorders:

Less frequent: Angioneurotic oedema, anaphylaxis, serum sickness-like syndrome, hypersensitivity vasculitis.

Nervous system disorders:

Less Frequent: Dizziness, headache, reversible hyperactivity and convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Gastrointestinal disorders:

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

Less frequent: Indigestion, antibiotic-associated colitis (Including pseudomembranous colitis and haemorrhagic colitis). Superficial tooth discolouration has been reported which can usually be removed by brushing. Abdominal pain, gastritis, stomatitis, glossitis, black “hairy” tongue, abnormal taste, tiredness and hot flushes have been reported.

Hepato-biliary disorders:

Less frequent: 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. Hepatitis, cholestatic jaundice. These events have been noted with other penicillins and cephalosporins, see section 4.4.

Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children. 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 rare 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.**

Skin and subcutaneous tissue disorders:

Less frequent: Skin rash, pruritus, urticaria, petechiae, purpura, diaphoresis, flushing, exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous

exfoliative-dermatitis, acute generalised exanthemous pustulosis (AGEP), drug reaction with eosinophilia and systemic syndrome (DRESS).

If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued. Serious and occasional fatal hypersensitivity (anaphylactic) reactions and angioneurotic oedema can occur with oral penicillin, see section 4.4.

Renal and urinary disorders:

Less Frequent: Interstitial nephritis, crystalluria

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8. Suspected adverse reactions can also be reported directly to the Holder of the Certificate of Registration (HCR) via Patientsafety.sacg@novartis.com.

4.9 Overdose

Cases of over dosage with CO-AMOXYCLAV ES SANDOZ are usually asymptomatic. If encountered, gastrointestinal symptoms (nausea, vomiting and diarrhoea) and disturbance of the fluid and electrolyte balances may be evident. They may be treated symptomatically, with attention to the water/electrolyte imbalance. CO-AMOXYCLAV ES SANDOZ may be removed from the circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

PHARMACOLOGICAL CLASSIFICATION: A 20.1.2 Penicillins

Pharmacotherapeutic group: Antibacterials for systemic use; betalactam antibacterials, penicillins; combinations of penicillins, including beta-lactamase inhibitors; ATC Code: J01CR02.

5.1 Pharmacodynamic properties

Mechanism of action

Potassium clavulanate has been shown *in vitro* to be an irreversible inhibitor of beta-lactamases.

The amoxicillin component of the formulations exerts a bactericidal action against many strains of Gram-positive and Gram-negative organisms. The clavulanic acid component has very little bactericidal action. It does however, by inactivation of susceptible beta-lactamases, protect amoxicillin from degradation by a large number of beta-lactamase enzymes produced by penicillin-resistant strains of organisms.

Inherently resistant organisms

Aerobic Gram-negative micro-organisms

Acinetobacter sp.

Citrobacter freundii

Enterobacter sp.

Legionella pneumophila

Morganella morganii

Providencia spp.

Pseudomonas sp.

Serrati sp.

Stenotrophomonas maltophilia

Other micro-organisms

Chlamydia trachomatis

Chlamydophila pneumonia

Chlamydophila psittaci

Coxiella burnetti

Mycoplasma pneumoniae

5.2 Pharmacokinetic properties

Absorption

The two components of CO-AMOXYCLAV ES SANDOZ, amoxicillin and clavulanic acid are fully dissociated in aqueous solution at physiological pH. Both components are well absorbed by the oral route of administration. Absorption of CO-AMOXYCLAV ES SANDOZ is optimised when taken at the start of a meal. Amoxicillin serum concentrations achieved with the CO-AMOXYCLAV ES SANDOZ combination are similar to those produced by the oral administration of equivalent doses of amoxicillin alone.

Distribution

Amoxicillin and clavulanic acid diffuse readily into most body tissues and fluids with the exception of the brain and spinal fluid. Neither amoxicillin nor clavulanic acid is highly protein bound, clavulanic acid is found to be approximately 25 % bound to human serum and amoxicillin approximately 18 % bound.

Biotransformation

Amoxicillin is partly excreted in the urine as the inactive metabolite (penicilloic acid) in quantities equivalent to 10 to 25 % of the initial dose. Clavulanic acid is extensively metabolised in man and the metabolites are eliminated in urine and faeces and as carbon dioxide in expired air.

Elimination

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

Approximately 60 to 70 % of the amoxicillin and 40 to 65 % of the clavulanic acid is excreted unchanged in urine during the first 6 hours after administration. Co-administration of probenecid has little effect on the excretion of the clavulanic acid component of the formulation but delays amoxicillin excretion.

Paediatric population

Pharmacokinetic studies performed in children, comparing CO-AMOXYCLAV ES SANDOZ three times a day and twice daily formulations, indicate that the elimination pharmacokinetics seen in adults also apply to children with mature kidney function.

The mean AUC values for amoxicillin are essentially the same following twice-a-day dosing or three-times-a-day dosing, in adults. No differences between the twice and three-time daily dosing regimens are seen when comparing the amoxicillin $T_{1/2}$, or C_{max} after normalisation for the different doses of amoxicillin administered. Similarly, no differences are seen for the clavulanate $T_{1/2}$, C_{max} or AUC values after appropriate dose normalisation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid, anhydrous (E330), caramel flavour [flavouring components (≈4,4 %), maize maltodextrin (≈80,0 %), triethyl citrate E 1505 (≈10,6 %), residual moisture (≈5,0 %)], microcrystalline cellulose and carmellose sodium, microcrystalline cellulose (E460), orange flavour [flavouring preparations, natural flavouring substances, maize maltodextrin (60 %), modified maize starch E1450 (16 %), buthylated hydroxyanisole (BHA) E320 (<0,1 %)], raspberry flavour [flavouring components (≈3,2 %), maize maltodextrin (≈80,0 %), propylene glycol E120 (≈6,0 %), glyceryl triacetate E1518 (≈5,7 %), triethyl citrate E1505 (≈0,1%), residual moisture (≈5,0 %)], saccharin sodium (E954), colloidal anhydrous silica (E551), silicon dioxide (E551), sodium citrate (E331) and xanthan gum (E415).

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Dry Powder: Store below 25 °C in the original package to protect from moisture.

Reconstituted suspension: Store in a refrigerator (2 to 8 °C) and use within 10 days.

Discard any unused portion after 10 days.

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

6.5 Nature and contents of container

CO-AMOXYCLAV ES SANDOZ 50 mL: 100 mL amber glass bottle with white plastic screw cap with a sealing cone and a tamper evident ring, containing powder for reconstitution to 50 mL packed with a 5 mL plastic dosing pipette.

CO-AMOXYCLAV ES SANDOZ 100 mL: 180 mL amber glass bottle with white plastic screw cap with a sealing cone and a tamper evident ring, containing powder for reconstitution to 100 mL packed with a 5 mL plastic dosing pipette.

6.6 Special precautions for disposal and other handling

Check cap seal is intact before use. Tap bottle until the powder flows freely. Add approximately 2/3 of the total amount of water for reconstitution (see table below) and shake vigorously to suspend powder.

Add remainder of the water and again shake vigorously.

Strength	**Volume of water to be added at reconstitution (mL)**	**Final volume of reconstituted oral suspension (mL)**
600 mg/42,9 mg/5 mL	46	50
600 mg/42,9 mg/5 mL	88	100

Shake the bottle well before each dose.

Disposal

Any unused CO-AMOXYCLAV ES SANDOZ should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

Midrand

2090

8. REGISTRATION NUMBER

51/20.1.2/0478

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 September 2021

10. DATE OF REVISION OF THE TEXT

TBC

Additional country registration details:

Country	*Product name*	*Scheduling status (or Category of distribution)*	*Registration number*
Zimbabwe	Co-Amoxyclav ES Sandoz	P.P.	2018/7.1.2/5519

Pharmacological classification: 7.1.2 – Beta-lactamase resistant

Name and address of manufacturer:

Sandoz GmbH
Biochemiestraße 10

A-6250 Kundl
Austria

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