CO-AMOXICLAV S UNIMED and CO-AMOXICLAV SF UNIMED

SCHEDULING STATUS **S4**

1. NAME OF THE MEDICINE

CO-AMOXICLAV S UNIMED Powder for oral suspension

CO-AMOXICLAV SF UNIMED Powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CO-AMOXICLAV S UNIMED: Each 5 ml of the reconstituted suspension contains amoxicillin trihydrate equivalent to amoxicillin 125 mg and potassium clavulanate equivalent to clavulanic acid 31,25 mg.

Contains sweetener (Aspartame 5 mg/5 ml) (see section 4.4)

Sugar free.

CO-AMOXICLAV SF UNIMED: Each 5 ml of the reconstituted suspension contains amoxicillin trihydrate equivalent to amoxicillin 250 mg and potassium clavulanate equivalent to clavulanic acid 62,5 mg.

Contains sweetener (Aspartame 10 mg/5 ml) (see section 4.4)

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

CO-AMOXICLAV S UNIMED: Powder for oral suspension

White to off-white granular powder.

CO-AMOXICLAV SF UNIMED: Powder for oral suspension

White to off-white granular powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

CO-AMOXICLAV UNIMED 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, otitis media, recurrent tonsillitis.

• Lower respiratory tract infections, such as acute exacerbations of chronic bronchitis (caused by amoxicillin-resistant β-lactamase producing Escherichia *coli*, *Haemophilus influenzae* and *Haemophilus para-influenzae*), bronchopneumonia.

• Genito-urinary tract infections, such as cystitis, urethritis, pyelonephritis.

• Skin and soft tissue infections.

CO-AMOXICLAV UNIMED 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. Dosage depends on the age, weight and renal function of the patient and the severity of the infection. Duration of therapy should be appropriate to the indication and should not exceed 14 days without review.

Children 2-12 years

The dose of CO-AMOXICLAV UNIMED in children is 25-50 mg/kg/day of the 4 parts amoxicillin, 1 part clavulanic acid preparations (which corresponds to a daily dosage of the

equivalent of 20-40 mg/kg of amoxicillin and 5-10 mg/kg of clavulanic acid) to be taken in divided doses every eight hours, at the start of a meal.

	4: 1 Formulation
Directions for use	In divided doses, three times per day (every 8 hours), at the start of a meal
Lower dose (mg/kg/day)	20/5-40/10
Higher dose (mg/kg/day)	40/10-60/15

The lower dose is recommended for infections such as skin and soft tissue and recurrent tonsillitis. The higher dose is recommended for infections such as otitis media, sinusitis, lower respiratory tract infections and urinary tract infections. Children weighing 40 kg and over should be dosed according to adult recommendations.

Dosage guide

Amoxicillin-sensitive organisms				
Product	**Upper respiratory tract infections**	**Lower respiratory tract infections**	**Urinary tract infections**	**Skin and soft tissue infections**
CO-AMOXICLAV S UNIMED 13-21 kg (2-6 years)	5-10 ml [1] 8 hourly	5-10 ml [1] 8 hourly	5-10 ml [1] 8 hourly	5-10 ml [1] 8 hourly
CO-AMOXICLAV SF UNIMED 22-40 kg (7-12 years)	5-10 ml [1] 8 hourly	5-10 ml [1] 8 hourly	5-10 ml [1] 8 hourly	5-10 ml [1] 8 hourly
[1] To correspond to a dosage of 25-50 mg/kg/day				

Amoxicillin-resistant organisms				
Product	Upper respiratory tract infections (otitis media) *H. influenzae, H. parainfluenzae*	Lower respiratory tract infections (bronchitis) *H. influenzae, H. parainfluenzae*	Urinary tract infections *E. coli. Klebsiella pneumomae*	Skin and soft tissue infections *Staphylococcus aureus*
CO-AMOXICLAV S UNIMED 13-21 kg (2-6 years)	5-10 ml [2] 8 hourly	5-10 ml [1] 8 hourly	5-10 ml [1] 8 hourly	5-10 ml [1] 8 hourly
CO-AMOXICLAV SF UNIMED 22-40 kg (7-12 years)	5-10 ml [2] 8 hourly	5-10 ml [1] 8 hourly	5-10 ml [1] 8 hourly	5-10 ml [1] 8 hourly
[1] To correspond to a dosage of 25-50 mg/kg/day **[2] To correspond to a dosage of 50 mg/kg/day**				

Children aged 2 months to 2 years

Children under 2 years should be dosed according to body weight. CO-AMOXICLAV S UNIMED and CO-AMOXICLAV SF UNIMED may be used in this age group.

Special populations

Renal impairment

Both amoxicillin and clavulanic acid are excreted by the kidneys and the serum half-life of each, but particularly of amoxicillin, increases in patients with renal failure. Therefore, the dose may need to be reduced or the dosing interval extended. Dosage adjustments are based on the maximum recommended level of amoxicillin. The following schedule is proposed:

Mild impairment	Moderate impairment	Severe impairment
Creatinine clearance greater than 30 ml/minute	**Creatinine clearance *10 to 30 ml/minute***	***Creatinine clearance less than 10 ml/minute***
No change in dosage.	15/3,75 mg/kg given 12 hourly.	15/3,75 mg/kg given as a single daily dose.
	Maximum amoxicillin dose: 30 mg/kg/day.	Maximum amoxicillin dose: 15 mg/kg/day.

No dosage recommendations can be made for premature infants.

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

Method of Administration

For oral administration only.

CO-AMOXICLAV UNIMED formulations should be taken immediately before a meal to minimise potential gastrointestinal intolerances.

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

4.3 Contraindications

- Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients of CO-AMOXICLAV UNIMED **(see 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).
- Previous history of amoxicillin/clavulanic-associated jaundice/hepatic dysfunction **(see section 4.8)**
- Safety in children under 2 months of age has not been established.

4.4 Special warnings and precautions for use

Prescribers must adhere to the principles of antibiotic stewardship.

Hypersensitivity reactions

Before initiating therapy with CO-AMOXICLAV UNIMED, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents **(see sections 4.3 and 4.8)**.

There have been reports of individuals with a history of penicillin hypersensitivity, who have experienced severe reactions when treated with cephalosporins. Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic can result in myocardial infarction (see section 4.8). 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. If an allergic reaction occurs, CO-AMOXICLAV UNIMED therapy must be discontinued and appropriate alternative therapy instituted: adrenaline, corticosteroids and antihistamines.

Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin/clavulanate (see section 4.8). DIES is an allergic reaction with the leading symptom of protracted vomiting (1 – 4 hours after intake of amoxicillin/clavulanate) in the absence of allergic skin or respiratory symptoms. Further symptoms could compromise abdominal pain, diarrhoea, hypotension or leucocytosis with neutrophilia. There have been severe cases including progression to shock.

Skin reactions

CO-AMOXICLAV UNIMED should be given with caution to patients with lymphatic leukaemia since they are especially susceptible to amoxicillin induced skin rashes. Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions (see section 4.5). The occurrence at 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-AMOXICLAV UNIMED discontinuation and contraindicates any subsequent administration of amoxicillin.

Amoxicillin-susceptible organisms

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. CO-AMOXICLAV UNIMED is not suitable for use when there is a high risk that the presumptive pathogens have reduced susceptibility or 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***.**

Infectious mononucleosis

Since CO-AMOXICLAV UNIMED 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. 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.

Antibiotic-associated colitis

Antibiotic-associated colitis has been reported with nearly all antibacterial agents 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. Antiperistaltic medicinal products are contraindicated in this situation.

Anticoagulants

Prolongation of prothrombin time has been reported in patients receiving CO-AMOXICLAV UNIMED. 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).

Overgrowth of non-susceptible microorganisms

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-AMOXICLAV UNIMED should be discontinued and/or appropriate therapy instituted.

Prolonged therapy

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function, is advisable during prolonged therapy. The use of this antibiotic 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 (see section 5.1).

Hepatic impairment

CO-AMOXICLAV UNIMED should be used with caution in patients with evidence of hepatic impairment (see sections 4.2, 4.3 and 4.8)**.** Changes in liver function tests have been observed in some patients receiving CO-AMOXICLAV UNIMED. Hepatic function should be monitored at regular intervals. Transient hepatitis and cholestatic jaundice have been reported (see section 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 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 (see section 4.8).

Renal impairment

In patients with renal impairment, the dose should be adjusted according to the degree of impairment (see section 4.2).

Convulsions

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

Crystalluria

In patients with reduced urine output, crystalluria (including acute renal injury) 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 in order to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained (see section 4.9).

Interference with serological testing

During treatment with amoxicillin, 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. The presence of clavulanic acid in CO-AMOXICLAV UNIMED may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

Important information regarding excipients: ASPARTAME

This medicine contains Aspartame (E951)

(CO-AMOXICLAV S UNIMED: 5 mg per each 5 ml)

(CO-AMOXICLAV SF UNIMED: 10 mg per each 5 ml).

Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly. Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.

4.5 Interaction with other medicines and other forms of interaction

- **Probenecid:** Concomitant use decreases the renal tubular secretion of amoxicillin, but does not affect clavulanic acid excretion, which may result in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.

- **Allopurinol:** 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-AMOXICLAV UNIMED and allopurinol administered concomitantly.

• **Oral anticoagulants:** Use with 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 acenocoumarin or warfarin and prescribed a course of amoxicillin. If co-administration 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 section 4.4 and 4.8).

• **Methotrexate:** Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

• **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 CO-AMOXICLAV UNIMED. 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.

• **Oral contraceptives:** CO-AMOXICLAV UNIMED may reduce the efficacy of oral contraceptives and patients should be warned accordingly (see section 4.6).

• **Alcohol:** No information is available about the concurrent use of CO-AMOXICLAV UNIMED and alcohol. However, the ingestion of alcohol whilst being treated with some other β-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-AMOXICLAV UNIMED.

4.6 Fertility, Pregnancy and Lactation

Women of childbearing potential / Contraception in males and females

Concurrent use of CO-AMOXICLAV UNIMED and oral contraceptives decreases the efficacy of the oral contraceptive. Patients should be strongly advised to use an alternative or additional method of contraception while taking this medicine (see section 4.5).

Pregnancy

Safety in pregnancy has not been established. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Limited data on the use of amoxicillin/clavulanic acid during pregnancy in humans do not indicate an increased risk of congenital malformations. In a single study in women with preterm, premature rupture of the foetal membrane it was reported that prophylactic treatment with amoxicillin/clavulanic acid may be associated with an increased risk of necrotising enterocolitis in neonates. There is limited information on the use of CO-AMOXICLAV UNIMED in pregnancy and its use should be avoided.

Breastfeeding

Both substances are excreted into breast milk (nothing is known of the effects of clavulanic acid on the breast-fed infant). CO-AMOXICLAV UNIMED may be administered during the period of lactation. The possibility of sensitisation should be taken into account. Diarrhoea and fungal infection of the mucous membranes is possible in the breast-fed infant, so breast-feeding might have to be discontinued. With the exception of the associated risk of sensitisation, there are no known detrimental effects for the breastfed 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 commonly reported adverse drug reactions are diarrhoea, nausea, vomiting, abdominal pain, skin rashes, urticaria and erythema multiforme, vaginitis, abnormal taste, headache, dizziness, tiredness and hot flushes. The incidence and severity of adverse effects, particularly nausea and diarrhoea is more often associated with higher oral dosages. In addition, as these symptoms are especially related to the potassium clavulanate component, where these gastro-intestinal symptoms occur and a higher concentration of amoxicillin is required, consideration should be given to administering the additional amoxicillin separately.

The following undesirable effects have been observed and reported during treatment with amoxicillin/clavulanic acid:

Infections and infestations

Frequent: Mucocutaneous candidiasis (including vaginitis).

Frequency unknown: Overgrowth of non-susceptible organisms.

Blood and lymphatic system disorders[3]

Frequent: Thrombocytopenic purpura, Eosinophilia

Less frequent: Reversible leukopenia (including neutropenia) and thrombocytopenia,

Frequency not known: Reversible agranulocytosis and haemolytic anaemia. Prolongation of

bleeding time and prothrombin time (Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. See sections 4.4 and 4.5).

Immune system disorders

Less frequent: Angio oedema, anaphylaxis, serum sickness-like syndrome, hypersensitivity vasculitis (see section 4.3 and 4.4).

Nervous system disorders

Less frequent: Dizziness, headache

Frequency unknown: Reversible hyperactivity and convulsions (Convulsions may occur in patients with impaired renal function or in those receiving high doses, see section 4.4), Aseptic meningitis

Cardiac disorders

Frequency unknown: Kounis syndrome (see section 4.4)

Gastrointestinal disorders

Frequent: Diarrhoea, Nausea, Vomiting (Nausea is more often associated with higher oral dosages. If gastrointestinal reactions are evident, they may be reduced by taking COAMOXICLAV UNIMED at the start of a meal.), Gastritis, Stomatitis, Glossitis, Enterocolitis

Less frequent: Indigestion,

Frequency unknown: Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis, see section 4.4). Superficial tooth discolouration has been reported which can usually be removed by brushing. Abdominal pain, black “hairy” tongue, abnormal taste, drug-induced enterocolitis syndrome, pancreatitis acute 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 β-lactam class antibiotics, but the significance of these findings is unknown.

Frequency unknown: Hepatitis and cholestatic jaundice. These events have been noted with other penicillins and cephalosporins (see section 4.4).

Skin and subcutaneous tissue disorders

Less frequent: Skin rash, pruritus, urticaria, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative-dermatitis, acute generalised exanthemous pustulosis (AGEP) (see section 4.4)

Frequency unknown: Drug reaction with eosinophilia and systemic symptoms (DRESS), Linear IgA

Renal and urinary disorders

Frequency unknown: Interstitial nephritis, Crystalluria (including acute renal injury - see sections 4.4 and 4.9)

Description of selected adverse reactions

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. 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.

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

4.9 Overdose

Symptoms and signs 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. Amoxicillin has been reported to precipitate in bladder catheters, predominantly after intravenous administration of large doses. A regular check of patency should be maintained (see section 4.4).

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: A 20.1.2 Penicillins

Pharmacotherapeutic group: Combination 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, in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall, thus leading to weakening of the cell wall, 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. The amoxicillin component of the formulations exerts a bactericidal action against many strains of Gram-positive and Gram-negative organisms. Clavulanic acid alone does not exert a clinically useful antibacterial effect. 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.

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.

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

The prevalence of resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

5.2 Pharmacokinetic Properties

Absorption

Amoxicillin and clavulanic acid are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Absorption is optimised when taken at the start of a meal. 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.

Amoxicillin and clavulanic acid serum concentrations achieved with amoxicillin/clavulanic acid are similar to those produced by the oral administration of equivalent doses of amoxicillin or clavulanic acid alone.

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 b.i.d and t.i.d 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 clavulanic acid $T_{1/2}$, C_{max} or AUC values after appropriate dose normalisation.

Distribution

Neither amoxicillin nor clavulanic acid is highly protein bound, with about 25 % of total plasma clavulanic acid and 18 % of total plasma amoxicillin bound. Amoxicillin and clavulanic acid diffuse readily into most body tissues and fluids with the exception of the brain and spinal fluid. The apparent volume of distribution is around 0.3-0.4 l/kg for amoxicillin and around 0.2 l/kg for clavulanic acid.

Biotransformation

Amoxicillin is partly excreted in the urine as the inactive metabolite 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 60-70 % of amoxicillin and 40-65 % clavulanic acid is excreted unchanged in urine during the first 6 hours after administration. Concomitant use

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

Special populations

Elderly

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 **(see section 4.2).**

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 drug 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 **(see section 4.2)**.

Hepatic impairment

Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals **(see sections 4.3 and 4.4)**.

Pharmacokinetic/pharmacodynamic relationship

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

Paediatric population

Pharmacokinetic studies performed in children, comparing amoxicillin/clavulanic acid 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 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.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity and toxicity to reproduction. Repeat dose toxicity studies performed in dogs with amoxicillin/clavulanic acid demonstrate gastric irritancy and vomiting, and discoloured tongue. Carcinogenicity studies have not been conducted with CO-AMOXICLAV UNIMED or its components.

6.PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silica, Colloidal anhydrous

Succinic acid

Hypromellose

Xanthan gum

Strawberry Guarana flavour

Aspartame (E951) (see section 4.4)

Silicon dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Dry powder: 18 months

Reconstituted oral suspension: 7 days

Reconstituted suspensions should be stored at 2 °C – 8 °C in a refrigerator for up to 7 days.

Do not freeze.

6.4 Special precautions for storage

Store the dry powder in the original container at or below 30 °C.

This medicinal product does not require any special temperature storage conditions.

For storage conditions of the reconstituted suspension, see section 6.3.

6.5 Nature and contents of container

150 ml HDPE translucent bottle closed with a white opaque polypropylene screw cap or a white opaque polypropylene child resistant closure with an induction sealing wad, for reconstitution to 100 ml suspension.

6.6 Special precautions for disposal and other handling

CO-AMOXICLAV S UNIMED: For reconstitution to 100 ml, first shake bottle to loosen powder, add 92 ml water, invert bottle and shake well until all the powder is dispersed.

CO-AMOXICLAV SF UNIMED: For reconstitution to 100 ml, first shake bottle to loosen powder, add 90 ml water, invert bottle and shake well until all the powder is dispersed.

When first reconstituted allow to stand for 5 min to ensure full dispersion. After reconstitution, the medicine appears as white to off white strawberry flavoured suspension.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unimed Healthcare (Pty) Ltd

Corner Birch Road & Bluegum Avenue,

Anchorville,

Lenasia, 1827

South Africa

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8. REGISTRATION NUMBER(S)

CO-AMOXICLAV S UNIMED: 50/20.1.2/0659

CO-AMOXICLAV SF UNIMED: 50/20.1.2/0660

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

4 May 2021

10. DATE OF REVISION OF THE TEXT

27 March 2025