SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

CO-AMOXICLAV 375 UNIMED Tablets

CO-AMOXICLAV 625 UNIMED Tablets

CO-AMOXICLAV 1000 UNIMED Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CO-AMOXICLAV 375 UNIMED: Each film-coated tablet contains Amoxicillin 250 mg (as amoxicillin trihydrate 286.70 mg) and Clavulanic acid 125 mg (as potassium clavulanate 277.77 mg).

CO-AMOXICLAV 625 UNIMED: Each film-coated tablet contains Amoxicillin 500 mg (as amoxicillin trihydrate 573.40 mg) and Clavulanic acid 125 mg (as potassium clavulanate 277.77 mg).

CO-AMOXICLAV 1000 UNIMED: Each film-coated tablet contains Amoxicillin 875 mg (as amoxicillin trihydrate 1033.44 mg) and Clavulanic acid 125 mg (as potassium clavulanate 277.77 mg).

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

CO-AMOXICLAV 375 UNIMED: Film coated tablets

White oval shaped film coated tablets, debossed with ‘A’ on one side and ‘63’ on other side.

CO-AMOXICLAV 625 UNIMED: Film coated tablets

White oval shaped film coated tablets, debossed with ‘A’ on one side and ‘64’ on other side.

CO-AMOXICLAV 1000 UNIMED: Film coated tablets

White coloured, capsule shaped, film coated tablets debossed with "A" on one side and with a score line in between "6" and "5" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

CO-AMOXICLAV UNIMED is indicated for the treatment of infections in adults caused by amoxicillin-resistant organisms producing β-lactamases sensitive to clavulanic acid (see sections 4.2, 4.4 and 5.1).

• Upper respiratory tract infections, such as sinusitis, recurrent otitis media, tonsillitis.

• Lower respiratory tract infections, such as bronchitis and bronchopneumonia.

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

• Skin and soft tissue infections

CO-AMOXICLAV UNIMED 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

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.

Adults

The adult dose for CO-AMOXICLAV 375 UNIMED is one tablet every eight hours at the start of a meal. For more severe infections and infections of the respiratory tract, the dose should be one CO-AMOXICLAV 625 UNIMED tablet every eight hours at the start of a meal, or one CO-AMOXICLAV 1000 UNIMED tablet every 12 hours at the start of a meal. Since CO-AMOXICLAV 375 UNIMED, CO-AMOXICLAV 625 UNIMED and CO-AMOXICLAV 1000 UNIMED tablets contain the same amount of clavulanic acid (125 mg as the potassium salt), two CO-AMOXICLAV 375 UNIMED tablets are not equivalent to one CO-AMOXICLAV 625

UNIMED tablet, and two CO-AMOXICLAV 625 UNIMED tablets are not equivalent to one CO-AMOXICLAV 1000 UNIMED 1000 tablet. Therefore, two CO-AMOXICLAV 375 UNIMED tablets should not be substituted for one CO-AMOXICLAV 625 UNIMED tablet or two CO-AMOXICLAV 625 UNIMED tablets for one CO-AMOXICLAV 1000 UNIMED tablet for the treatment of more serious infections.

Special populations

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:

CO-AMOXICLAV 375 UNIMED and CO-AMOXICLAV 625 UNIMED

Creatinine clearance greater than 30ml/minute: No dosage adjustment required.

Creatinine clearance 10 to 30ml/minute: One tablet twice daily.

Creatinine clearance less than 10ml/minute: One tablet once daily.

CO-AMOXICLAV 1000 UNIMED

Should not be used in patients with a glomerular filtration rate of less than 30 ml/minute. 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 infections**	**Lower respiratory tract infections**	**Urinary tract infections**	**Skin and soft tissue infections**

CO-AMOXICLAV UNIMED 375	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly
CO-AMOXICLAV UNIMED 625	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly
CO-AMOXICLAV UNIMED 1000	1 tablet 12-hourly	1 tablet 12-hourly	1 tablet 12-hourly	1 tablet 12-hourly

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 UNIMED 375	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly
CO-AMOXICLAV UNIMED 625	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly

CO-AMOXICLAV UNIMED 1000	1 tablet 12-hourly	1 tablet 12-hourly	1 tablet 12-hourly	1 tablet 12-hourly

Method of Administration

For oral administration only.

Tablets should be taken immediately before a meal.

During the administration of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to prevent any possibility of amoxicillin crystalluria.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Hypersensitivity to penicillins or cephalosporins. Cross-sensitivity between penicillins and cephalosporins is well documented.
- Patients with a previous history of amoxicillin/clavulanic-associated jaundice/hepatic dysfunction (see section 4.8).

4.4 Special warnings and precautions for use

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. Before initiating therapy with CO-AMOXICLAV UNIMED, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins, including CO-AMOXICLAV UNIMED. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8). 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, which have experienced severe reactions when treated with cephalosporins. If an allergic reaction occurs, CO-AMOXICLAV UNIMED should be discontinued and the appropriate therapy instituted. Serious anaphylactic reactions may require immediate emergency treatment with adrenaline. Oxygen, intravenous steroids and airway management, including intubation may also be required.

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 comprise abdominal pain, diarrhoea, hypotension or leucocytosis with neutrophilia. There have been severe cases including progression to shock.

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, in the presence of which there is a high incidence of morbilliform rash if amoxicillin is used. CO-AMOXICLAV UNIMED should be avoided if infectious mononucleosis is suspected.

Prolonged use may result in overgrowth of non-susceptible organisms.
Pseudomembranous enterocolitis has been reported. The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving Aerobacter, Pseudomonas or Candida) the agent should be discontinued and/or appropriate therapy instituted.
Prolongation of prothrombin time has been reported rarely in patients receiving CO-AMOXICLAV UNIMED. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently.

Pseudomembranous enterocolitis and 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). 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 generalised exanthematous pustulosis (AGEP) have been reported in patients taking beta-lactam antibiotics such as CO-AMOXICLAV UNIMED. When SCAR is suspected CO-AMOXICLAV UNIMED should be discontinued.

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

The occurrence at the 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.

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

Impaired hepatic function: Changes in liver function tests have been observed in some patients receiving CO-AMOXICLAV UNIMED. Transient hepatitis and cholestatic jaundice has been reported. CO-AMOXICLAV UNIMED should be used with caution in patients with evidence of hepatic dysfunction.

Impaired renal function: In patients with moderate or severe renal impairment CO-AMOXICLAV UNIMED dosage should be adjusted (see Section 4.2).

Crystalluria: In patients with reduced urine output, crystalluria (including acute renal injury) has been observed very rarely, predominantly with parenteral therapy. During 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 4.8 and 4.9).

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

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

Amoxicillin is excreted in the milk; there is no data on the excretion of clavulanic acid in human milk. Therefore, caution should be exercised when CO-AMOXICLAV UNIMED is administered to a nursing woman. (see Section 4.6)
The use of CO-AMOXICLAV UNIMED 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.

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.

4.5 Interaction with other medicines and other forms of interaction

Probenecid

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

Oral contraceptives

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

Allopurinol

The concomitant administration of allopurinol and amoxicillin substantially increases the incidence of skin rashes in patients receiving both agents as compared to patients receiving amoxicillin alone. It is not known whether this potentiation of amoxicillin rashes is due to allopurinol or the hyperuricaemia present in these patients.

Tetracyclines and other bacteriostatic drugs

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

Oral anticoagulants

Oral anticoagulants and 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 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 sections 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 amoxicillin plus clavulanic acid.

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.

Interaction with laboratory parameters

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

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

The safety of CO-AMOXICLAV UNIMED in pregnancy has not been established.

Lactation

Both substances are excreted into breast milk (nothing is known of the effects of clavulanic acid on the breast-fed infant). Consequently, diarrhoea and fungus infection of the mucous membranes are possible in the breast-fed infant, so that breast-feeding might have to be discontinued. The possibility of sensitisation should be taken into account.

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 frequently reported undesirable effects are diarrhoea, nausea, vomiting, indigestion, abdominal pain, skin rashes, urticaria and erythema multiforme, vaginitis, genital moniliasis, abnormal taste, headache, dizziness, tiredness and hot flushes. The incidence and severity of adverse effects, particularly nausea and diarrhoea, increased with the higher recommended dose and can be minimised by administering CO-AMOXICLAV UNIMED at the start of a meal. In addition, as these symptoms are especially related to the potassium clavulanate component, where these gastrointestinal symptoms occur and a higher concentration of amoxicillin is required, consideration should be given to administering the additional amoxicillin separately.

Infections and infestations:

Frequent: Mucocutaneous candidiasis

Frequency unknown: Overgrowth of non-susceptible organisms

Blood and lymphatic system disorders:

Frequency unknown: Haemolytic anaemia, reversible thrombocytopenia, thrombocytopenic purpura, eosinophilia, reversible (including neutropenia), agranulocytosis, platelet dysfunction.

Immune system disorders:

Frequent: Serum sickness-like syndrome, anaphylactic (hypersensitivity) reactions.

Frequency unknown: Hypersensitivity vasculitis, angioedema.

Nervous system disorders:

Less frequent: Dizziness, Headache, Tiredness

Frequency unknown: Reversible hyperactivity, Convulsions, Aseptic meningitis

Cardiac disorders:

Frequency unknown: Kounis syndrome (see section 4.4)

Gastrointestinal disorders:

Frequent: Diarrhoea, nausea, vomiting, indigestion, abdominal pain, abnormal taste, gastritis, stomatitis, black hairy tongue, enterocolitis, antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis)

Less frequent: Oral candidiasis

Frequency unknown: Clostridium difficile colitis, glossitis, drug-induced enterocolitis syndrome, pancreatitis acute

Hepatobiliary disorders:

Frequency unknown: Hepatitis, cholestatic jaundice, hepatic dysfunction

Skin and subcutaneous tissue disorders:

Frequent: Urticaria, pruritus, skin rashes

Less frequent: Bullous exfoliative dermatitis, hives, itching, erythema multiforme

Frequency unknown: Stevens-Johnson syndrome, acute generalised exanthematous pustulosis, toxic epidermal necrolysis, Linear IgA

Renal and urinary disorders:

Frequency unknown: Interstitial nephritis, crystalluria (including acute renal injury, dysuria or urinary retention, proteinuria

Reproductive system and breast disorders:

Frequent: Vaginitis, genital moniliasis

Less frequent: Vaginal candidiasis.

General disorders and administration site conditions:

Frequent: Hot flushes.

Frequency unknown: Chest pain, oedema, chills, fatigue, malaise, epistaxis.

Investigations:

Less frequent: Moderate raise in aspartate transaminase (AST) and/or alanine transaminase (ALT).

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

Signs and Symptoms of overdose

Overdose with amoxicillin is usually asymptomatic. Gastrointestinal effects such as nausea, vomiting and diarrhoea and symptoms of water and electrolyte imbalance 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.

Gastrointestinal symptoms may 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.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties

Pharmacological Classification: A 20.1.2 Penicillins

Mechanism of Action

Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more penicillin-binding proteins in the biosynthetic pathway of bacterial peptidoglycan, leading to

weakening of the cell wall, which is usually 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 penicillin. 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.

The clavulanic acid alone does not exert a clinically useful antibacterial effect.

It does however, by inactivation of susceptible β-lactamases, protect amoxicillin from degradation by a large number of β-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 penicillin-binding proteins, 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.

Species for which acquired resistance may be a problem:

Aerobic Gram-positive micro-organisms

Enterococcus faecium

Aerobic Gram-negative micro-organisms

Escherichia coli

Klebsiella oxytoca

Klebsiella pneumoniae

Proteus mirabilis

Proteus vulgaris

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. Following oral administration, amoxicillin and clavulanic acid are approximately 70 % bioavailable.

The pharmacokinetics of both components are closely allied, and neither are adversely affected by the presence of food in the stomach.

The plasma profiles of both components are similar and the time to peak plasma concentration (T_{max}) in each case is approximately one hour.

After an oral dose of 2 parts amoxicillin and 1-part clavulanic acid, taken at the start of a meal, a mean peak serum level of 5,7 µg amoxicillin and 3,8 µg clavulanic acid per millilitre was achieved within one hour in healthy volunteers. Doubling the dose virtually doubles the peak serum level.

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.

Distribution

About 18 % of total plasma amoxicillin and 25 % of total plasma clavulanic acid is bound to protein. The apparent volume of distribution is around 0.3-0.4 l/kg for Amoxicillin and around 0.2 l/kg for clavulanic acid. Amoxicillin does not adequately distribute into the cerebrospinal fluid. From animal studies there is no evidence for significant tissue retention of drug-derived material for either component. Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanic acid can also be detected in breast milk (see section 4.6).

Biotransformation

Amoxicillin is partly excreted in the urine as the inactive 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.

64,9 % of amoxicillin and 37,5 % of clavulanic acid are excreted unchanged in the urine in the first 6 hours after an oral dose of 2 to 1 amoxicillin/clavulanic acid tablets.
Various studies have found the urinary excretion to be 50-85 % for amoxicillin and between 27-60 % for clavulanic acid over a 24-hour period. In the case of clavulanic acid, the largest amount of drug is excreted during the first 2 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

Age: 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 new-borns) 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. 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.

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 acid (see section 4.2).

Hepatic impairment: Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

Pharmacokinetic/pharmacodynamic relationship

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

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 amoxicillin/clavulanic acid.

6.PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Microcrystalline Cellulose

Purified Water

Sodium starch glycolate

Colloidal Silicon, dioxide

Magnesium Stearate

Tablet film coat:

Opadry white

Isopropyl Alcohol

Methylene Chloride

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 30 ºC.

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Triple laminated aluminium foil blister pack further packed in pre-printed cartons containing 2 blisters of 5 tablets each.

6.6 Special Precautions For Disposal

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unimed Healthcare (Pty) Ltd

Corner Birch Road & Bluegum Avenue,

Anchorville,

Lenasia,

1827

South Africa

Tel: +27 11 056 6999

8. REGISTRATION NUMBER(S)

CO-AMOXICLAV 375 UNIMED: 50/20.1.2/0975

CO-AMOXICLAV 625 UNIMED: 50/20.1.2/0976

CO-AMOXICLAV 1000 UNIMED: 50/20.1.2/0977

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

4 May 2021

10. DATE OF REVISION OF TEXT

22 November 2024