Amoxicillin trihydrate equivalent to amoxicillin 875 mg Clavulanate potassium equivalent to clavulanic acid 125 mg

Professional Information

CLAVUMED 1 g

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CLAVUMED 1 g Film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains amoxicillin trihydrate equivalent to 875 mg amoxicillin plus potassium clavulanate:microcrystalline cellulose (1:1) equivalent to 125 mg clavulanic acid.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets.

White to off-white film coated capsule shaped tablets debossed with **"RX509"** on one side and score line on the other**.**

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

Amoxicillin trihydrate
equivalent to amoxicillin 875 mg Clavulanate potassium
equivalent to clavulanic acid 125 mg

4.1 Therapeutic indications

CLAVUMED 1 g is indicated for the treatment of infections caused by amoxicillin-resistant organisms producing beta-lactamases sensitive to clavulanic acid:

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

Lower respiratory tract infections, such as bronchitis and bronchopneumonia.

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

Skin and soft tissue infections.

Clavumed 1 g 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

CLAVUMED 1 g 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.

Dosages:

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

Adult: The adult dose for **Clavumed 1 g** is one tablet every 12 hours at the start of a meal.

The following schedule is proposed:

Clavumed 1 g should not be used in patients with a glomerular filtration rate of < 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 Infection**	**Lower Respiratory Tract Infection**	**Urinary Tract Infection**	**Skin & Soft Tissue Infections**
Clavumed 1 g	1 tablet 12-hourly	1 tablet 12-hourly	1 tablet 12-hourly	1 tablet 12-hourly

Amoxicillin- Resistant Organisms				
Product	**Upper Respiratory Tract Infection (otitis media)** ***H. influenzae, H. para-influenzae***	**Lower Respiratory Tract Infection (bronchitis)** ***H. influenzae, H. para-influenzae***	**Urinary Tract Infection** ***E. coli, Klebsiella pneumoniae***	**Skin & Soft Tissue Infections** ***Staphylo-coccus aureus***
Clavumed 1 g	1 tablet 12-hourly	1 tablet 12-hourly	1 tablet 12-hourly	1 tablet 12-hourly

Special populations

Elderly: No dose adjustment is considered necessary

Impaired renal function*:* Both amoxicillin and clavulanic acid are excreted by 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. Dose adjustments are based on the maximum recommended level of amoxicillin.

Method of administration

Clavumed 1 g is for oral use.

4.3 Contraindications

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Hypersensitivity to amoxicillin, clavulanic acid, any of the penicillins, or to any of the excipients of

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Clavumed 1 g.

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

History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid.

4.4 Special warnings and precautions for use

Prescribers must adhere to the principles of antibiotic stewardship.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy.

Before initiating therapy with **Clavumed 1 g**, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins (or other beta-lactam agents), or other allergens. 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, **Clavumed 1 g** 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.

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

Pseudomembranous enterocolitis has been reported.

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin and clavulanic acid. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently.

Impaired hepatic function:

Changes in liver function tests have been observed in some patients receiving **Clavumed 1 g**. It should be used with care in patients with evidence of severe hepatic dysfunction.

Transient hepatitis and cholestatic jaundice has been reported. **Clavumed 1 g** should be used with caution in patients with evidence of hepatic dysfunction. 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

Clavumed 1 g should not be used in patients with glomerular filtration rate of less than 30 ml/min.

Antibiotic-associated colitis has been reported with nearly all antibacterial agents including amoxicillin and may range in severity from mild to life threatening. 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, **Clavumed 1 g** immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-

peristaltic medicinal products are contraindicated in this situation.

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (AGEP). This reaction requires amoxicillin and clavulanic potassium discontinuation and contra-indicates any subsequent administration of amoxicillin.

Convulsions may occur in patients with impaired renal function or in those receiving high doses.

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

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function, is advisable during prolonged therapy. Since amoxicillin and clavulanic acid 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. Amoxicillin and clavulanic acid should be given with caution to patients with lymphatic leukaemia since they are especially susceptible to amoxicillin induced skin rashes.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Aerobacter, Pseudomonas* or *Candida),* the agent should be discontinued and/or appropriate therapy instituted.

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Impaired renal function:

In patients with moderate or severe renal impairment, **Clavumed 1 g** dosage should be adjusted.

In patients with reduced urine output, crystalluria has been observed very rarely, 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.

The use of **Clavumed 1 g** 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.

The presence of clavulanic acid in **Clavumed 1 g** may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

There have been reports of positive test results using the Bio-Rad Laboratories Platelia *Aspergillus* EIA test in patients receiving amoxicillin/clavulanic acid who were subsequently found to be free of *Aspergillus* infection. Cross-reactions with non-*Aspergillus* polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia *Aspergillus* EIA test have been reported. Therefore, positive test results in patients receiving amoxicillin/clavulanic acid should be interpreted cautiously and confirmed by other diagnostic methods.

4.5 Interaction with other medicines and other forms of interaction

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 acenocoumarol 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.

Probenecid

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin, but does not affect clavulanic acid excretion. Concurrent use with **Clavumed 1 g** may result in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.

Oral contraceptives

Clavumed 1 g 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

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

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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 tests:

It is recommended that when testing for the presence of glucose in urine during **Clavumed 1 g** 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

Use in pregnancy

The safety of **Clavumed 1 g** in pregnancy has not been estabilished.

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. Use should be avoided during pregnancy.

Lactation

Amoxicillin is distributed in breast milk. Although significant problems in humans have not been documented, the use of amoxicillin by nursing mothers may lead to sensitisation, diarrhoea, candidiasis, and skin rash in the infant. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the doctor.

Use should be avoided during breastfeeding.

4.7 Effects on the 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.

4.8 Undesirable effects

Body System	Frequent	Less Frequent	Frequency unknown
Infections and Infestations	• Mucocutaneous candidosis		• Overgrowth of non-susceptible organisms

Blood and the lymphatic system disorders		• Prolongation of bleeding time and prothrombin time	• Reversible agranulocytosis • Reversible thrombocytopenia • Thrombocytopenic purpura

			• Thrombocytosis • Eosinophilia • Reversible leucopenia (including neutropenia) • Agranulocytosis • Anemia • Haemolytic anaemia
Immune system disorders		• Hypersensitivity vasculitis • Bullous exfoliative dermatitis • Toxic epidermal necrolysis • Stevens-Johnson syndrome	• Serum-sickness-like syndrome • Serious and occasional fatal anaphylactic reactions • Angioedema
Nervous system disorders	• Headache • Dizziness • Tiredness	• Reversible hyperactivity • Convulsions	• Aseptic meningitis

Gastro-intestinal disorders	• Diarrhoea • Nausea • Vomiting • Abdominal pain • Abnormal taste • Indigestion		• Gastritis • Stomatitis • Glossitis • Black 'hairy' tongue • Enterocolitis, • Mucocutaneous

			candidiasis and antibiotic associated colitis (including pseudomembranous colitis and haemorrhagic colitis).
Hepatobiliary disorders		• Death	• Hepatitis • Cholestatic jaundice • Moderate rise in aspartate transaminase (AST) and/or alanine transaminase (ALT).

Skin and subcutaneous tissue disorders	• Skin rashes • Erythema multiforme • Urticaria • Hot flushes	• Pruritus • Acute generalised exanthemous pustulosis (AGEP)	• DRESS (Drug reaction with eosinophilia and systemic symptoms) • Stevens-Johnson syndrome • Toxic epidermal necrolysis, • Bullous exfoliative-dermatitis • Hypersensitivity

			dermatitis
Renal and urinary disorders		• Interstitial nephritis	• Crystalluria
Reproductive system and breast disorders	• Vaginitis • Genital moniliasis		
General disorders and administrative site conditions			• Superficial tooth discoloration (usually removed by brushing)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of

Clavumed 1g is important. It allows continued monitoring of the benefit/risk balance of the **Clavumed 1g**. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Overdosage with **Clavumed 1 g** is usually asymptomatic. However, gastro-intestinal effects such as nausea, vomiting and diarrhoea may be evident and symptoms of water and electrolyte imbalance should be treated symptomatically.

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Adequate fluid intake and urinary output must be maintained to minimize 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

Pharmacotherapeutic group: Combinations of penicillins, incl beta-lactamase inhibitors; ATC code: J01CR02

Bacteriologic action

Clavumed 1 g is a combination of amoxicillin and clavulanic acid.

Bacteriology

Spectrum - **Clavumed 1 g** is name for a formulation containing 7 parts of a broad spectrum penicillin, amoxicillin and 1 part of potassium clavulanate. Potassium clavulanate has been 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 gonorrhoeae* and *Bacteroides fragilis*. Potassium clavulanate does not inactivate the chromosomally mediated (Sykes Type I Cephalosporinase) beta-lactamases produced by *Acinetobacter* species, *Citrobacter* species, *Enterobacter*, Indole positive *Proteus*, *Providencia*, species and *Serratia marcescens*. *In vitro* the formulation showed synergism against amoxicillin- resistant organism, with no evidence of antagonism and the activity was not reduced in the presence of serum. (*In vitro* activity does not necessarily imply *in vivo* efficacy).

Bactericidal action – The amoxicillin component of the formulation 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.

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.

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

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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 pneumonia
$ Natural intermediate susceptibility in the absence of acquired mechanism of resistance.

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 plasma profiles of both components are similar and the time to peak plasma concentration (T_{max}) in each case is approximately one hour. The pharmacokinetics of amoxicillin and clavulanic acid are closely allied and neither is adversely affected by the presence of food in the stomach.

Distribution: About 25 % of total plasma clavulanic acid and 18 % of total plasma amoxicillin 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.

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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. The elimination half-life of amoxicillin is approximately 1 hour. Co-administration of probenecid has little effect on the excretion of the clavulanic acid component of the formulation. Small amounts of amoxicillin are also excreted in the faeces and bile.

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 irritation and vomiting, and discoloured tongue.

Carcinogenicity studies have not been conducted with amoxicillin/clavulanic acid or its components.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core ingredients are:

colloidal anhydrous silica,

Eudragit E 100 (Basic butylated methacrylate copolymer),

magnesium stearate,

microcrystalline cellulose (PH 112),

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povidone (K30) and

sodium starch glycolate (Type A).

Film coating ingredients are:

Opadry 03B58965 white consisting of:

hypromellose

macrogol/PEG 400

talc and

titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

36 months

6.4 Special precautions for storage

Store at or below 25 °C, in the original package, protected from light and moisture.

6.5 Nature and contents of container

Carton contains 10 tablets packed in PVC/PVdC blister pack in pouch.

PVC/PVdC blister pack in pouch:

Clear PVC film coated with PVdC on the inner side with the lidding of hard tempered, aluminium foil coated with heat seal lacquer on inner side. One blister to be put in laminated pouch along with 1g sachet containing molecular sieve.

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Pouch is four layered laminated bag (structure: Polyester film/ Aluminium foil/ Polyester film/ Polyethylene).

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. HOLDER OF CERTIFICATE OF REGISTRATION

RANBAXY PHARMACEUTICALS (PTY) LTD

14 Lautre Road, Stormill, Ext.1,

Roodepoort, 1724

South Africa

8. REGISTRATION NUMBER(S)

50/20.1.2/0228

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

11 May 2021

10. DATE OF REVISION OF THE TEXT