SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

CLAVUMED 375 (film -coated tablet)

CLAVUMED 625 mg (film -coated tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CLAVUMED 375

Each tablet contains:

Amoxicillin trihydrate equivalent to amoxicillin 250 mg and

Potassium clavulanate equivalent to clavulanic acid 125 mg

Butylhydroxytoluene (as antioxidant) 0,46 % m/m

CLAVUMED 625 mg

Each tablet contains:

Amoxicillin trihydrate equivalent to amoxicillin 500 mg and

Potassium clavulanate equivalent to clavulanic acid 125 mg

Butylhydroxytoluene (as antioxidant) 0,46 % m/m

Sugar free.

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Clavumed 375

White to off-white oval shaped biconvex, film coated tablets imprinted with `R375' in black ink on one side.

Clavumed 625

White to off-white oval shaped biconvex, film coated tablets imprinted with `R625' in black ink on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CLAVUMED formulations are 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 tablet formulation 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

For Oral Formulations

Tablets should be taken immediately before a meal.

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.

Adults

The adult dose for CLAVUMED 375 and 625 Tablets is one CLAVUMED 375 Tablet every eight hours at the start of a meal. For more severe infections and infection of the respiratory tract, the dose should be one CLAVUMED 625 Tablet every eight hours at the start of a meal.
Since CLAVUMED 375, 625 and 1 g tablets contain the same amount of clavulanic acid (125 g as the potassium salt), two CLAVUMED 375 tablets are not equivalent to one CLAVUMED 625 tablet and two CLAVUMED 625 tablets are not equivalent to one CLAVUMED 1 g. Therefore, two CLAVUMED 375 tablets should not be substituted for one CLAVUMED 625 tablet or two CLAVUMED 625 tablets for one CLAVUMED 1 g tablet for the treatment of more severe 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.

- Mild impairment (creatinine clearance greater than 30 ml/min): No change in dosage.
- Moderate impairment (creatinine clearance 10 to 30 ml/min): 1 Tablet every 12 hours.

- 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 375	1 tablet 8 hourly	-	1 tablet 8 hourly	1 tablet 8 hourly
Clavumed 625	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly

Amoxicillin-Resistant Organisms				
Product	**Upper Respiratory Tract Infection (Otitis media)**	**Lower Respiratory Tract Infection (Bronchitis)**	**Urinary Tract Infection**	**Skin & Soft Tissue Infections**
Clavumed 375	-	-	1 tablet 8 hourly	1 tablet 8 hourly
Clavumed 625	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to penicillins, and cephalosporins other beta-lactam medicines (e.g carbapenem or monobactam) or to any of the excipients (see section 6.1). Cross-sensitivity between penicillins and cephalosporins is well documented.
- Clavumed is contra-indicated in patients with a previous history of amoxicillin/clavulanic acid associated jaundice/hepatic dysfunction.

4.4 Special warnings and precautions for use

Hypersensitivity reactions:

- Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8*).* Before initiating therapy with CLAVUMED, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, other beta-lactam medicines 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 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.
- CLAVUMED 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.

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 hpurs 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.

Non-susceptible microorganisms:

- Since CLAVUMED 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.
- The use of CLAVUMED 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.
- CLAVUMED 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. CLAVUMED should not be used to treat penicillin-resistant *S pneumoniae.*

Overgrowth of non-susceptible microorganisms

- Prolonged use may result in overgrowth of non-susceptible organisms.
- *Pseudomembranous enterocolitis* has been reported.
- Antibiotic-associated colitis has been reported. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of CLAVUMED. Should antibiotic-associated colitis occur, CLAVUMED should immediately be discontinued and a doctor should be consulted.
- Anti-peristaltic medicines are contraindicated in this situation.

Prolonged therapy:

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

- 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.

Anticoagulants:

- Prolongation of prothrombin time has been reported rarely in patients receiving CLAVUMED. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently (see section 4.5)

Impaired hepatic function

- Changes in liver function tests have been observed in some patients receiving CLAVUMED. It should be used with care in patients with evidence of severe hepatic dysfunction.
- CLAVUMED should be used with caution in patients with evidence of hepatic dysfunction (see section 4.3)
- Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. The hepatic events are usually reversible. However, in extremely rare circumstances, death has been reported. These have almost always been cases associated with serious underlying disease or concomitant medication (see section 4.8)**.**
- Transient hepatitis and cholestatic jaundice has been reported.

Impaired renal function

- In patients with moderate or severe renal impairment the CLAVUMED dosage should be adjusted (see section 4.2)
- CLAVUMED should not be used in patients with a glomerular filtration rate of less than 30 ml/minute (See section 4.2)

Convulsions:

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

Crystalluria:

- In patients with reduced urine output, crystalluria (including acute rental injury) has been observed very rarely, predominantly with parenteral therapy. When high doses are administered, adequate fluid intake and urinary output must be maintained in order to reduce the possibility of amoxicillin crystalluria (see section 4.8 and 4.9)

Jarisch-Herxheimer reaction:

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

Lymphatic leukaemia

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

Use in lactation

- Amoxicillin is excreted in breast milk; there are no data on the excretion of clavulanic acid in human milk. Therefore, caution should be exercised when CLAVUMED is administered to a woman that is breastfeeding her baby. (see section 4.6)
- The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of actute generalised exanthemous pustulosis (AGEP) (see section 4.8). This reaction requires CLAVUMED discontinuation and contraindicates any subsequent administration amoxicillin.

Interferance with laboratory tests

- During treatment with CLAVUMED 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 (see section 4.5)

Interference with serological testing

- CLAVUMED may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

Sodium content

CLAVUMED contains less than 1 mmol sodium (23 mg) per tablet, essentially sodium free. When high doses are administered, adequate fluid intake and urinary output must be maintained. The sodium content must be taken into account in patients on a sodium-restricted diet if the administration of high doses is necessary.

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 CLAVUMED may result in increased and prolonged blood levels of amoxicillin, but not of clavulanic acid.

Oral contraceptives:

- CLAVUMED may reduce the efficacy of oral contraceptives and patients should be warned accordingly.

Allopurinol:

- The concomtant administration of allopurinol and ampicillin substantially increases the incidence of skin rashes in patients receiving both agents as compared to patients receiving ampicillin alone (see section 4.4).
- 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 CLAVUMED and allopurinol administered concurrently.

Tetracyclines:

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

Interaction with laboratory tests

- It is recommended that when testing for the presence of glucose in urine during CLAVUMED treatment, enzymatic glucose oxidase methods should be used. Due to the high urinary concentrations of amoxicillin, false positive readings are common with chemical methods (see section 4.4 ‘Interference with laboratory tests)

Oral anticoagulants:

- The prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of CLAVUMED. Moreover, adjustments in the dose of oral anticoagulants may be necessary (see sections 4.4 and 4.8)

Methotrexate:

- CLAVUMED 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 (MPC) has been reported following commencement of oral CLAVUMED. Close monitoring should be performed during the combination and shortly after antibiotic treatment.

4.6 Fertility, pregnancy and lactation

Woman of childbearing potential

CLAVUMED may reduce the efficacy of oral contraceptives and patients should be warned accordingly (see section 4.5)

Pregnancy

The safety of **Clavumed** in pregnancy has not been established.

Breastfeeding

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

Fertility

No available fertility data

4.7 Effects on ability to drive and use machines

Clavumed may cause allergic reactions, dizziness, and tiredness or convulsions which may influence mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and / or sound coordination and vision (see section 4.4 & 4.8).

Caution is advised for patients not to drive or use machines, until their individual susceptibility to the effects of CLAVUMED is known.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse effects are diarrhoea, nausea, vomiting, indigestion, 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, increased with the higher recommended dose and can be minimized by administering CLAVUMED at the start of a meal. 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 side-effects considered at least possibly related to the treatment are listed below by body system, organ class and frequency (wherever applicable).

The following adverse reactions have been reported and may occur with CLAVUMED:

The following adverse reactions have been reported and may occur with CLAVUMED.

Tabulated list of adverse reactions

Body System	Undesirable effect		
	Frequency	**Less Frequency**	**Frequency not known**
Infections and infestations:	*Mucocutaneous candidiasis*		Overgrowth of non-susceptible organisms
Blood and the lymphatic system disorders[5]	Thrombocytopenic Purpura, Eosinophilia	Reversible leucopenia (including neutropenia) and thrombocytopenia	Haemolytic anaemia Prolongation of bleeding time prothrombin time (see section 4.4) reversible agranulocytosis
Immune system disorders (see section 4.3 & 4.4)			Fatal hypersensitivity (anaphylactic) reactions and angioneurotic oedema, Serum sickness-like syndrome, Hypersensitivity vasculitis, Stevens-Johnson syndrome, Bullous exfoliative dermatitis and toxic epidermal necrolysis (see section 4.4)
Nervous system disorders	Tiredness and hot slushes	Dizziness, Headache,	Reversible Hyperactivity Convulsions (see section 4.4), Aseptic meningitis
Cardiac disorders			Kounis syndrome (see section 4.4)
Gastrointestinal disorders [1]:	Nausea, Vomitting, Diarrhoea, Gastritis, Stomatitis, Glossitis, Enterocolitis	Indigestion, mucocutaneous candidiasis	Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis (see section 4,4),

			Black hairy tongue, Drug-induced enterocolitis syndrome (DIES) (see section 4.4), Pancreatitis acut**e.**
Hepato-biliary Disorders [2]:		Increased aspartate transaminase (AST), alanine transaminase (ALT) [3]	Hepatitis and cholestatic jaundice[7]
Skin and subcutaneous tissue disorders[4]:		Skin rashes, Pruritus and urticaria, serum-sickness-like Erythema multiforme, bullous exfoliative dermatitis, toxic epidermal necrolysis	Acute generalised exanthemous pustulosis (AGEP) (see section 4,4), Drug reaction with eosinophilia and systemic symptoms (DRESS), Linear IgA disease, Stevens-Johnson syndrome, hypersensitivity vasculitis,
Renal and urinary disorders:			Interstitial nephritis, Crystalluria (including acute renal injury) (see section 4.4 and 4.9)
Reproductive system and breast disorders	Vaginitis		

General disorders and administration site conditions		Superficial tooth discolouration[6]	

[1]Nausea is more often associated with higher oral doses. If gastrointestinal reactions are evident, they may be reduced by taking CLAVUMED with a meal.

[2]The events may be severe, and occur predominantly in adult or elderly patients. 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. **The hepatic effects are usually reversible. However, in extremely rare circumstances, death has been reported. These have almost always been cases associated with serious underlying disease or concomitant medication.**

[3]A moderate rise in AST and/or ALT has been noted in patients treated with CLAVUMED.

[4]Whenever such reactions occur, CLAVUMED should be discontinued. Serious and occasional fatal hypersensitivity (anaphylactic) reactions and angionerotic oedema can occur with oral penicillin (see section 4.4).

[5]These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1 % of the patients treated with CLAVUMED. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly.

[6]Superficial tooth discolouration has been reported especially with the suspension and chewable tablet formulations. It can usually be removed by brushing.

[7]These events have been noted with other penicillins and cephalosporins (see section 4.4)

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Applicants may include additional, dedicated contact details for the reporting of side effects directly to the HCR.

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

Symptoms:

- Overdosage with amoxicillin is usually asymptomatic.
- Gastro-intestinal effects such as nausea, vomiting and diarrhoea may be evident and symptoms of water and electrolyte imbalance should be treated symptomatically.
- Adequate fluid intake and urinary output must be maintained to minimize the possibility of crystalluria.

Treatment:

- 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

Pharmacotherapeutic group: Combinations of penicillins, incl. beta-lactamase Inhibitors;

ATC code: J01CR02.

Mechanism of action:

CLAVUMED is a combination of amoxicillin and clavulanic acid.

Amoxicillin is a semi-synthetic semisynthetic beta-lactamase-susceptible penicillin which has *in vitro* bactericidal activity against a broad spectrum of non beta-lactamase-producing Gram-positive and Gram-negative organisms. The spectrum of activity does not include those organisms which produce beta-lactamases, namely resistant staphylococci and all strains of *Pseudomonas, Klebsiella* and *Enterobacter*.

Clavulanic acid 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 inluenzae, Neisseria gonorrhoae* and *Bacteroides fragilis*. Clavulanic acid does not inactivate the chromosomally mediated (Sykes Type 1 Cephalosporinase) beta-lactamases produced by *Acinetobacte*r species, *Citrobacter* species, *Enterobacter*, indole positive *Proteus*, *Providencia* species and *Serratia marcescens*. *In vitro* the formulation showed synergism against amoxicillin-resistant organisms, 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). The clavulanic acid component has very little bactericidal action.

5.2 Pharmacokinetic properties

Amoxicillin:

Absorption

Amoxicillin is stable in the presence of acidic gastric secretions. Peak blood levels are achieved 1-2 hours after administration. There is a linear dose response in peak serum levels.

The pharmacokinetics of amoxicillin and clavulanic acid are closely allied and neither is adversely affected by the presence of food in the stomach.

Distribution

Approximately 18 % of the total amoxicillin content is protein bound. Amoxicillin diffuse readily into most body tissues with the exception of the brain and spinal fluid. Inflammation generally increases the permeability of the meninges to penicillin and this may apply to amoxicillin.

Excretion

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.

6 PHARMAECEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

CLAVUMED tablets also contain the following excipients:

Colloidal Anhydrous Silica

Croscarmellose Sodium

Hydroxypropyl methylcellulose

Microcrystalline cellulose

Magnesium stearate

Talc

Tablet film-coating consisting of:

Hypromellose

Macrogol 400

Isopropyl alcohol

Purified water

Talc

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C, protected from light and moisture.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Clavumed 375

Aluminium strip pack containing 15 and 100 tablets in a carton.

Clavumed 625

Aluminium strip pack containing 15 tablets in a carton.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF THE 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)

Clavumed 375: 33/20.1.2/0461

Clavumed 625: 33/20.1.2/0462

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 6 April 2022 – CLAVUMED 375

Date of registration: 6 April 2022-CLAVUMED 625 mg

10. DATE OF REVISION OF THE TEXT

28 November 2024