SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

CLAMENTIN 1000 mg (film-coated tablet)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CLAMENTIN 1000 mg tablets contain amoxicillin trihydrate equivalent to amoxicillin 875 mg and potassium clavulanate equivalent to clavulanic acid 125 mg.

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White to light yellow, oblong, biconvex tablet, scored on both sides. Approximately 10 x 22 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CLAMENTIN 1000 mg formulation 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.

CLAMENTIN 1000 mg 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

CLAMENTIN 1000 mg should be taken immediately before a meal.

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 is one CLAMENTIN 1000 mg tablet every 12 hours at the start of a meal.

Special populations

Renal impairment:

- Both amoxicillin and clavulanic acid are excreted by the kidneys and the serum half-life of each increase 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.
- CLAMENTIN 1000 mg should not be used in patients with creatinine clearance 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 & Soft Tissue Infections
CLAMENTIN 1000 mg	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)	Lower Respiratory Tract Infections (Bronchitis)	Urinary Tract Infections	Skin & Soft Tissue Infections
CLAMENTIN 1000 mg	1 Tablet 12 hourly	1 Tablet 12 hourly	1 Tablet 12 hourly	1 Tablet 12 hourly

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to the amoxicillin or clavulanic acid, to any of the other beta-lactam medicines (e.g. penicillins, cephalosporins, carbapenem or monobactam) or to any of the excipients listed in section 6.1. Cross-sensitivity between penicillins and cephalosporins is well documented.
- CLAMENTIN 1000 mg is contraindicated in patients with a previous history of jaundice/hepatic dysfunction due to amoxicillin/clavulanic acid.

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 CLAMENTIN 1000 mg, 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, CLAMENTIN 1000 mg 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.
- CLAMENTIN 1000 mg 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 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.

- 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 CLAMENTIN 1000 mg discontinuation and contraindicates any subsequent administration of amoxicillin.

Non-susceptible microorganisms:

- CLAMENTIN 1000 mg is not suitable for use when there is a high risk that the presumptive pathogens have reduced susceptibility or resistance to beta-lactam medicines that is not mediated by beta-lactamases susceptible to inhibition by clavulanic acid. CLAMENTIN 1000 mg should not be used to treat penicillin-resistant *S. pneumoniae.*
- Skin Rash in Patients with Mononucleosis: Since CLAMENTIN 1000 mg 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 (morbilliform rash) if amoxicillin is used. CLAMENTIN 1000 mg should be avoided if infectious mononucleosis is suspected.
- Prescribing CLAMENTIN 1000 mg in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of medicine-resistant bacteria. Sensitivity testing should, therefore, be carried out whenever possible, to demonstrate the appropriateness of therapy.

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 CLAMENTIN 1000 mg. Should antibiotic-associated colitis occur,

CLAMENTIN 1000 mg should immediately be discontinued and a doctor should be consulted. Anti-peristaltic medicines are contraindicated in this situation.

Prolonged therapy:

- Periodic assessment of organ function, 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*), CLAMENTIN 1000 mg should be discontinued and/or appropriate therapy instituted.

Anticoagulants:

- Prolongation of prothrombin time has been reported rarely in patients receiving CLAMENTIN 1000 mg. 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 CLAMENTIN 1000 mg.
- CLAMENTIN 1000 mg 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 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 (*see section 4.8*).
- Transient hepatitis and cholestatic jaundice have been reported.

Impaired renal function:

- In patients with moderate or severe renal impairment CLAMENTIN 1000 mg dosage should be adjusted (*see section 4.2*).

- CLAMENTIN 1000 mg should not be used in patients with creatinine clearance less than 30 ml/minute.

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 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 CLAMENTIN 1000 mg to patients with syphilis, as the Jarisch-Herxheimer reaction may occur in these patients.

Lymphatic leukaemia:

- CLAMENTIN 1000 mg should be given with caution to patients with lymphatic leukemia since they are especially susceptible to amoxicillin induced skin rashes.

Use in lactation:

- 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 CLAMENTIN 1000 mg is administered to a woman that is breastfeeding her baby.

Interference with laboratory tests:

- During treatment with CLAMENTIN 1000 mg, 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:

- CLAMENTIN 1000 mg 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 CLAMENTIN 1000 mg may result in increased and prolonged blood levels of amoxicillin (but not of clavulanic acid), co-administration with probenecid is therefore not recommended.

Oral contraceptives:

- CLAMENTIN 1000 mg may affect intestinal flora, leading to lower oestrogen reabsorption and reduced efficacy of oral contraceptives. Patients should be warned accordingly.

Allopurinol:

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

Tetracyclines:

- Tetracyclines and other bacteriostatic medicines may interfere with the bactericidal effects of CLAMENTIN 1000 mg.

Interaction with laboratory tests:

- High urine concentrations of amoxicillin may result in false-positive reactions when testing for the presence of glucose in urine using non-enzymatic methods. Since this effect may also occur with CLAMENTIN 1000 mg, it is recommended that glucose tests based on enzymatic glucose oxidase reactions be used (*see section 4.4*

'Interference with laboratory tests').

- Following administration of amoxicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone, and estradiol has been noted.

Oral anticoagulants:

- Abnormal prolongation of prothrombin time (increased international normalised ratio (INR)) has been reported in patients receiving amoxicillin and oral anticoagulants. The prothrombin time or internationally normalised ratio should be carefully monitored with the addition or withdrawal of CLAMENTIN 1000 mg. Moreover, adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (*see sections 4.4 and 4.8*).

Methotrexate:

- CLAMENTIN 1000 mg 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) has been reported following commencement of oral CLAMENTIN 1000 mg. Close monitoring should be performed during the combination and shortly after antibiotic treatment.

4.6 Fertility, pregnancy and lactation

Woman of childbearing potential

CLAMENTIN 1000 mg may reduce the efficacy of oral contraceptives and patients should be warned accordingly (*see section 4.5*).

Pregnancy

The safety of CLAMENTIN 1000 mg in pregnancy has not been established.

Breastfeeding

Amoxicillin as contained in CLAMENTIN 1000 mg is distributed into breast milk. Although significant problems in humans have not been documented, the use of CLAMENTIN 1000 mg by breastfeeding mothers may lead to sensitisation, diarrhoea, *Candidiasis* and skin rash in the infant. Therefore, caution should be exercised when CLAMENTIN 1000 mg is administered to a woman that is breastfeeding her baby.

4.7 Effects on ability to drive and use machines

CLAMENTIN 1000 mg may cause allergic reactions, dizziness 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*).

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 minimised by administering CLAMENTIN 1000 mg 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.

Tabulated list of adverse reactions

System Organ Class	CLAMENTIN 1000 mg Side Effects
Infections and Infestations	
Frequent:	Mucocutaneous candidiasis, vaginal mycosis
Frequency unknown:	Overgrowth of non-susceptible organisms
Blood and lymphatic system disorders[5]	
Frequent:	Thrombocytopenic purpura, eosinophilia
Less frequent:	Reversible leucopenia (including neutropenia), thrombocytopenia, thrombocytosis, prolongation of bleeding time and prothrombin time *(see section 4.4)*
Frequency unknown:	Reversible agranulocytosis, haemolytic anaemia
Immune system disorders *(see sections 4.3 & 4.4)*	
Frequency unknown:	Fatal hypersensitivity (anaphylactic) reactions, angioneurotic oedema, serum sickness-like syndrome (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia, and frequently fever), hypersensitivity vasculitis, anaphylaxis

Psychiatric disorders	
Less frequent:	Agitation, anxiety, behavioural changes, confusion, insomnia
Nervous system disorders	
Less frequent:	Dizziness, headache, reversible hyperactivity, convulsions[6] *(see section 4.4)*
Frequency unknown:	Aseptic meningitis
Cardiac disorders	
Frequency unknown:	Kounis syndrome *(see section 4.4)*
Gastrointestinal disorders[1]	
Frequent:	Diarrhoea, nausea, vomiting, gastritis, stomatitis, glossitis, enterocolitis, indigestion
Frequency unknown:	Antibiotic-associated colitis (including pseudomembranous colitis, haemorrhagic colitis) *(see section 4.4)*, black hairy tongue, drug-induced enterocolitis syndrome (DIES) *(see section 4.4)*, pancreatitis acute
Hepato-biliary disorders[2]	
Less frequent:	Increased aspartate transaminase (AST) and/or alanine transaminase (ALT)[3]
Frequency unknown:	Hepatitis, cholestatic jaundice[9]

Skin and subcutaneous tissue disorders[4]	
Less frequent:	Skin rash, pruritus, urticaria, erythema multiforme, acute generalised exanthemous pustulosis (AGEP) *(see section 4.4)*, bullous exfoliative dermatitis, toxic epidermal necrolysis (TEN)
Frequency unknown:	Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), linear IgA disease, symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome)
Renal and urinary disorders	
Less frequent:	Interstitial nephritis
Frequency unknown:	Haematuria, crystalluria (including acute renal injury) *(see section 4.9)*[8]
General disorders and administrative site conditions	
Frequency unknown:	Superficial tooth discolouration[7]

[1] Nausea is more often associated with higher oral doses. If gastrointestinal reactions are evident, they may be reduced by taking CLAMENTIN 1000 mg 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 medicines.

[3] A moderate rise in AST and/or ALT has been noted in patients treated with beta-lactam class antibiotics.

[4] Whenever such reactions occur, CLAMENTIN 1000 mg should be discontinued. Serious and occasional fatal hypersensitivity (anaphylactic) reactions and angioneurotic 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 CLAMENTIN 1000 mg. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly.

[6] Convulsions may occur with impaired renal function or in those receiving high doses.

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

[8] *See section 4.9.*

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

4.9 Overdose

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

Overdosage with amoxicillin is usually asymptomatic. However, gastrointestinal symptoms including nausea, vomiting and diarrhoea may be evident, and symptoms of water and electrolyte imbalance should be treated symptomatically. Rash, hyperactivity, or drowsiness have also been observed in a small number of patients.

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

Interstitial nephritis resulting in oliguric renal failure has been reported in a small number of patients after overdosage with amoxicillin.

Amoxicillin crystalluria, in some cases leading to renal failure, has been observed. Adequate fluid intake and diuresis should be maintained to reduce this risk.

Renal impairment appears to be reversible with cessation of medicine administration. High blood levels may occur more readily in patients with impaired renal function because of decreased renal clearance of both amoxicillin and clavulanate.

In the case of overdosage, discontinue CLAMENTIN 1000 mg and treat symptomatically, instituting supportive measures as required. If the overdosage is very recent and there is no contraindication, an attempt at emesis or other means of removal of the medicine from the stomach may be performed. Both amoxicillin and clavulanic acid can be removed from the circulation by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.1.2 Penicillins

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

Mechanism of action:

CLAMENTIN 1000 mg is a combination of amoxicillin and clavulanic acid. Amoxicillin binds to penicillin-binding proteins within the bacterial cell wall and inhibits bacterial cell wall synthesis. Amoxicillin exerts a bactericidal action against many strains of Gram-positive and Gram-negative organisms. Clavulanic acid is a beta-lactam structurally related to penicillin, with very little bactericidal action. It does however, by inactivation of susceptible beta-lactamases, protect amoxicillin from beta-lactamase enzyme degradation produced by penicillin-resistant strains of organisms.

Mechanism of Resistance:

Resistance to penicillins may be mediated by destruction of the beta-lactam ring by a beta-lactamase, altered affinity of penicillin for target, or decreased penetration of the antibiotic to reach the target site. Amoxicillin alone is susceptible to degradation by beta-lactamases, and therefore its spectrum of activity does not include bacteria that produce these enzymes. Amoxicillin/clavulanic acid has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections (*in vitro* activity does not necessarily imply *in vivo* efficacy):

Gram-positive bacteria:

Staphylococcus aureus

Streptococcus pneumoniae

Gram-negative bacteria:

Haemophilus influenzae

Haemophilus para-influenzae

Klebsiella pneumoniae

Moraxella catarrhalis

5.2 Pharmacokinetic properties

Absorption:

Amoxicillin and clavulanic acid are well absorbed from the gastrointestinal tract after oral administration. 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:

Neither amoxicillin nor clavulanic acid is highly protein bound; amoxicillin has been found to be approximately 18 % bound to human serum and clavulanic acid approximately 25 % bound.

Amoxicillin diffuses readily into most body tissues and fluids, with the exception of the brain and spinal fluid. Inflammation generally increases the permeability of the meninges to penicillins and this may apply to amoxicillin. Animal experiments indicate that clavulanic acid is well distributed in body tissues.

Elimination:

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.

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 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Croscarmellose cellulose, magnesium stearate, microcrystalline cellulose, povidone, silicon dioxide colloidal, talc.

Tablet film-coat consisting of:

Ethyl cellulose aqueous dispersion, hypromellose, talc, titanium dioxide, triethyl citrate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25°C.

Store in a cool place.

Protect from light and moisture.

6.5 Nature and contents of container

Tablets are packed in aluminium foil, soft, 30 µm, with PE coating, printed for sealing package.

10, 15, 16, 21, 30, 50, 90, 100 or 500 tablets will be packed in a cardboard box.

6.6 Special precautions for disposal and other handling of the product

No special requirements for disposal.

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

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 November 2007

10 DATE OF REVISION OF TEXT

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