1.3.1.1 Professional Information for medicines for human use

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

CLAMENTIN S (125/31,25 mg, powder for suspension)

CLAMENTIN SF (250/62,5 mg, powder for suspension)

2 QUALITIVE AND QUANTITIVE COMPOSITION

CLAMENTIN S: Powder for suspension. When reconstituted according to instructions each 5 ml contains amoxicillin trihydrate equivalent to 125 mg amoxicillin and potassium clavulanate equivalent to 31,25 mg clavulanic acid.

CLAMENTIN SF: Powder for suspension forte. When reconstituted according to instructions each 5 ml contains amoxicillin trihydrate equivalent to 250 mg amoxicillin and potassium clavulanate equivalent to 62,5 mg clavulanic acid.

Contains sweetener: Every ml of oral suspension contains 2,5 mg aspartame (E951).

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

CLAMENTIN S:

White powder for reconstitution to an off-white suspension.

CLAMENTIN SF:

White powder for reconstitution to an off-white suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CLAMENTIN formulations are indicated for the treatment of infections caused by amoxicillin resistant organisms producing β -lactamases sensitive to clavulanic acid:

- Upper respiratory tract, such as sinusitis, otitis media or tonsillitis.
- Lower respiratory tract, such as bronchitis (caused by amoxicillin resistant β-lactamase producing *Escherichia coli, Haemophilus influenzae* and *Haemophilus para-influenzae)* or pneumonia.
- Urinary tract infections, such as cystitis, urethritis or pyelonephritis.
- Skin and soft tissues.

CLAMENTIN formulations will also be effective in the treatment of infections caused by amoxicillin sensitive organisms at the appropriate amoxicillin dosage since in this situation the clavulanic acid component does not contribute to the therapeutic effect.

4.2 Posology and method of administration

Posology

Suspensions should be taken immediately before a meal.

General Information:

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

Paediatric population:

- The dose of CLAMENTIN in children is 25-50 mg/kg/day of the 4 parts amoxicillin,

1-part clavulanic acid preparations (which corresponds to a daily dosage of the equivalent of 20-40 mg/kg of amoxicillin and 5-10 mg/kg of clavulanic acid) to be taken in divided doses every eight hours, at the start of a meal.

Dosage guide:

Amoxicillin-Sensitive Organisms

Product	**Upper Respiratory Tract Infections**	**Lower Respiratory Tract Infections**	**Urinary Tract Infections**	**Skin & Soft Tissue Infections**
CHILDREN:				
CLAMENTIN S (9-18 kg)	5-10 ml [1] 8 hourly	5-10 ml [1] 8 hourly	5-10 ml [1] 8 hourly	5-10 ml [1] 8 hourly
CLAMENTIN SF (18-37 kg)	5 ml [1] 8 hourly	5 ml [1] 8 hourly	5 ml [1] 8 hourly	5 ml [1] 8 hourly

Amoxicillin-Resistant Organisms

Product	Upper Respiratory Tract Infections (Otitis media) *H. Influenza* *H. para influenza*	Lower Respiratory Tract Infections (Bronchitis) *H. Influenza* *H. para influenza*	Urinary Tract Infections *Klebsiella pneumoniae*	Skin & Soft Tissue Infections *Staphylococcus aueus*
CHILDREN:				
CLAMENTIN S (9-18 kg)	5-10 ml [2] 8 hourly	5-10 ml [2] 8 hourly	5-10 ml [2] 8 hourly	5-10 ml [2] 8 hourly
CLAMENTIN SF (18-37 kg)	5 -10 ml [2] 8 hourly	5 -10 ml [2] 8 hourly	5 -10 ml [2] 8 hourly	5 -10 ml [2] 8 hourly

1) To correspond to a dosage of 25-50 mg/kg/day

2) To correspond to a dosage of 50 mg/kg/day

Method of administration

- For oral use.

4.3 Contraindications

- Hypersensitivity to the active substances, penicillins and cephalosporins or to any of the excipients listed in section 6.1.

- History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam medicines (e.g. a cephalosporin, carbapenem or monobactam).
- Safety in pregnancy has not been established.
- Safety in children under 6 months of age has not been established.
- CLAMENTIN is contraindicated in patients with a previous history of CLAMENTIN-associated jaundice/hepatic dysfunction.

4.4 Special warnings and precautions for use

Hypersensitivity reactions:

- Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction *(see section 4.8)*. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity, who have experienced severe reactions when treated with cephalosporins. Before initiating therapy with any penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens.

  If an allergic reaction occurs, CLAMENTIN should be discontinued and the appropriate therapy instituted: adrenaline, corticosteroids and antihistamines.
- Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin/clavulanate *(see section 4.8)*. DIES is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after intake of amoxicillin/clavulanate) in the absence of allergic skin or respiratory symptoms.

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

Non-susceptible microorganisms:

- CLAMENTIN 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 are not mediated by beta-lactamases susceptible to inhibition by clavulanic acid. CLAMENTIN should not be used to treat penicillin-resistant *S. pneumoniae.*
- Since CLAMENTIN 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.
- The use of this antibiotic CLAMENTIN 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.

Overgrowth of non-susceptible microorganisms:

- Prolonged use may occasionally result in overgrowth of non-susceptible organisms.
- Antibiotic-associated colitis has been reported with nearly all antibacterial medicines including CLAMENTIN and may range in severity from mild to life threatening (*see section 4.8*). Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of CLAMENTIN. Should antibiotic-associated colitis occur, CLAMENTIN 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 function, 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 should be discontinued and/or appropriate therapy instituted.

Anticoagulants:

- Prolongation of prothrombin time has been reported. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (*see sections 4.5 and 4.8*).

Impaired hepatic function:

- Changes in liver function tests have been observed in some patients receiving CLAMENTIN. It should be used with care in patients with evidence of severe hepatic dysfunction.
- Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. 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 medicines known to have the potential for hepatic effects (*see section 4.8*).

Transient hepatitis and cholestatic jaundice have been reported.

Impaired renal function:

- In patients with moderate or severe renal impairment, the CLAMENTIN dosage should be adjusted.

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. During the administration of high doses of CLAMENTIN, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria.

Lymphatic leukaemia:

- CLAMENTIN 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 exercise when CLAMENTIN is administered to a woman that is breastfeeding her baby.
- 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 discontinuation and contraindicates any subsequent administration of amoxicillin.

Interference with laboratory tests:

- During treatment with CLAMENTIN, 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 may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

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CLAMENTIN contains aspartame:

- CLAMENTIN contains 2.5 mg of aspartame (E951) per ml. Aspartame is a source of phenylalanine and is hydrolysed in the gastrointestinal tract when orally ingested. It may be harmful if the patient has phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

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

Allopurinol:

- The concurrent administration of allopurinol and ampicillin C increases substantially the incidence of rashes in patients receiving both medicines as compared to patients receiving ampicillin alone.
- It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricaemia present in these patients.
- There is no data on CLAMENTIN and allopurinol administered concurrently.

Alcohol:

- No information is available about the concurrent use of CLAMENTIN and alcohol.
- However, the ingestion of alcohol whilst being treated with some other β -lactam antibiotics has precipitated a disulfiram (Antabuse) like reaction in some patients. Therefore, the ingestion of alcohol should be avoided during and for several days after treatment with CLAMENTIN.

Oral contraceptives:

- Following administration of ampicillin to pregnant woman a transient decrease in plasma concentration of total conjugate oestriol, oestriol-glucuronide, conjugated oestrone and oestradiol has been noted. This effect may also occur with amoxicillin and therefore CLAMENTIN.
- In common with other broad-spectrum antibiotics, CLAMENTIN may reduce the efficacy of oral contraceptives and patients should be warned accordingly.

Oral anticoagulants:

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

Methotrexate:

- CLAMENTIN 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. Close monitoring should be performed during the combination and shortly after antibiotic treatment.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

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

Pregnancy

Safety in pregnancy has not been established.

Breastfeeding

Amoxicillin is excreted in breast milk; there are no data on the excretion of clavulanic acid in human milk. Therefore, caution should be exercise when CLAMENTIN is administered to a woman that is breastfeeding her baby.

4.7 Effects on ability to drive and use machines

CLAMENTIN may cause allergic reactions, dizziness or convulsions and may thus have an effect on 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 were diarrhoea, nausea, vomiting, abdominal pain, skin rashes, urticaria and erythema multiforme, vaginitis, abnormal taste, headache, dizziness, tiredness and hot flushes.

The incidence and severity of adverse effects, particularly nausea and diarrhoea, increased with the higher recommended dose and can be minimised by administering CLAMENTIN 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.

Tabulated list of adverse reactions

Body System	**Undesirable effect**		
	Frequent	**Less frequent**	**Frequency not known**
Infections and Infestations:	*Mucocutaneous candidosis*		Overgrowth of non-susceptible organisms
Blood and the lymphatic system disorders [3]:	Thrombocytopenic purpura, Eosinophilia	Reversible leucopenia (including neutropenia), Thrombocytopenia	Reversible agranulocytosis, Haemolytic anaemia, Prolongation of bleeding time and prothrombin time *(see section 4.4)*
Immune system disorders (*see section 4.3 & 4.4*):			Angioneurotic oedema, Serum sickness-like syndrome, Hypersensitivity vasculitis

Nervous system disorders:		Dizziness, Headache	Reversible hyperactivity, Convulsions *(see section 4.4),* Aseptic meningitis
Cardiac disorders:			Kounis syndrome *(see section 4.4)*
Gastrointestinal disorders [1]:	Diarrhoea, Nausea[6], Vomiting, Gastritis Stomatitis, Glossitis, Enterocolitis	Indigestion	Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) (*see section 4..4)*, Black hairy tongue, Tooth discolouration[8], Drug-induced enterocolitis syndrome, Pancreatitis acute
Hepato-biliary disorders [4]		Rises in AST and/or ALT [5]	Hepatitis and cholestatic jaundice[7]
Skin and subcutaneous tissue disorders [2]		Skin rash, Pruritis, Urticaria,	Stevens-Johnson syndrome,

		Erythema multiforme	Toxic epidermal necrolysis, Bullous exfoliative dermatitis, Acute generalised exanthemous pustulosis (AGEP) (*see section 4.4*), Drug reaction with eosinophilia and systemic symptoms (DRESS), Linear IgA disease
Renal and urinary disorders:			Interstitial nephritis, Crystalluria (including acute renal injury) (*see section 4.9*)

[1] If gastro-intestinal reactions are evident, they may be reduced by taking CLAMENTIN at the start of a meal.

[2] Whenever such reactions occur, CLAMENTIN should be discontinued. Serious and occasional fatal hypersensitivity (anaphylactic) reactions and angioneurotic oedema can occur with oral penicillin (*see section 4.4*).

[3] 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.

[4] 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.

[5] A moderate rise in Aspartate transaminase and/or Alanine transaminase has been noted in patients treated with CLAMENTIN, the significance of these findings is unknown.

[6] Nausea is more often associated with higher oral doses. If gastrointestinal reactions are evident, they may be reduced by taking amoxicillin/clavulanic acid with a meal.

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

[8] Superficial tooth discolouration has been reported very rarely in children. Good oral hygiene may help to prevent tooth discolouration as it can usually be removed by brushing.

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 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

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

Symptoms:

- Nausea, vomiting and diarrhoea may occur with overdosing.
- Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Treatment:

- Treatment is symptomatic and supportive.

1.3.1.1 Professional Information for medicines for human use

- Amoxicillin as contained in CLAMENTIN may be removed from 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

A.20.1.2 Penicillins

5.1 Pharmacodynamic properties

PHARMACOLOGICAL CLASSIFICATION:

Pharmacotherapeutic group and ATC code:

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

Mechanism of action:

a) Bacteriology

(i) Spectrum:

CLAMENTIN is the group name for formulations containing 2, 4 and 5 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 11-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 1 *Cephalosporinase*) β-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 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).

(ii) Bactericidal action:

The amoxicillin component of the formulations 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 β-lactamases, protect amoxicillin from degradation by a large number of β-lactamase enzymes produced by penicillin resistant strains of organisms.

b) Absorption

The pharmacokinetics of amoxicillin and clavulanic acid are closely allied and neither are adversely affected by the presence of food in the stomach. Doubling the dose virtually doubles the peak serum levels.

c) Excretion

Co-administration of probenecid has little effect on the excretion of the clavulanic acid component of the formulation.

d) Stability

The 4 parts amoxicillin and 1-part clavulanic acid CLAMENTIN S and SF powder for suspension and suspension forte are stable at room temperature (25 °C) for two years. When reconstituted the suspensions are stable for 7 days if kept in a refrigerator (5 °C) and should be used within 7 days.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aspartame, Hydroxypropyl methylcellulose, dried (Hypromellose), Silicon Dioxide (anhydrous), Silica Colloidal Anhydrous, Xanthan Gum, Succinic Acid, Golden Syrup Dry Flavour, Raspberry Dry Flavour, Orange Dry Flavour 1, Orange Dry Flavour 2

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Dry powder: 24 months

Reconstituted suspension: 7 days

Once reconstituted store CLAMENTIN S and CLAMENTIN SF in a refrigerator at 2 °C – 8 °C and use within 7 days.

6.4 Special precautions for storage

Store CLAMENTIN dry powder at or below 30 °C.

Store CLAMENTIN dry powder in a cool, dry place.

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

6.5 Nature and contents of container

CLAMENTIN S:

Amber or clear bottles containing white powder for reconstitution to CLAMENTIN suspension.

CLAMENTIN SF:

Amber or clear bottles containing white powder for reconstitution to CLAMENTIN suspension forte.

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 medicines or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

Viatris South Africa (Pty) Ltd

4 Brewery Street

Isando, 1609

Gauteng

Republic of South Africa

8 REGISTRATION NUMBER(S)

CLAMENTIN S (suspension):

29/20.1.2/0540

CLAMENTIN SF (suspension forte):

29/20.1.2/0541

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 November 1995

10 DATE OF REVISION OF TEXT

19 February 2024