National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

1. NAME OF THE MEDICINALPRODUCT

SUGAM 375MG ((AMOXICILLIN AND CLAVULANATE POTASSIUM TABLETS USP)

2. QUALITATIVE AND QUANTITATIVECOMPOSITION

Each film coated tablet contains: Amoxicillin Trihydrate USP
Equivalent to Amoxicillin 250 mg Clavulanate Potassium USP
Equivalent to Clavulanic Acid 125 mg
Excipients q.s

3. PHARMACEUTICALFORM

Film coated tablet for oral administration

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Amoxicillin & Clavulanate Potassium tablets USP are indicated for the treatment of the following infections in adults and children :

- Acute bacterial sinusitis (adequately diagnosed)
- Acute otitis media
- Acute exacerbations of chronic bronchitis (adequately diagnosed)
- Community acquired pneumonia
- Cystitis
- Pyelonephritis
- Skin and soft tissue infections in particular cellulites, animal bites, severe dental abscess with spreading cellulites.
- Bone and joint infections, in particular osteomyelitis.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Doses are expressed throughout in terms of amoxicillin/Clavulanic acid content except when doses are stated in terms of an individual component. The dose of Amoxicillin & Clavulanate Potassium that is selected to treat an individual infection should take into account:

• The expected pathogens and their likely susceptibility to antibacterial agents

• The severity and the site of the infection

• The age, weight and renal function of the patient as shown below. The use of alternative presentations of Amoxicillin & Clavulanate Potassium (e.g. those that provide higher doses of amoxicillin and/or different ratios of amoxicillin to clavulanic acid) should be considered as necessary. For adults and children ≥ 40 kg, this formulation of Amoxicillin & Clavulanate Potassium tablets USP provides a total daily dose of 1500 mg amoxicillin/375 mg clavulanic acid, when administered as recommended below. For children < 40 kg, this formulation of Amoxicillin & Clavulanate Potassium tablets USP provides a maximum daily dose of 2400 mg

SUGAM 375 MG

(AMOXICILLIN AND CLAVULANATE POTASSIUM TABLETS USP) 24 amoxicillin/600 mg clavulanic acid, when administered as recommended below. If it is considered that a higher daily dose of amoxicillin is required, it is recommended that another preparation of Amoxicillin & Clavulanate Potassium tablets USP is selected in order to avoid administration of unnecessarily high daily doses of clavulanic acid. The duration of therapy should be determined by the response of the patient. Some infections (e.g. osteomyelitis) require longer periods of treatment. Treatment should not be extended beyond 14 days without review. Adults and children ≥ 40 kg One 250 mg/125 mg dose taken three times a day. Children < 40 kg 20 mg/5 mg/kg/day to 60 mg/15 mg/kg/day given in three divided doses. Children may be treated with Amoxicillin & Clavulanate Potassium tablets, suspensions or paediatric sachets. As the tablets cannot be divided, children weighing less than 25 kg must not be treated with Amoxicillin & Clavulanate Potassium tablets. The table below presents the received dose (mg/kg body weight) in children weighing 25 kg to 40 kg upon administering a single 250/125 mg tablet.

Body weight [kg]	40	35	30	25	Single dose recommended [mg/kg body weight] (see above
Amoxicillin [mg/kg body weight] per single dose (1 filmcoated tablet)	12.5	14.3	16.7	20.0	6.67 – 20
Clavulanic acid [mg/kg body weight] per single dose (1 filmcoated tablet)	3.1	3.6	4.2	5.0	1.67 - 5

Children aged 6 years and below or weighing less than 25 kg should preferably be treated with Amoxicillin & Clavulanate Potassium suspension or paediatric sachets. No clinical data are available on doses of Amoxicillin & Clavulanate Potassium 4:1 formulations higher than 40 mg/10 mg/kg per day in children under 2 years. Elderly No dose adjustment is considered necessary. Renal impairment Dose adjustments are based on the maximum recommended level of amoxicillin. No adjustment in dose is required in patients with creatinine clearance (CrCl) greater than 30 ml/min. Adults and children ≥ 40 kg

CrCl: 10-30 ml/min	15 mg/3.75 mg/kg twice daily (maximum 500 mg/125 mg twice daily).
CrCl < 10 ml /min	15 mg/3.75 mg/kg as a single daily dose (maximum 500 mg/125 mg).
Haemodialysis	15 mg/3.75 mg/kg per day once daily. Prior to haemodialysis 15 mg/3.75 mg/kg. In order to restore circulating drug levels, 15 mg/3.75 mg per kg should be administered after haemodialysis.

Hepatic impairment
Dose with caution and monitor hepatic function at regular intervals.
Method of administration
Amoxicillin & Clavulanate Potassium tablets USP is for oral use. Administer at the start of a meal to minimise potential gastrointestinal intolerance and optimize absorption of amoxicillin/clavulanic acid. 4.3
Contraindications
Hypersensitivity to the active substances, to any of the penicillin or to any of the excipients. History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another betalactam agent (e.g. a cephalosporin, carbapenem or monobactam). History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid

4.3 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Before initiating therapy with amoxicillin/clavulanic acid, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other betalactam agents . Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. If an allergic reaction occurs, amoxicillin/clavulanic acid therapy must be discontinued and appropriate alternative therapy instituted. In the case that an infection is proven to be due to an amoxicillin-susceptible organisms(s) then consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance. This presentation of Amoxicillin & Clavulanate Potassium tablets 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. This presentation should not be used to treat penicillin-resistant S. pneumonia. Convulsions may occur in patients with impaired renal function or in those receiving high doses. Amoxicillin/clavulanic acid 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. Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. Prolonged use may occasionally result in overgrowth of non-susceptible organisms. The occurrence at the treatment initiation of a feverish

generalised erythema associated with pustula may be a symptom of acute generalized exanthemous pustulosis (AGEP).

This Slight interference with copper reduction methods (Benedict's, Fehling's, Clinitest) may be observed. However, this should not lead to false-positive results, as may be experienced with some other cephalosporins.

As a false negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase methods are used to determine blood/plasma glucose levels in patients receiving cefuroxime sodium.

reaction requires Amoxicillin/clavulanic acid discontinuation and contra-indicates any subsequent administration of amoxicillin. Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment. Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children. 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. Antibiotic-associated colitis has been reported with nearly all antibacterial agents 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, amoxicillin/clavulanic acid should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic medicinal products are contra-indicated in this situation. Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy. Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin/clavulanic acid. 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. In patients with renal impairment, the dose should be adjusted according to the degree of impairment. 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. During treatment with amoxicillin, enzymatic glucose oxidase methods should be used whenever testing for the presence of glucose in urine because false positive results may occur with non-enzymatic methods. The presence of Clavulanic acid in Amoxicillin & Clavulanate Potassium tablets 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.

Interaction with other medicinal products 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.

Methotrexate

Penicillin may reduce the excretion of methotrexate causing a potential increase in toxicity.

Probenecid

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.

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.

4.6. Pregnancy and Lactation

Pregnancy

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. 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, unless considered essential by the physician.

Lactation

Both substances are excreted into breast milk (nothing is known of the effects of clavulanic acid on the breast-fed infant). Consequently, diarrhoea and fungus infection of the mucous membranes are possible in the breast-fed infant, so that breast-feeding might have to be discontinued. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and vomiting.

The ADRs derived from clinical studies and post-marketing surveillance with Amoxicillin/clavulanic acid, sorted by MedDRA System Organ Class are listed below. The following terminologies have been used in order to classify the occurrence of undesirable effects.

Very common (≥1/10)

Common (≥1/100 to<1/10)

Uncommon (≥1/1,000 to <1/100)

Rare (≥1/10,000 to <1/1000)

Very rare (<1/10000)

The frequency categories assigned to the adverse reactions below are estimates, as for most reactions suitable data for calculating incidence are not available. In addition the incidence of adverse reactions associated with cefuroxime sodium may vary according to the indication.

Data from clinical trials were used to determine the frequency of very common to rare adverse reactions. The frequencies assigned to all other adverse reactions (i.e. those occurring at <1/10,000) were mainly determined using post-marketing data, and refer to a reporting rate rather than a true frequency.

Treatment related adverse reactions, all grades, are listed below by MedDRA body system organ class, frequency and grade of severity. The following convention has been utilised for the classification of frequency: very common ≥ 1/10; common ≥ 1/100 to < 1/10, uncommon ≥ 1/1,000 to < 1/100; rare ≥ 1/10,000 to < 1/1,000; very rare < 1/10,000 and not known (cannot be estimated from the available data).

Infections and infestations	
Mucocutaneous candidosis	Common
Overgrowth of non-susceptible organisms	Not known
Blood and lymphatic system disorders	
Reversible leucopenia (including	Rare

neutropenia)	
Thrombocytopenia	Rare
Reversible agranulocytosis	Not known
Haemolytic anaemia	Not known
Prolongation of bleeding time and prothrombin time1	Not known
Immune system disorders	
Angioneurotic oedema	Not known
Anaphylaxis	Not known
Serum sickness-like syndrome	Not known
Hypersensitivity vasculitis	Not known
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Reversible hyperactivity	Not known
Convulsions	Not known
Aeseptic meningitis	Not known

Gastrointestinal disorders	
Diarrhoea	Very common
Nausea	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis	Not known
Black hairy tongue	Not known
Hepatobiliary disorders	
Rises in AST and/or ALT	Uncommon
Hepatitis	Not known
Cholestatic jaundice	Not known
Skin and subcutaneous tissue disorders known	
Skin rash	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon
Erythema multiforme	Rare
Stevens-Johnson syndrome	Not known
Toxic epidermal necrolysis	Not known
Bullous exfoliative-dermatitis	Not known
Acute generalised exanthemous pustulosis (AGEP)	Not known
Renal and urinary disorders	
Interstitial nephritis	Not known
Crystalluria	Not known

4.9 Overdose

Symptoms and signs of overdose

Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed . Convulsions may occur in patients with impaired renal function or in those receiving high doses. Amoxicillin has been reported to precipitate in bladder catheters, predominantly after intravenous administration of large

doses. A regular check of patency should be maintained.

Treatment of intoxication

Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance. Amoxicillin/clavulanic acid can be removed from the circulation by haemodialysis.

5. **PHARMACOLOGICAL PROPERTIES**

5.1 Pharmacodynamic properties

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

Mode of action

Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death. Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes. Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some betalactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

PK/PD relationship

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

Mechanisms of resistance

The two main mechanisms of resistance to amoxicillin/clavulanic acid are:

- Inactivation by those bacterial beta-lactamases that are not themselves inhibited by clavulanic acid, including class B, C and D.
- Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target. Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance, particularly in Gram-negative bacteria.

Breakpoints

MIC breakpoints for amoxicillin/clavulanic acid are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Organism	Susceptibility Breakpoints (μg/ml)		
	Susceptible	Intermediate	Resistant
Haemophilus influenzae1	≤ 1	-	> 1
Moraxella catarrhalis	≤ 1	-	> 1
Staphylococcus aureus	≤ 2	-	> 2
Coagulase negative staphylococci	≤ 0.25	-	> 0.25
Enterococcus	≤ 4	8	> 8
Streptococcus A, B, C, G	≤ 0.25	-	> 0.25
Streptococcus pneumoniae	≤ 0.5 1	1-2	2 > 2
Enterobacteriaceae	-	-	> 8
Gram negative Anaerobes	≤ 4	8	> 8
Gram-positive Anaerobes	≤ 4	8	> 8
Non-species related breakpoints	≤ 2	4-8	4-8

1. The reported values are for Amoxicillin concentrations. For susceptibility testing purposes, the concentration of Clavulanic acid is fixed at 2 mg/l.

2 .The reported values are Oxacillin concentrations.

3. Breakpoint values in the table are based on Ampicillin breakpoints.

4. The resistant breakpoint of R>8 mg/l ensures that all isolates with resistance mechanisms are reported resistant.

5. Breakpoint values in the table are based on Benzylpenicillin breakpoints.

The prevalence of resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections as necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

5.2 Pharmacokinetic properties

Absorption

Amoxicillin and clavulanic acid, are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Absorption of amoxicillin/clavulanic acid is optimised when taken at the start of a meal. 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 (Tmax) in each case is approximately one hour. Amoxicillin and clavulanic acid serum concentrations achieved with amoxicillin/clavulanic acid are similar to those produced by the oral administration of equivalent doses of amoxicillin or clavulanic acid alone.

Distribution

About 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. Following intravenous administration, both amoxicillin and clavulanic acid have been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid. From animal studies there is no evidence for significant tissue retention of drug-derived material for either component. Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanic acid can also be detected in breast milk. Both amoxicillin and clavulanic acid have been shown to cross the placental barrier.

Biotransformation

Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10 to 25% of the initial dose. Clavulanic acid is extensively metabolized in man and eliminated in urine and faeces and as carbon dioxide in expired air.

Elimination

The major route of elimination for amoxicillin is via the kidney, whereas for clavulanic acid it is by both renal and non-renal mechanisms. Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/h in healthy subjects. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of single Amoxicillin & Clavulanate Potassium 250 mg/125 mg or 500 mg/125 mg tablets. Various studies have found the urinary excretion to be 50-85% for amoxicillin and between 27-60% for clavulanic acid over a 24 hour period. In the case of clavulanic acid, the largest amount of drug is excreted during the first 2 hours after administration. Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid .

Age

The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and older children and adults. For very young children (including preterm newborns) in the first week of life the interval of administration should not exceed twice daily administration due to immaturity of the renal pathway of elimination. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Gender

Following oral administration of amoxicillin/clavulanic acid to healthy males and female subjects, gender has no significant impact on the pharmacokinetics of either amoxicillin or clavulanic acid.

Renal impairment

The total serum clearance of amoxicillin/clavulanic acid decreases proportionately with decreasing renal function. The reduction in drug clearance is more pronounced for amoxicillin than for clavulanic acid, as a higher proportion of amoxicillin is excreted via the renal route. Doses in renal impairment must therefore prevent undue accumulation of amoxicillin while maintaining adequate levels of clavulanic acid .

Hepatic impairment

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

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity and toxicity to reproduction. Repeat dose toxicity studies performed in dogs with amoxicillin/Clavulanic acid demonstrate gastric irritancy and vomiting, and discolored tongue. Carcinogenicity studies have not been conducted with Amoxicillin & Clavulanate Potassium tablets USP or its components

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactive ingredients: Colloidal silicon dioxide

Microcrystalline cellulose

Sodium starch glycolate

Magnesium Stearate

Coating excipients : Opadry white

Isopropyl alcohol

Methylene chloride

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precaution for storage

Store below 25C. Protect from light.

Keep out of reach of children.

6.5 Nature and contents of container

ALU-ALU blister pack

6.6 Special precautions for disposal and other handling

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

6. APPLICANT

JAWA INTERNATIONALLTD.

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Isolo, Lagos, Nigeria

E-mail: spjawasil@gmail.com

8. MANUFACTURER

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