**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 228.5 DRY SYRUP (Amoxicillin & Clavulanate Potassium for Oral Suspension USP)

## 2. Qualitative and quantitative composition

Each 5ml (After reconstitution) contains:
Amoxicillin Trihydrate USP
Equivalent to Amoxicillin 200 mg
Clavulanate Potassium USP
Equivalent to Clavulanic Acid 28.5 mg
Excipients q.s
Supply with 60 ml (2×30ml) sterile water for injection BP for reconstitution.

## 3. Pharmaceutical form

Powder for oral suspension

## 4. Clinical particulars

### 4.1 Therapeutic indications

Amoxicillin and clavulanate potassium for oral suspension is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:
**Lower Respiratory Tract Infections**–caused by β-lactamase-producing strains of Haemophilus influenzae and Moraxella (Branhamella) catarrhalis.
**Otitis Media-**caused by β-lactamase-producing strains of Haemophilus influenzae and Moraxella (Branhamella) catarrhalis.
**Sinusitis**– caused by β-lactamase-producing strains of Haemophilus influenzae and Moraxella (Branhamella) catarrhalis.
**Skin and Skin Structure Infections**– caused by β-lactamase-producing strains of Staphylococcus aureus, Escherichia coli and Klebsiella spp.
**Urinary Tract Infections**– caused by β-lactamase-producing strains of Escherichia coli, Klebsiella spp. and Enterobacter spp. While amoxicillin and clavulanate potassium for oral suspension is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to amoxicillin and clavulanate potassium treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and β-lactamase-producing organisms susceptible to amoxicillin and clavulanate potassium should not require the addition of SUGAM 228.5 DRY SYRUP (AMOXICILLIN & CLAVULANATE POTASSIUM FOR ORAL SUSPENSION USP) Formulations Pvt. Ltd. 28 another antibiotic. Because amoxicillin has greater in vitro activity against Streptococcus pneumoniae than does ampicillin or penicillin, the majority of S. pneumoniae strains with intermediate susceptibility to ampicillin or penicillin are fully susceptible to amoxicillin and amoxicillin and clavulanate potassium. Bacteriological studies, to determine the causative organisms and their susceptibility to amoxicillin and clavulanate potassium, should be performed together with any indicated surgical procedures. Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to amoxicillin and clavulanate potassium when there is reason to believe the infection may involve any of the β-lactamaseproducing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate.

### 4.2 Posology and method of administration

**Dosage**
**Pediatric Patients**
Based on the amoxicillin component, amoxicillin and clavulanate potassium for oral suspension should be dosed as follows: Neonates and infants aged < 12 weeks (3 months) Due to incompletely developed renal

function affecting elimination of amoxicillin in this age group, the recommended dose of amoxicillin and clavulanate potassium for oral suspension is 30 mg/kg/day divided q12h, based on the amoxicillin component. Clavulanate elimination is unaltered in this age group. Experience with the 200 mg/28.5 mg per 5 mL formulation in this age group is limited and, thus, use of the 125 mg/31.25 mg per 5 mL oral suspension is recommended.

Patients aged 12 weeks (3 months) and older

| INFECTIONS | DOSING REGIMEN | |
|---|---|---|
| | q12h | q8h |
| | 200 mg/28.5 mg per 5 mL or 400 mg/57 mg per 5 mL oral | 125 mg/31.25 mg per 5 mL or 250 mg/62.5 mg per 5 mL oral suspension |
| Otitis media sinusitis, lower respiratory tract infections, and | 45 mg/kg/day q12h | 40 mg/kg/day q8h |
| Less severe infections | 25 mg/kg/day q12h | 20 mg/kg/day q8h |

The q12h regimen is recommended as it is associated with significantly less diarrhea. However, the formulations contain aspartame and should not be used by phenylketonurics.

Duration of therapy studied and recommended for acute otitis media is 10 days.

**Adults**

Adults who have difficulty swallowing may be given the 125 mg/31.25 mg per 5 mL or 250 mg/62.5 mg per 5 mL suspension in place of the 500 mg tablet. The 200 mg/28.5 mg per 5 mL suspension or the 400mg/57 mg per 5 mL suspension may be used in place of the 875 mg tablet. See dosage recommendations above for children weighing 40 kg or more.

**Directions for Mixing Oral Suspension**

Prepare a suspension at time of dispensing as follows: Tap bottle until all the powder flows freely. Add approximately 2/3 of the total amount of water for reconstitution (see table below) and shake vigorously to suspend powder. Add remainder of the water and again shake vigorously. Each teaspoonful (5 mL) will contain 200 mg amoxicillin and 28.5 mg of clavulanic acid as the potassium salt.

Note: SHAKE ORAL SUSPENSION WELL BEFORE USE Reconstituted suspension must be stored under refrigeration(2-8 0 c) and discarded after 7 days.

**Administration**

Reconstituted amoxicillin and clavulanate potassium for oral suspension may be taken without regard to meals; however, absorption of clavulanate potassium is enhanced when amoxicillin and clavulanate potassium for oral suspension is administered at the start of a meal. To minimize the potential for gastrointestinal intolerance, amoxicillin and clavulanate potassium for oral suspension should be taken at the start of a meal.

**4.3 Contraindications**

Amoxicillin and clavulanate potassium for oral suspension is contraindicated in patients with a history of allergic reactions to any penicillin. It is also contraindicated in patients with a previous history of amoxicillin and clavulanate potassium-associated cholestatic jaundice/hepatic dysfunction.

**4.4 Special warnings and precautions for use**

Serious and occasionally fatal hypersensitivity (anaphylactic) 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/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 amoxicillin and clavulanate potassium, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. If an allergic reaction occurs, amoxicillin and clavulanate potassium should be discontinued and the appropriate therapy instituted. Serious anaphylactic reactions require immediate

emergency treatment with epinephrine. Oxygen, intravenous steroids and airway management, including intubation, should also be administered as indicated. Pseudomembranous colitis has been reported with nearly all antibacterial agents, including amoxicillin and clavulanate potassium, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by Clostridium difficile is one primary cause of "antibiotic associated colitis." After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against Clostridium difficile colitis. Amoxicillin and clavulanate potassiumshould be used with caution in patients with evidence of hepatic dysfunction. Hepatic toxicity associated with the use ofamoxicillin and clavulanate potassium is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications. Prescribing amoxicillin and clavulanate potassium for oral suspension USP in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. While amoxicillin and clavulanate potassium possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy. A high percentage of patients with mononucleosis who receive ampicillin develop an erythematous skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. The possibility of super infections with mycotic or bacterial pathogens should be kept in mind during therapy. If super infections occur (usually involving Pseudomonas or Candida), the drug should be discontinued and/or appropriate therapy instituted.

**4.5 Interaction with other medicinal products and other forms of interaction**

Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with amoxicillin and clavulanate potassium may result in increased and prolonged blood levels of amoxicillin. Coadministration of probenecid cannot be recommended. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with amoxicillin and clavulanate potassium and allopurinol administered concurrently. In common with other broad-spectrum antibiotics, amoxicillin and clavulanate potassium may reduce the efficacy of oral contraceptives.

**Drug/Laboratory Test Interactions**

Oral administration of amoxicillin and clavulanate potassium will result in high urine concentrations of amoxicillin. High urine concentrations of ampicillin may result in false-positive reactions when testing for the presence of glucose in urine using Clinitest®, Benedict's Solution or Fehling's Solution. Since this effect may also occur with amoxicillin and therefore amoxicillin and clavulanate potassium, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix®) be used. Following administration of ampicillin to pregnant women a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone and estradiol has been noted. This effect may also occur with amoxicillin and therefore amoxicillin and clavulanate potassium.

**4.6 Pregnancy and lactation**

Reproduction studies performed in pregnant rats and mice given amoxicillin and clavulanate potassium at oral dosages up to 1200 mg/kg/day, equivalent to 7200 and 4080 mg/m2/day, respectively (4.9 and 2.8 times the maximum human oral dose based on body surface area), revealed no evidence of harm to the fetus due to amoxicillin and clavulanate potassium. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**Labor and Delivery**

Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of amoxicillin and clavulanate potassium in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary. In a single study in women with premature rupture of fetal membranes, it was reported that prophylactic treatment with amoxicillin and clavulanate potassium may be associated with an increased risk of necrotizing enterocolitis in neonates.

**Nursing Mothers**

Ampicillin class antibiotics are excreted in the milk; therefore, caution should be exercised when amoxicillin and clavulanate potassium is administered to a nursing woman.

**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.

**4.8 Undesirable effects**

Amoxicillin and clavulanate potassium is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug-related side effects. From the original premarketing studies, where both pediatric and adult patients were enrolled, the most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%). The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: abdominal discomfort, flatulence and headache. In pediatric patients (aged 2 months to 12 years), one U.S./Canadian clinical trial was conducted which compared amoxicillin and clavulanate potassium 45 mg/6.4 mg/kg/day (divided q12h) for 10 days versus amoxicillin and clavulanate potassium 40 mg10 mg/kg/day (divided q8h) for 10 days in the treatment of acute otitis media. A total of 575 patients were enrolled and only the suspension formulations were used in this trial. Overall, the adverse event profile seen was comparable to that noted above. However, there were differences in the rates of diarrhea, skin rashes/urticaria, and diaper area rashes. The following adverse reactions have been reported for ampicillin class antibiotics:

**Gastrointestinal**

Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black “hairy” tongue, mucocutaneous candidiasis, enterocolitis, and hemorrhagic/pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See WARNINGS.)

**Hypersensitivity Reactions**

Skin rashes, pruritus, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), acute generalized exanthematous pustulosis and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis) have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin. (See WARNINGS.)

**Liver**

A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with amoxicillin and clavulanate potassium. It has been reported more

commonly in the elderly, in males, or in patients on prolonged treatment. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued. The hepatic dysfunction, which may be severe, is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications.

**Renal**
Interstitial nephritis and hematuria have been reported rarely.

**Hemic and Lymphatic Systems**
Anemia, including hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. 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 amoxicillin and clavulanate potassium. There have been reports of increased prothrombin time in patients receiving amoxicillin and clavulanate potassium and anticoagulant therapy concomitantly.

**Central Nervous System**
Agitation, anxiety, behavioral changes, confusion, convulsions, dizziness, insomnia, and reversible hyperactivity have been reported rarely

**Miscellaneous**
Tooth discoloration has been reported very rarely in children. Good oral hygiene may help to prevent tooth discoloration as it can usually be removed by brushing.

**4.9 Overdose**
Following overdosage, patients have experienced primarily gastrointestinal symptoms including stomach and abdominal pain, vomiting, and diarrhea. Rash, hyperactivity, or drowsiness have also been observed in a small number of patients. In the case of overdosage, discontinue amoxicillin and clavulanate potassium, treat symptomatically, and institute 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 drug from the stomach may be performed. A prospective study of 51 pediatric patients at a poison center suggested that overdosages of less than 250 mg/kg of amoxicillin are not associated with significant clinical symptoms and do not require gastric emptying. Interstitial nephritis resulting in oliguric renal failure has been reported in a small number of patients after overdosage with amoxicillin. Renal impairment appears to be reversible with cessation of drug administration. High blood levels may occur more readily in patients with impaired renal function because of decreased renal clearance of both amoxicillin and clavulanate. Both amoxicillin and clavulanate are removed from the circulation by hemodialysis.

**5. Pharmacological properties**
**5.1 Pharmacodynamic properties**
**Pharmacological group:** β-lactam antibacterials; combination of penicillin and beta-lactamase inhibitor
**ATC code :J01CR02** Amoxicillin/clavulanic acid has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections.
**Gram-Positive Aerobes**
Staphylococcus aureus (β-lactamase and non-β-lactamase producing)
**Gram-Negative Aerobes**
Enterobacter species (Although most strains of Enterobacter species are resistant in vitro, clinical efficacy has been demonstrated with amoxicillin and clavulanate potassium in urinary tract infections caused by these organisms.) Escherichia coli (β-lactamase and non-β-lactamase producing) Haemophilus influenzae (β-lactamase and non-β-lactamase producing) Klebsiella species (All known strains are β-lactamase producing) Moraxella catarrhalis (β-lactamase and non-β-lactamase producing) The following in vitro data are available, but their clinical significance is unknown.

Amoxicillin/clavulanic acid exhibits in vitro minimal inhibitory concentrations (MICs) of 0.5 mcg/mL or less against most (≥ 90%) strains of Streptococcus pneumoniae‡5 MICs of 0.06 mcg/mL or less against most (≥ 90%) strains of Neisseria gonorrhoeae; MICs of 4 mcg/mL or less against most (≥ 90%) strains of staphylococci and anaerobic bacteria; and MICs of 8 mcg/mL or less against most (≥ 90%) strains of other listed organisms. However, with the exception of organisms shown to respond to amoxicillin alone, the safety and effectiveness of amoxicillin/clavulanic acid in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

**Gram-Positive Aerobes**
Enterococcus faecalis
Staphylococcus epidermidis (β-lactamase and non-β-lactamase producing)
Staphylococcus saprophyticus (β-lactamase and non-β-lactamase producing)
Streptococcus pneumoniae
Streptococcus pyogenes
viridans group Streptococcus

**Gram-Negative Aerobes**
Eikenella corrodens (β-lactamase and non-β-lactamase producing)
Neisseria gonorrhoeae (β-lactamase and non-β-lactamase producing)
Proteus mirabilis (β-lactamase and non-β-lactamase producing)

**Anaerobic Bacteria**
Bacteroides species, including Bacteroides fragilis (β-lactamase and non-β-lactamase producing)
Fusobacterium species (β-lactamase and non-β-lactamase producing) Peptostreptococcus species

**5.2 Pharmacokinetic properties**
Amoxicillin and clavulanate potassium are well absorbed from the gastrointestinal tract after oral administration of amoxicillin and clavulanate potassium. Dosing in the fasted or fed state has minimal effect on the pharmacokinetics of amoxicillin. While amoxicillin and clavulanate potassium can be given without regard to meals, absorption of clavulanate potassium when taken with food is greater relative to the fasted state. In one study, the relative bioavailability of clavulanate was reduced when amoxicillin and clavulanate potassium was dosed at 30 and 150 minutes after the start of a high fat breakfast. The safety and efficacy of amoxicillin and clavulanate potassium have been established in clinical trials where amoxicillin and clavulanate potassium was taken without regard to meals. Microbiology: Amoxicillin is a semisynthethic antibiotic with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. Amoxicillin is, however, susceptible to degradation by β-lactamases and, therefore, the spectrum of activity does not include organisms which produce these enzymes. Clavulanic acid is a β-lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range of β-lactamase enzymes commonly found in microorganisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid mediated β-lactamases frequently responsible for transferred drug resistance. The formulation of amoxicillin and clavulanic acid in amoxicillin and clavulanate potassium protects amoxicillin from degradation by β-lactamase enzymes and effectively extends the antibiotic spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other β-lactam antibiotics. Thus, amoxicillin and clavulanate potassium possesses the distinctive properties of a broad-spectrum antibiotic and a β-lactamase inhibitor.

**5.3 Preclinical safety data**
**a) Acute toxicity**
The LD50 of clavulanic acid (potassium salt) is determined by the potassium content. Administration of clavulanic acid (potassium salt) together with amoxicillin does not result in any unexpected or synergistic toxicity.
**b) Chronic toxicity/subchronic toxicity**
The animal species used in chronic toxicity studies were rats and dogs. Solely after high doses

(corresponding to 20- to 50-fold the maximal human dose) were mild haematological and blood-chemical changes observed, which regressed completely following discontinuation of therapy.

**c) Mutagenic and tumorigenic potential**

In-vitro and in-vivo studies did not reveal any signs of any mutagenic effects of the combination of amoxicillin and clavulanic acid.

**d) Reproduction toxicity**

Reproduction toxicity studies in rats did not show any adverse effects of the combination on fertility and no teratogenic effects were evident. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, strength of contractions and duration of contractions. The relevance of these findings in humans is unknown.

## 6. Pharmaceutical particulars

### 6.1 List of excipients

Colloidal Silicon dioxide
Succinic acid
Hypromellose
Xanthan gum
Orange flavour
Aspartame
Syloid AL –FP

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

Dry powder: 24 months. Reconstituted suspensions: 7 days when stored in a refrigerator (2-8°C).

### 6.4 Special precautions for storage

Store below 250 c, protect from light

### 6.5 Nature and contents of container

70 ml HDPE bottle containing creamy white crystalline powder. The bottle is labelled and fitted plastic plug and closed with cap. This bottle is packed in monocarton along with pack insert and silica gel bag ,10 ml measuring cup and 60ml (2 ×30ml) sterile water for injection BP.

### 6.6 Special precautions for disposal and other handling

Prepare a suspension at time of dispensing as follows: Tap bottle until all the powder flows freely. Add approximately 2/3 of the total amount of water for reconstitution (see table below) and shake vigorously to suspend powder. Add remainder of the water and again shake vigorously. Each teaspoonful (5 mL) will contain 200 mg amoxicillin and 28.5 mg of clavulanic acid as the potassium salt.

## 7. APPLICANT

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**8. MANUFACTURER**

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