Summary of Product Characteristics

SAM-CLAV™ Tablet

SAM-CLAV™ Suspension / Drops

SAM-CLAV™

(Amoxicillin + Clavulanic Acid)

1. NAME OF THE PRODUCT

SAM-CLAV™ (Amoxicillin + Clavulanic Acid) 375mg Tablet

SAM-CLAV™ DS (Amoxicillin + Clavulanic Acid) 625mg Tablet

SAM-CLAV™ Forte (Amoxicillin + Clavulanic Acid) 1000mg Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SAM-CLAV™ 375mg Tablet

Each film-coated tablet contains:

Amoxicillin Trihydrate Eq. to Amoxicillin……250mg

Potassium Clavulanate Eq. to Clavulanic Acid……125mg

SAM-CLAV™ DS 625mg Tablet

Each film-coated tablet contains:

Amoxicillin Trihydrate Eq. to Amoxicillin……...500mg

Potassium Clavulanate Eq. to Clavulanic Acid……125mg

SAM-CLAV™ Forte 1000mg Tablet

Each film-coated tablet contains:

Amoxicillin Trihydrate Eq. to Amoxicillin……..……875mg

Potassium Clavulanate Eq. to Clavulanic Acid……125mg

3. PHARMACEUTICAL FORM

Film-coated tablet

Appearance:

SAM-CLAV™ 375mg Tablet: White to almost white colored, oblong, film coated tablets with beveled edges and scored on both sides.

SAM-CLAV™ DS 625mg Tablet: White to almost white colored, oblong, biconvex film coated tablets, plain on both sides.

SAM-CLAV™ Forte 1000mg Tablet: White to off-white colored, oblong shape film coated tablet, bifurcated line on both sides.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

SAM-CLAV™ tablet is 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 cellulitis, animal bites and severe dental abscess with spreading cellulitis.
- Bone and joint infections, in particular osteomyelitis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

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 SAM-CLAV™ tablet 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 SAM-CLAV™ tablet (e.g., those that provide higher doses of amoxicillin and/or different ratios of amoxicillin to clavulanic acid) should be considered as necessary.

SAM-CLAV™ 375mg Tablet:

For adults and children ≥ 40kg, this formulation of SAM-CLAV™ provides a total daily dose of 750mg amoxicillin/375mg 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 SAM-CLAV™ is selected in order to avoid administration of unnecessarily high daily doses of clavulanic acid. Treatment should not be extended beyond 14 days without review.

Adults and children ≥ 40kg: One tablet to be taken three times a day.

Children < 40kg: SAM-CLAV™ 250mg/125mg film-coated tablets are not recommended in children < 40kg.

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 30ml/min.

Adults and children ≥ 40kg:

CrCL: 10-30ml/min	250mg/125mg twice daily
CrCL < 10ml/min	250mg/125mg once daily
Haemodialysis	Two doses of 250mg/125mg every 24 hours, plus two doses of 250mg/125mg during dialysis, to be repeated at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased)

Children < 40kg: In children < 40kg with creatinine clearance less than 30ml/min, the use of Amoxicillin/clavulanic acid presentations with an amoxicillin to clavulanic acid ratio of 2:1 is not recommended, as no dose adjustments are available. In such patients, SAM-CLAV™ formulations with an amoxicillin to clavulanic acid ratio of 4:1 are recommended.
Hepatic impairment: Dose with caution and monitor hepatic function at regular intervals.

SAM-CLAV DS™ 625mg Tablet:
For adults and children ≥ 40kg, SAM-CLAV DS™ 625mg tablet provides a total daily dose of 1500mg amoxicillin/ 375mg clavulanic acid, when administrated as recommended below.
For children < 40kg, this tablet of SAM-CLAV DS™ provides a maximum daily dose of 2400mg amoxicillin/600mg 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/clavulanic acid is selected in order to avoid administration of unnecessarily high 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 ≥ 40kg: One tablet 500mg/125mg taken three times a day.
Children < 40kg: 20mg/5mg/kg/day to 60mg/15mg/kg/day given in three divided doses. Children may be treated with SAM-CLAV DS™ tablets or suspensions. As the tablets cannot be divided, children weighing less than 25kg must not be treated with SAM-CLAV DS™ tablets. The table below presents the received dose (mg/kg/body weight) in children weighing 25kg to 40kg upon administering a single 500mg/125mg tablet.

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

Children aged 6 years and below should preferably be treated with SAM-CLAV™ suspension.

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 30ml/min.

Adults and children ≥ 40kg

CrCl: 10-30ml/min	500mg/125mg twice daily
CrCl < 10ml/min	500mg/125mg once daily
Haemodialysis	500mg/125mg every 24 hours, plus 500mg/125mg during dialysis, to be repeated at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased)

Children < 40kg:

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

Hepatic impairment: Dose with caution and monitor hepatic function at regular intervals.

SAM-CLAV™ Forte 1000mg Tablet:

For adults and children ≥ 40kg, this formulation of SAM-CLAV™ Forte provides a total daily dose of 1750mg amoxicillin and 250mg clavulanic acid with twice

daily dosing and 2625mg amoxicillin and 375mg clavulanic acid with three times daily dosing, when administered as recommended below. For children < 40kg, this formulation of SAM-CLAV™ Forte provides a maximum daily dose of 1000-2800mg amoxicillin and 143-400mg 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 / Clavulanic acid 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: Recommended doses:

- standard dose (for all indications): one SAM-CLAV™ Forte 875mg/125mg tablet twice a day
- higher dose (particularly for infections such as otitis media, sinusitis, lower respiratory tract infections and urinary tract infections): one SAM-CLAV™ Forte 875mg/125mg tablet three times a day

Children < 40kg: Children may be treated with SAM-CLAV™ Forte tablets or suspension.

Recommended doses:

- 25mg/3.6mg/kg/day to 45mg/6.4mg/kg/day given as two divided doses;
- Up to 70mg/10mg/kg/day given as two divided doses may be considered for some infections (such as otitis media, sinusitis and lower respiratory tract infections).

As the tablets cannot be divided children weighing less than 25kg must not be treated with SAM-CLAV™ Forte tablets.

The table below presents the received dose (mg/kg body weight) in children weighing 25kg to 40kg upon administering a single 875mg/125mg tablet.

Body weight [kg]	40	35	30	25	Single dose recommended [mg/kg body weight]
Amoxicillin [mg/kg body weight] per single dose (1 film-coated tablet)	21.9	25.0	29.2	35.0	12.5-22.5 (up to 35)
Clavulanic acid [mg/kg body weight] per single dose (1 film-coated tablet)	3.1	3.5	4.2	5.0	1.8-3.2 (up to 5)

Children weighing less than 25kg should preferably be treated with SAM-CLAV™ suspension.

Elderly: No dose adjustment is considered necessary.
Renal impairment: No dose adjustment is required in patients with creatinine clearance (CrCl) greater than 30ml/min. In patients with creatinine clearance less than 30ml/min, the use of amoxicillin/clavulanic acid presentations with an amoxicillin to clavulanic acid ratio of 7:1 is not recommended, as no recommendations for dose adjustments are available.
Hepatic impairment: Dose with caution and monitor hepatic function at regular intervals.

Method of administration:
Amoxicillin/Clavulanic acid tablets are for oral use.
Administer amoxicillin/clavulanic acid 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 penicillins or to any of the excipients.
- History of a severe immediate hypersensitivity reaction (e.g., anaphylaxis) to another beta-lactam agent (e.g., a cephalosporin, carbapenem or monobactam).
- History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Before initiating therapy with amoxicillin/clavulanic acid, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, clavulanic acid and cephalosporins or other beta-lactam agents.
Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse 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. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to amoxicillin/clavulanic acid. 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.
Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin/clavulanic acid. DIES is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after amoxicillin/clavulanic acid administration) 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. 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/clavulanic acid 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.pneumoniae.*
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 an 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 generalised exanthemous pustulosis (AGEP). This reaction requires amoxicillin/clavulanic acid discontinuation and contraindicates any subsequent administration of amoxicillin.
Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment. 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 including amoxicillin and may range in severity from mild to life threatening. 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. 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 (including acute renal injury) 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/clavulanic acid may cause a nonspecific 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.

Information about Sodium content: This medicine contains less than 1mmol sodium (23mg) per tablet, that is to say essentially 'sodium-free'.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTIONS:

Oral anticoagulants: Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, 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: Penicillins 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. Close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

4.6. FERTILITY, PREGNANCY AND LACTATION:

Pregnancy: The use of amoxicillin/clavulanic acid during pregnancy in humans do not indicate an increased risk of congenital malformations. Use should be avoided during pregnancy, unless considered essential by the physician.

Breast-feeding: 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. The possibility of sensitisation should be taken into account. 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 reaction, dizziness, convulsions), which may influence the ability to drive and use machines.

4.8. UNDESIRABLE EFFECTS:

List of adverse reactions:

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 < 1/1,000); Very rare (< 1/10,000); Not known (cannot be estimated from the available data).

Infections and infestations:

Common: Mucocutaneous candidosis.

Not known: Overgrowth of non-susceptible organisms.

Blood and lymphatic system disorders:

Rare: Reversible leucopaenia (including *neutropaenia*), thrombocytopaenia.

Not known: Reversible agranulocytosis, haemolytic anaemia, prolongation of bleeding time and prothrombin time.

Cardiac disorders:

Not known: Kounis syndrome.

Immune system disorders:

Not known: Angioneurotic oedema, anaphylaxis, serum sickness-like syndrome, hypersensitivity vasculitis.

Nervous system disorders:

Uncommon: Dizziness, headache.

Not known: Aseptic meningitis, reversible hyperactivity, convulsions.

Gastrointestinal disorders:

Very common: Diarrhoea.

Common: Nausea, vomiting.

Uncommon: Indigestion.

Not known: Drug-induced enterocolitis syndrome, pancreatitis acute, Antibiotic-associated colitis, black hairy tongue.

Hepatobiliary disorders:

Uncommon: Rises in AST and/or ALT.

Not known: Hepatitis, cholestatic jaundice, cholangitis.

Skin and subcutaneous tissues disorders:

Uncommon: Skin rash, pruritus, urticaria.

Rare: Erythema multiforme.

Not known: Linear IgA disease, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative-dermatitis, acute generalised exanthemous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome).

Renal and urinary disorders:

Not known: Interstitial nephritis, crystalluria (including acute renal injury).

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: Combination of penicillins, incl. beta-lactamase inhibitors,

ATC code: J01CR02.

Mechanism 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 beta-lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

Mechanism 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.

5.2. PHARMACOKINETICS 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 (T_{max}) in each case is approximately one hour.

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. 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. Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid.

5.3. PRECLINICAL SAFETY DATA:

Non-clinical 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 discoloured tongue.

Carcinogenicity studies have not been conducted with amoxicillin/clavulanic acid or its components.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

SAM-CLAV™ 375mg Tablet:

- Aerosil
- Crospovidone/Polyvinylpolypyrolidone
- Crosslinked Carboxymethyl Cellulose Sodium
- Magnesium Stearate
- Talc
- Micro Crystalline Cellulose
- Hydroxypropyl Cellulose
- Ethylcellulose
- Polysorbate
- Triethyl Citrate
- Titanium Dioxide
- Ethanol

SAM-CLAV™ DS 625mg Tablet:

- Aerosil
- Crospovidone/Polyvinylpolypyrolidone
- Crosslinked Carboxymethyl Cellulose Sodium
- Magnesium Stearate
- Talc
- Micro Crystalline Cellulose
- Hydroxypropyl Cellulose
- Ethylcellulose
- Polysorbate
- Triethyl Citrate
- Titanium Dioxide
- Ethanol

SAM-CLAV™ Forte 1000mg Tablet:

- Aerosil
- Crospovidone/Polyvinylpolypyrolidone
- Crosslinked Carboxymethyl Cellulose Sodium
- Magnesium Stearate
- Talc
- Micro Crystalline Cellulose
- Hydroxypropyl Cellulose

- Ethylcellulose
- Polysorbate
- Triethyl Citrate
- Titanium Dioxide
- Ethanol

6.2. INCOMPATIBILITIES:

Not applicable

6.3. SHELF LIFE:

See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:

Do not store over 25°C, and protect from heat, light and moisture.
Improper storage may deteriorate the medicine.
Keep out reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:

SAM-CLAV™ **375mg Tablet:** Aluminium strip packing, pack size is 6's.

SAM-CLAV™ DS **625mg Tablet:** Aluminium strip packing, pack size is 6's.

SAM-CLAV™ Forte **1000mg Tablet:** Aluminium strip packing, pack size is 6's.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:

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

6.7. DRUG PRODUCT SPECIFICATIONS:

SAM-CLAV™ **375mg Tablet:** USP Specs.

SAM-CLAV™ DS **625mg Tablet:** USP Specs.

SAM-CLAV™ Forte **1000mg Tablet:** USP Specs.

7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured for:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, Off Hub River Road, S.I.T.E., Karachi-Pakistan
www.samipharma.com
Mfg Lic. No. 000072

Manufactured by:
CSH Pharmaceuticals (Pvt.) Ltd.
32-Km Ferozepur Road, Lahore

8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)

SAM-CLAV™ **375mg Tablet:** 129164

SAM-CLAV™ DS **625mg Tablet:** 129162

SAM-CLAV™ Forte **1000mg Tablet:** 129163

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

SAM-CLAV™ **375mg Tablet:** 18th August, 2025

SAM-CLAV™ DS **625mg Tablet:** 18th August, 2025

SAM-CLAV™ Forte **1000mg Tablet:** 18th August, 2025

10. DATE OF REVISION OF THE TEXT

سیم-کلیو™ ٹیبلٹ

(اموکسی سلین + کلیوولینک ایسڈ)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

بچوں کی پہنچ سے دور رکھیں۔

دوا کو ۲۵ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں،

گرمی، روشنی اور نمی سے محفوظ رکھیں ورنہ دوا خراب ہو جائیگی۔

SAM-CLAV™

(Amoxicillin + Clavulanic Acid)

1. NAME OF THE PRODUCT

SAM-CLAV™ (Amoxicillin + Clavulanic Acid) 156.25mg/5ml Suspension

SAM-CLAV™ DS (Amoxicillin + Clavulanic Acid) 312.50mg/5ml Suspension

SAM-CLAV™ Forte (Amoxicillin + Clavulanic Acid) 457mg/5ml Suspension

SAM-CLAV™ (Amoxicillin + Clavulanic Acid) 62.5mg/ml Drops

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SAM-CLAV™ 156.25mg/5ml Suspension

Each 5ml contains (reconstituted):

Amoxicillin Trihydrate Eq. to Amoxicillin…….....125mg

Potassium Clavulanate Eq. to Clavulanic Acid……...31.25mg

SAM-CLAV™ DS 312.50mg/5ml Suspension

Each 5ml contains (reconstituted):

Amoxicillin Trihydrate Eq. to Amoxicillin……..250mg

Potassium Clavulanate Eq. to Clavulanic Acid……...62.50mg

SAM-CLAV™ Forte 457mg/5ml Suspension

Each 5ml contains (reconstituted):

Amoxicillin Trihydrate Eq. to Amoxicillin……..400mg

Potassium Clavulanate Eq. to Clavulanic Acid…….....57mg

SAM-CLAV™ 62.5mg/ml Drops

Each ml contains (reconstituted):

Amoxicillin Trihydrate Eq. to Amoxicillin……..50mg

Potassium Clavulanate Eq. to Clavulanic Acid……....12.5mg

3. PHARMACEUTICAL FORM

Powder for oral suspension

Appearance:

SAM-CLAV™ 156.25mg/5ml Suspension: White to yellowish white crystalline powder.

SAM-CLAV™ DS 312.50mg/5ml Suspension: White to yellowish white crystalline powder.

SAM-CLAV™ Forte 457mg/5ml Suspension: White to yellowish white crystalline powder.

SAM-CLAV™ 62.5mg/ml Drops: White to yellowish white crystalline powder.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

SAM-CLAV™ is indicated for the treatment of the following infections:

- 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 cellulitis, animal bites, severe dental abscess with spreading cellulitis.
- Bone and joint infections, in particular osteomyelitis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

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 / Clavulanic acid 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 / Clavulanic acid (e.g. those that provide higher doses of amoxicillin and/or different ratios of amoxicillin to clavulanic acid) should be considered as necessary.

For SAM-CLAV™ Suspension and SAM-CLAV DS™ Suspension:

For adults and children ≥ 40kg, this formulation of Amoxicillin / Clavulanic acid provides a total daily dose of 1500mg amoxicillin/375mg clavulanic acid, when administered as recommended below. For children < 40kg, this formulation of Amoxicillin / Clavulanic acid provides a maximum daily dose of 2400mg amoxicillin/600mg 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 / Clavulanic acid 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 ≥ 40kg: One 500mg/125mg dose taken three times a day.
Children < 40kg: 20mg/5mg/kg/day to 60mg/15mg/kg/day given in three divided doses.
Children may be treated with Amoxicillin / Clavulanic acid tablets, suspensions or paediatric sachets. Children aged 6 years and below should preferably be treated with SAM-CLAV™ suspension or paediatric sachets.
No clinical data are available on doses of Amoxicillin / Clavulanic acid 4:1 formulation higher than 40mg/10mg/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 30ml/min.
Adults and children ≥ 40kg

CrCl: 10-30ml/min	500mg/125mg twice daily
CrCl < 10ml/min	500mg/125mg once daily
Haemodialysis	500mg/125mg every 24 hours, plus 500mg/125mg during dialysis, to be repeated at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased)

Children < 40 kg

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

Hepatic impairment: Dose with caution and monitor hepatic function at regular intervals.

For SAM-CLAV™ Forte Suspension:
For adults and children ≥ 40kg, this formulation of SAM-CLAV™ Forte Suspension provides a total daily dose of 1750mg amoxicillin/250mg clavulanic acid with twice daily dosing and 2625mg amoxicillin/375mg clavulanic acid with three times daily dosing, when administered as recommended below.

For children < 40 kg, this formulation of SAM-CLAV™ Forte Suspension provides a maximum daily dose of 1000-2800mg amoxicillin/143-400mg 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 SAM-CLAV™ Forte Suspension 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 ≥ 40kg:

Recommended doses:

- standard dose: (for all indications) 875mg/125mg two times a day;
- higher dose - (particularly for infections such as otitis media, sinusitis, lower respiratory tract infections and urinary tract infections): 875mg/125mg three times a day.

Children < 40kg:

Children may be treated with SAM-CLAV™ Forte Suspension tablets, suspensions or paediatric sachets.
Recommended doses:

- 25mg/3.6mg/kg/day to 45mg/6.4mg/kg/day given as two divided doses;
- Up to 70mg/10mg/kg/day given as two divided doses may be considered for some infections (such as otitis media, sinusitis and lower respiratory tract infections).

No clinical data are available for SAM-CLAV™ Forte Suspension 7:1 formulation regarding doses higher than 45 mg/6.4mg/kg per day in children under 2 years.

There are no clinical data for SAM-CLAV™ Forte Suspension 7:1 formulation for patients under 2 months of age. Dosing recommendations in this population therefore cannot be made.

Elderly: No dose adjustment is considered necessary.

Renal impairment: No adjustment in dose is required in patients with creatinine clearance (CrCl) greater than 30ml/min. In patients with creatinine clearance less than 30ml/min, the use of SAM-CLAV™ Forte Suspension presentations with an amoxicillin to clavulanic acid ratio of 7:1 is not recommended, as no recommendations for dose adjustments are available.

Hepatic impairment: Dose with caution and monitor hepatic function at regular intervals.

For SAM-CLAV™ Drops:

Infants: SAM-CLAV™ drops should be administered orally using the supplied doser. The doser is graduated to permit accurate and reproducible volumes to be dispensed. Children should be dosed according to body weight. A similar dose should be administered once every eight hours.

Weight (kg)	Volume (ml) of SAM-CLAV™ Drops
1	0.13
1.5	0.20
2	0.27
2.5	0.33
3	0.40
3.5	0.47
4	0.53
4.5	0.60
5	0.67
5.5	0.73
6	0.80
6.5	0.87
7	0.93
7.5	1.00
8	1.07
8.5	1.14
9	1.20
9.5	1.27
10	1.34

Renal impairment

Creatinine Clearance greater than 30mL/min: No adjustment necessary.

Creatinine Clearance 10 to 30mL/min: The recommended dose mentioned in table above, given twice daily instead of three times per day*.

Creatinine Clearance less than 10mL/min: The recommended dose mentioned in table above, given once daily instead of three times per day*.

*In more serious cases this dose may be doubled.

Hepatic impairment: Dose with caution and monitor hepatic function at regular intervals.

Method of administration

- SAM-CLAV™ is for oral use.
- Administer at the start of a meal to minimize potential gastrointestinal intolerance and optimise absorption of amoxicillin/clavulanic acid.
- Space the doses evenly during the day, at least 4 hours apart.
- Shake the bottle before each dose.

DIRECTION FOR RECONSTITUTION:

Shake bottle to loosen the mass. Add freshly boiled and cooled water below the mark given on bottle label then shake to make homogeneous suspension. Add further same water up to the mark of bottle label and shake vigorously to form uniform suspension.

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 beta-lactam agent (e.g. a cephalosporin, carbapenem or monobactam).
- History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid.

4.4. 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 beta-lactam agents.

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse 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. 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.

Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin/clavulanate. DIES is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after drug use) 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.

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/Clavulanic Acid 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. pneumoniae.*

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 generalized erythema associated with pustula may be a symptom of acute generalized exanthemous pustulosis (AGEP). This reaction requires Amoxicillin/Clavulanic Acid discontinuation and contraindicates 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 contraindicated 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 (including acute renal injury) 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 may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.
SAM-CLAV™ suspension contains aspartame, it should be administered with caution in patients with phenylketonuria. Aspartame is hydrolysed in the gastrointestinal tract when orally ingested. One of the major hydrolysis products is phenylalanine.
This medicine contains less than 1mmol sodium (23mg) per dose, that is to say essentially 'sodium-free'

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS:

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: Penicillins 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 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. FERTILITY, PREGNANCY AND LACTATION:

Pregnancy: Limited data on the use of amoxicillin/clavulanic acid during pregnancy in humans do not indicate an increased risk of congenital

malformations. The use of amoxicillin/clavulanic acid should be avoided during pregnancy, unless considered essential by the physician.

Breast-feeding: 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:

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 diarrhea, 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 <1/1,000), Very Rare (<1/10,000), Not known (cannot be estimated from the available data).

Infections and infestations:

Common: Mucocutaneous candidosis

Not known: Overgrowth of non-susceptible organisms

Blood and lymphatic system disorders:

Rare: Reversible leucopenia (including neutropenia), thrombocytopenia.

Not known: Reversible agranulocytosis, haemolytic anaemia, prolongation of bleeding time and prothrombin time

Immune system disorders:

Not known: Angioneurotic oedema, anaphylaxis, serum sickness-like syndrome, hypersensitivity vasculitis

Nervous system disorders:

Uncommon: Dizziness, headache

Not known: Reversible hyperactivity, convulsions, aseptic meningitis

Cardiac disorders:

Not known: Kounis syndrome

Gastrointestinal disorders:

Common: Diarrhoea, nausea, vomiting.

Uncommon: Indigestion

Not known: Antibiotic-associated colitis, black hairy tongue, tooth discoloration, drug-induced enterocolitis syndrome, pancreatitis acute.

Hepatobiliary disorders:
Uncommon: Rises in AST and/or ALT
Not known: Hepatitis, cholestatic jaundice
Skin and subcutaneous tissues disorders:
Uncommon: Skin rash, pruritus, urticaria
Not known: Drug reaction with eosinophilia and systemic symptoms (DRESS), stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative-dermatitis, acute generalized exanthemous pustulosis (AGEP), linear IgA disease
Rare: Erythema multiforme
Renal and urinary disorders:
Not known: Interstitial nephritis, crystalluria (including acute renal injury)

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.
- Amoxicillin crystalluria, in some cases leading to renal failure, has been observed.

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.
Mechanism 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 beta-lactamase 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.

5.2. PHARMACOKINETICS 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 (T_{max}) in each case is approximately one hour.
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 0.3-0.4l/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. 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. Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid.

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/Clavulanic Acid or its components.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

SAM-CLAV™ 156.25mg/5ml Suspension:

- Mannitol
- Aerosil
- Methocel
- Xanthan Gum
- Succinic Acid
- Sodium Saccharine
- Silicon Dioxide
- Aspartame
- Pineapple Flavor

SAM-CLAV™ DS 312.50mg/5ml Suspension:

- Mannitol
- Aerosil
- Methocel
- Xanthan Gum
- Succinic Acid
- Sodium Saccharine
- Silicon Dioxide
- Aspartame
- Pineapple Flavor

SAM-CLAV™ Forte 457mg/5ml Suspension:

- Mannitol
- Aerosil
- Methocel
- Xanthan Gum
- Succinic Acid
- Sodium Saccharine
- Silicon Dioxide
- Aspartame
- Pineapple Flavor

SAM-CLAV™ 62.5mg/ml Drops:

- Mannitol
- Aerosil
- Methocel
- Xanthan Gum
- Succinic Acid
- Sodium Saccharine
- Silicon Dioxide
- Aspartame
- Pineapple Flavor

6.2. INCOMPATIBILITIES:

Not applicable

6.3. SHELF LIFE:

Unopened bottle: See expiry on the pack.
Reconstituted Suspension: 07 days

6.4. SPECIAL PRECAUTIONS FOR STORAGE:

Do not store over 25°C, and protect from heat, light and moisture.
Improper storage may deteriorate the medicine.
The reconstituted suspension should be stored in refrigerator (2-8°C), so that potency of the product remains stable and be used within 07 days.
Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:

SAM-CLAV™ 156.25mg/5ml Suspension:
Clear amber glass bottle (USP Type-III) with aluminium cap, pack size is 90ml.

SAM-CLAV™ DS 312.50mg/5ml Suspension:
Clear amber glass bottle (USP Type-III) with aluminium cap, pack size is 90ml.

SAM-CLAV™ Forte 457mg/5ml Suspension:
Clear amber glass bottle (USP Type-III) with aluminium cap, pack size is 70ml.

SAM-CLAV™ 62.5mg/ml Drops:
Clear amber glass bottle (USP Type-III) with aluminium cap, pack size is 20ml.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:

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

6.7. DRUG PRODUCT SPECIFICATIONS:

SAM-CLAV™ 156.25mg Suspension: USP Specs.

SAM-CLAV™ DS **312.50mg/5ml Suspension:** USP Specs.

SAM-CLAV™ Forte **457mg/5ml Suspension:** USP Specs.

SAM-CLAV™ **62.5mg/ml Drops:** USP Specs.

7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured for:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, Off Hub River Road, S.I.T.E., Karachi-Pakistan
www.samipharma.com
Mfg Lic. No. 000072

Manufactured by:
CSH Pharmaceuticals (Pvt.) Ltd.
32-Km Ferozepur Road, Lahore

8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)

SAM-CLAV™ **156.25mg Suspension:** 129160

SAM-CLAV™ DS **312.50mg/5ml Suspension:** 129161

SAM-CLAV™ Forte **457mg/5ml Suspension:** 129382

SAM-CLAV™ **62.5mg/ml Drops:** 130856

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

SAM-CLAV™ **156.25mg Suspension:** 18th August, 2025

SAM-CLAV™ DS **312.50mg/5ml Suspension:** 18th August, 2025

SAM-CLAV™ Forte **457mg/5ml Suspension:** 17th September,2025

SAM-CLAV™ **62.5mg/ml Drops:** 30th October,2025

10. DATE OF REVISION OF THE TEXT

سیم-کلیو™ سسپینشن

(اموکسی سلین + کلیوولینک ایسڈ)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

بچوں کی پہنچ سے دور رکھیں۔

دوا کو ۲۵ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں،

گرمی، روشنی اور نمی سے محفوظ رکھیں ورنہ دوا خراب ہو جائیگی۔

تیار شدہ سسپینشن کو ریفریجریٹر (۲ سے ۸ ڈگری سینٹی گریڈ) میں رکھیں

تاکہ دوا کی تاثیر برقرار رہے اور ۷ یوم کے اندر استعمال کر لیں۔