1.3.1
Summary Of Product Characteristics (SPC)

1.3.1.1 Product information for health professionals

1. NAME OF THE MEDICINAL PRODUCT

1.1 Invented Name of the Medicinal Product

G-CLAV 228.5

Amoxicillin 200mg & Clavulanic Acid 28.5mg

1.2 Strength

Amoxicillin 200mg /5 ml suspension.

Clavulanic Acid 28.5mg /5 ml suspension.

1.3 Pharmaceutical Form

Powder for Oral Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml of reconstituted suspension contains:

Amoxicillin (As Trihydrate) USP

Equivalent to Amoxicillin ……..…200 mg

Diluted Potassium Clavulanate BP

Equivalent to Clavulanic Acid ……..28.5 mg

Excipients……..q.s.

For a full list of excipients see section 6.1

3. PHARMACEUTICAL FORM

Powder for Oral Suspension

An off- white colour granular powder filled in opaque white colour bottle. On reconstitution with water it forms an off white colour thick suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

G-CLAV 228.5 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 (beta)-lactamase-producing strains of Haemophilus influenzae and Moraxella (Branhamella) catarrhalis.

Otitis Media: caused by (beta)-lactamase-producing strains of Haemophilus influenzae and Moraxella (Branhamella) catarrhalis.

Sinusitis: caused by (beta)-lactamase-producing strains of Haemophilus influenzae and Moraxella (Branhamella) catarrhalis.

Skin and Skin Structure Infections: caused by (beta)-lactamase-producing strains of Staphylococcus aureus, Escherichia coli and Klebsiella spp.

Urinary Tract Infections: caused by (beta)-lactamase-producing strains of Escherichia coli, Klebsiella spp. and Enterobacter spp.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Method of administration: Oral administration.

The dose of G-CLAV 228.5 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 usual recommended daily dosage for children is 25 mg/kg/day in divided doses.

Acute bacterial Sinusitis	Under 1 year: 2.5 mL twice daily
	1-6 years: 5 mL twice daily
	6 – 12 years: 10 mL twice daily
Severe Infections	The above dosage may be increased to thrice daily

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.

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 (CrCI) greater than 30 mL/min.

Method of administration: Hepatic Impairment: Dose with caution and monitor hepatic function at regular intervals.

G-CLAV 228.5 is for oral use. Administer at the start of a meal to minimise potential gastrointestinal intolerance and optimise absorption of amoxicillin/clavulanic acid.

4.3 CONTRAINDICATIONS

Serious Hypersensitivity Reactions

Amoxicillin and clavulanate potassium suspension is contraindicated in patients with a history of serious hypersensitivity reactions (e.g., anaphylaxis or Stevens-Johnson syndrome) to amoxicillin, clavulanate or to other beta-lactam antibacterial drugs (e.g., penicillins and cephalosporins).

Cholestatic Jaundice/Hepatic Dysfunction

Amoxicillin and clavulanate potassium suspension is contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with amoxicillin and clavulanate potassium suspension.

4.4 WARNING AND PRECAUTION

Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam antibacterials, including amoxicillin and clavulanate potassium suspension. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. Before initiating therapy with amoxicillin and clavulanate potassium suspension, careful inquiry should be made regarding

previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, amoxicillin and clavulanate potassium suspension should be discontinued and appropriate therapy instituted.

Hepatic Dysfunction

Hepatic dysfunction, including hepatitis and cholestatic jaundice has been associated with the use of amoxicillin and clavulanate potassium suspension. Hepatic toxicity is usually reversible; however, deaths have been reported. Hepatic function should be monitored at regular intervals in patients with hepatic impairment.

Clostridium difficile Associated Diarrhea (CDAD)

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including amoxicillin and clavulanate potassium suspension, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

Skin Rash in Patients with Mononucleosis

A high percentage of patients with mononucleosis who receive amoxicillin develop an erythematous skin rash. Thus, amoxicillin and clavulanate potassium suspension should not be administered to patients with mononucleosis.

Potential for Microbial Overgrowth

The possibility of superinfections with fungal or bacterial pathogens should be considered during therapy. If superinfection occurs, amoxicillin/clavulanate potassium suspension should be discontinued and appropriate therapy instituted.

Development of Drug-Resistant Bacteria

Prescribing amoxicillin and clavulanate potassium suspension in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient, and increases the risk of the development of drug-resistant bacteria.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Probenecid

Probenecid decreases the renal tubular secretion of amoxicillin but does not delay renal excretion of clavulanic acid. Concurrent use with amoxicillin and clavulanate potassium may result in increased and prolonged blood concentrations of amoxicillin. Coadministration of probenecid is not recommended.

Oral Anticoagulants

Abnormal prolongation of prothrombin time (increased international normalized ratio [INR]) has been reported in patients receiving amoxicillin and oral anticoagulants. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently with amoxicillin and clavulanate potassium. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

Allopurinol

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

Oral Contraceptives

Amoxicillin and clavulanate potassium may affect intestinal flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral estrogen/progesterone contraceptives.

Effects on Laboratory Tests

High urine concentrations of amoxicillin 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 clavulanate potassium, it is recommended that glucose tests based on enzymatic glucose oxidase reactions be used.

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

4.6 PREGNANCY AND LACTATION

Pregnancy

Teratogenic Effects: Pregnancy Category B. Reproduction studies performed in pregnant rats and mice given amoxicillin and clavulanate potassium (2:1 ratio formulation of amoxicillin:clavulanate) at oral doses up to 1200 mg/kg/day revealed no evidence of harm to the fetus due to amoxicillin and clavulanate potassium. The amoxicillin doses in rats and mice (based on body surface area) were approximately 4 and 2 times the maximum recommended adult human oral dose (875 mg every 12 hours). For clavulanate, these dose multiples were approximately 9 and 4 times the maximum recommended adult human oral dose (125 mg every 8 hours). 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.

Lactation:

Amoxicillin has been shown to be excreted in human milk. Amoxicillin/clavulanate potassium use by nursing mothers may lead to sensitization of infants. Caution should be exercised when amoxicillin/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. 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 frequencies assigned to all other undesirable effects (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.

The following convention has been used for the classification of frequency.

very common	>1/10
common	>1/100 and <1/10
uncommon	>1/1000 and <1/100
rare	>1/10,000 and <1/1000
very rare	<1/10,000

Infection and infestations

common	Mucocutaneous candidiasis, Blood and lymphatic system disorders
rare	Reversible leucopenia (including neutropenia and thrombocytopenia)
very rare	Reversible agranulocytosis and haemolyticanaemia. Prolongation of bleeding time and prothrombin time Immune system disorders
Very rare	Angioneuroticoedema, anaphylaxis, serum stickness-like syndrome, hypersensitivity vasculitis
Nervous system disorders	
uncommon	Dizziness, headache
very rare	Reversible hyperactivity and convulsions. Convulsion may occur in patients with impaired renal function or in those receiving high doses.
Gastrointestinal disorders	

Adults: Common	Nausea, Vomiting
Children: Common	Diarrhoea, nausea, vomiting. Nausea is more often associated with higher oral dosages. If gastrointestinal reactions are evident, they may be reduced by taking GRECLAV at the start of a meal
uncommon	Indigestion
very rare	Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis). Black hairy tongue Superficial tooth discolouration has been reported very rarely in children. Good oral hygiene may help to prevent tooth discolouration as it can usually be removed by brushing.
Hepatobiliary disorders	
uncommon	A moderate rise in AST and/or ALT has been noted in patients treated with beta-Iactam class antibiotics, but significanse of these findings is unknown.
very rare	Hepatitis and cholestatic jaundice.
Skin and subcutaneous tissue disorders	
Uncommon	Skin rash, pruritus, urticaria
Rare	Erythema multiforme
Very Rare	Stevens-Jonson syndrome, toxic epidermal necrolysis bullous exfoliative-dermatitis, acute generalized exanthemouspustulosis (AGEP) if any hypersensitivity dermatitis reaction occurs, treatment should be discontinued. Renal and urinary disorders
Very Rare	Interstitial nephritis, crystalluria (see Overdose)

4.9 OVERDOSE

Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident.

Gastrointestinal symptoms may be treated symptomatically with attention to the water electrolyte balance.

Amoxicillin Crystalluria, in some cases leading to renal failure, has been observed (see Warnings and Precautions).

Amoxicillin and clavulanate potassium for oral suspension can be removed from the circulations 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 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 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 optimized 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 0.3-0.41/kg for amoxicillin and around 0.2l/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 I/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 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-lite 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

TOXICOLOGICAL DATA

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic potential.

Amoxicillin and clavulanate potassium for oral suspension (4:1 ratio formulation of amoxicillin:clavulanate) was non-mutagenic in the Ames bacterial mutation assay, and the yeast gene conversion assay. Amoxicillin and clavulanate potassium for oral suspension was weakly positive in the mouse lymphoma assay, but the trend toward increased mutation frequencies in this assay occurred at doses that were also associated with decreased cell survival. Amoxicillin and clavulanate potassium for oral suspension was negative in the mouse micronucleus test, and in the dominant lethal assay in mice. Potassium clavulanate alone was tested in the Ames bacterial mutation assay and in the mouse micronucleus test, and was negative in each of these assays.

Amoxicillin and clavulanate potassium for oral suspension (2:1 ratio formulation of amoxicillin:clavulanate) at oral doses of up to 1,200 mg/kg/day was found to have no effect on fertility and reproductive performance in rats. Based on body surface area, this dose of amoxicillin is approximately 4 times the maximum recommended adult human oral dose (875 mg every 12 hours). For clavulanate, the dose multiple is approximately 9 times higher than the maximum recommended adult human oral dose (125 mg every 8 hours), also based on body surface area.

6. PHARMACEUTICAL PARTICULARS

None

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Two years.

6.4 Special precautions for storage

Store below 30°C. Protected from light.

6.5 Nature and contents of container

Available as bottle pack of 100 ml packed in a carton along with pack insert.

6.6 Special precautions for disposal and other Special handling

Not Applicable

7. Marketed by:

GREENLIFE PHARMACEUTICALS LTD.

2, Bank Lane, Off Town Planning Way,

Ilupeju, lagos,

Nigeria.