1.3.1
Summary Of Product Characteristics (SPC)

1.3.1 Product information for health professionals

1.3.1.1 NAME OF THE MEDICINAL PRODUCT

1.3.1.2 Invented Name of the Medicinal Product

G-CLAV 625

Amoxicillin 500mg & Clavulanic Acid 125mg

1.3.1.3 Strength

Amoxicillin 500mg /tablet.

Clavulanic Acid 125mg /tablet.

1.3.1.4 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Amoxicillin Trihydrate USP

eq. to Amoxicillin.....500 mg

Diluted Potassium Clavulanate BP

eq. to Clavulanic Acid .. ..125 mg

Excipients .....q.s.

Approved colour use

For a full list of excipients see section 6.1

1.3.1.5 PHARMACEUTICAL FORM

Film coated tablet.

A white coloured, elongated, biconvex, film coated tablets.

1.3.1.6 CLINICAL PARTICULARS

1.3.1.6.1 Therapeutic indications

G-CLAV 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.

1.3.1.6.2 POSOLOGY AND METHOD OF ADMINISTRATION

Method of administration: Oral administration.

Adults:

For more severe infections and infections of the respiratory tract, the dose should be 1 Amoxicillin and Clavulanate Potassium Tablet every 12 hours.

1.3.1.6.3 CONTRAINDICATIONS

G-CLAV is contraindicated in patients with a history of allergic reactions to any penicillin. It is also contraindicated in patients with a previous history of **G-CLAV** associated cholestatic jaundice/hepatic dysfunction.

1.3.1.6.4 WARNING AND PRECAUTION

General: While Amoxicillin and Clavulanate Potassium Tablets 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 superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving Pseudomonas or Candida), the drug should be discontinued and/or appropriate therapy instituted.

1.3.1.6.5 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 Tablets may result in increased and prolonged blood levels of amoxicillin. Co - administration 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 Tablets and allopurinol administered concurrently.

In common with other broad - spectrum antibiotics, Amoxicillin and Clavulanate Potassium Tablets may reduce the efficacy of oral contraceptives.

Drug/Laboratory Test Interactions: Oral administration of Amoxicillin and Clavulanate Potassium Tablets 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' Solution or Feh - ling's Solution. Since this effect may also occur with amoxicillin and therefore Amoxicillin and Clavulanate

Potassium Tablets, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix® or Tes - Tape®) 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 Tablets.

1.3.1.6.6 PREGNANCY AND LACTATION

Pregnancy

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Limited data on the use of amoxicillin/clavulanic acid during pregnancy in humans do not indicate an increased risk of congenital malformations. In a single study in women with preterm, premature rupture of the foetal membrane it was reported that prophylactic treatment with amoxicillin/clavulanic acid may be associated with an increased risk of necrotising enterocolitis in neonates. Use should be avoided during pregnancy, unless considered essential by the physician.

Breastfeeding

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.

1.3.1.6.7 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

1.3.1.6.8 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 / 6.4 mg / kg / day (divided q12h) for 10 days versus Amoxicillin and Clavulanate Potassium 40 / 10 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 tablet 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.

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) 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. 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 have 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 Augmentin. 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.

1.3.1.6.9 OVERDOSE

Most patients have been asymptomatic following over dosage or have experienced primarily gastrointestinal symptoms including stomach and abdominal pain, vomiting, and diarrhea. Rash, hyperactivity, or drowsiness has also been observed in a small number of patients.

In the case of overdosage, discontinue **G-CLAV**, 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. 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.

1.3.1.7 PHARMACOLOGICAL PROPERTIES

1.3.1.7.1 Pharmacodynamic properties

Amoxicillin

Amoxicillin is an orally active member of the penicillin family. The penicillin nucleus consists of a thiazolidone ring connected to a β-lactam ring to which is attached a side-chain. The side-chain determines most of the pharmacological and antibacterial properties of the penicillin in question. In the case of Amoxicillin the benzyl ring in the side-chain extends the range of antimicrobial activity into the Gram-negative bacteria. Amoxicillin kills bacteria by interfering with the synthesis of the bacterial cell wall. Peptidoglycan is a heteropolymeric structure that provides the cell wall with mechanical stability. The final stage in the synthesis of peptidoglycan involves the completion of the cross-linking when the terminal glycine residue of the pentaglycine bridge is linked to the fourth residue of the pentapeptide (D-alanine). The transpeptidase enzyme that performs this step is inhibited by penicillins and cephalosporins. As a result the bacterial cell wall is weakened, the cell swells and then ruptures. Amoxicillin is readily hydrolyzed by the staphylococcal penicillinase.

Clavulanate Potassium

Clavulanic acid has poor intrinsic antimicrobial activity and is effective primarily as a ‘suicide’ inhibitor of β-lactamases containing a nucleophilic serine residue at their active sites. Mass spectrometry studies with the TEM-2β- lactamases suggest a mechanism for

the reaction of clavulanate which involves acylation at Ser-70. Subsequent decarboxylation is followed either by cross-linking with Ser-130 to form a vinyl ether or by reformation of unmodified enzyme via a Ser-70 linked aldehyde. However, subinihibitory concentrations of clavulanate alone to cause changes in the composition of the bacterial cell wall which appear to be the consequence of suppressed D,Dcarboxypeptidase activity. Clavulanic acid is active mainly against plasmid-mediated penicillinases and has no useful activity against chromosomal cephalosporinases. It does, however, have some effect against chromosomal penicillinase and against chromosomal cephalosporinases. It does, however, have some effect against chromosomal penicillinase and against chromosomal broad spectrum β-lactamase. Clavulanic acid is not used on its own but in combination with either amoxicillin or ticarcillin. In both cases the addition of clavulanic acid extends the spectrum of that antibiotic to some β-lactamase-producing microorganisms. Under the selection pressured caused by the extensive clinical use of β-lactam-β-lactamase inhibitor combinations, resistant variants of β- lactamase have evolved. Among plasmid-borne genes from 27 strains resistant to amoxicillin and β-lactamase inhibitor combinations, mutations were found which resulted in amino acid change at positions 69,244,275 and 276 and a mutation at nucleoside position 162 in the promoter region. In a study in *Escherichia coli* the predominant mechanism of resistance was hyperproduction of a β- lactamase isoelectrically cofocusing with TEM-1.

1.3.1.7.2 Pharmacokinetic properties

Absorption: Amoxicillin and clavulanic acid, are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Absorption of amoxicillin/clavulanic acid is optimised when taken at the start of a meal. Following oral administration, amoxicillin and clavulanic acid are approximately 70% bioavailable. The plasma profiles of both components are similar and the time to peak plasma concentration (T_{max}) in each case is approximately one hour.

The pharmacokinetic results for a study, in which amoxicillin/clavulanic acid (500 mg/125 mg) & amoxicillin/clavulanic acid (875 mg/125 mg) tablets was administered in the fasting state to groups of healthy volunteers are presented below.

Drug Administration	**Mean Pharmacokinetic Parameters**				
		C_{max} (Mcg/ml)	T_{max} (Hours)	$AUC_{(0-24h)}$ (h.mg/L)	$T_{1/2}$ (Hours)
Amoxicillin	Amox dose				
Amoxicillin and Clavulanic acid 500/125 mg	500 mg	11.64 ± 2.78	1.50 (1.0 – 2.0)	53.52 ± 12.31	1.19 ± 0.21

Drug Administration	**Mean Pharmacokinetic Parameters**				
		C_{max} (Mcg/ml)	T_{max} (Hours)	$AUC_{(0-24h)}$ (h.mg/L)	$T_{1/2}$ (0-6Hours%)
Clavulanic acid	CVA dose				
Amoxicillin and Clavulanic acid 500/125 mg	125 mg	2.18 ± 0.99	1.25 (1.0 – 2.0)	10.16 ± 3.04	0.96 ± 0.12

Distribution: About 25% of total plasma clavulanic acid and 18% of total plasma amoxicillin is bound to protein. The apparent volume of distribution is around 0.3-0.4 l/kg for amoxicillin and around 0.2 l/kg for clavulanic acid.

Following intravenous administration, both amoxicillin and clavulanic acid have been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus.

Amoxicillin does not adequately distribute into the cerebrospinal fluid.

From animal studies there is no evidence for significant tissue retention of drug-derived material for either component. Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanic acid can also be detected in breast milk.

Both amoxicillin and clavulanic acid have been shown to cross the placental barrier.

Biotransformation

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

Elimination: The major route of elimination for amoxicillin is via the kidney, whereas for clavulanic acid it is by both renal and non-renal mechanisms.

Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/h in healthy subjects. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of single Augmentin 250 mg/125 mg or 500 mg/125 mg tablets. Various studies have found the urinary excretion to be 50-85% for amoxicillin and between 27-60% for clavulanic acid over a 24 hour period. In the case of clavulanic acid, the largest amount of drug is excreted during the first 2 hours after administration.

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

Age

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

Gender

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

Renal impairment

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

Hepatic impairment

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

1.3.1.7.3 Preclinical safety data

TOXICOLOGICAL DATA

Amoxicillin

Amoxicillin has no mutagenic potential, as confirmed by extensive high-dose experimentation on rats and mice. Studies in rats and mice given up to 10 times the human dose together with clavulanic acid, did not demonstrate any adverse effects in the fetus.

Acute toxicity was investigated in mice, rats and dogs and the LD_{50} by the oral, intramuscular and intravenous routes was found to be in excess of 500 $mg.kg^{-1}$. At this concentration there were no signs of toxic effect regardless of the route of administration.

Rats and dogs were given repeated daily doses of 200, 500 and 2000 $mg.kg^{-1}$ for a period of 26 weeks. Observations were made of clinical condition, body weight, food and intake, behavior, hematology and clinical chemistry.

Clavulanate Potassium

Extensive testing in laboratory animals and human volunteers has not demonstrated serious toxic effects other than gastrointestinal disturbances, but insufficient data are available to be certain about the absence of any teratogenic effect. The administration of amoxicillin and clavulanic acid to rats and mice at 10 times the usual human dose had no adverse fetal effects.

1.3.1.8 PHARMACEUTICAL PARTICULARS

1.3.1.8.1 None

1.3.1.8.2 Incompatibilities: Not applicable.

1.3.1.8.3 Shelf life: Two years.

1.3.1.8.4 Special precautions for storage

Store below 30°C. Protected from light.

1.3.1.8.5 Nature and contents of container

Available as tablets of 02 x 07 blister in a carton with insert.

1.3.1.8.6 Special precautions for disposal and other Special handling

For the treatment of children and infants, the 24-tablets pack should be prescribed. The prescriber and pharmacist should instruct the parent or care giver on the posology for their child and that a variable number of tablets (depending on the child's body weight) will be requested for the full treatment. Therefore, the whole pack may not be used. After successful treatment the remaining tablets should be discarded or returned to the pharmacist.

1.3.1.9 Marketed by:

GREENLIFE PHARMACEUTICAL LIMITED
No.2 Bank lane. Off town Planning Way,
Ilupeju, Lagos - Nigeria

1.3.1.10 Manufactured by:

THEON PHARMACEUTICALS LTD.
Vill. Saini Majra, Nalagarh,
Distt. Solan, (H.P.)-174101, INDIA