KETACLAV 625
(Amoxicillin and Clavulanate Potassium Tablets BP)

1. NAME OF THE MEDICINAL PRODUCT

KETACLAV 625 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Amoxicillin Trihydrate BP	
Equivalent to Amoxicillin	: 500 mg.
Diluted Potassium Clavulanate BP	
Equivalent to Clavulanic Acid	: 125 mg.
Excipients	: Q.S.
Colour	: Titanium Dioxide BP

3. PHARMACEUTICAL FORM

Tablets
For oral administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

KETACLAV 625 is indicated for the treatment of the following infections in adults and children:
• Acute bacterial sinusitis
• Acute otitis media
• Acute exacerbations of chronic bronchitis
• 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

Adults and children ≥ 40 kg
One 500 mg/125 mg dose taken three times a day.
Children < 40 kg
20 mg/5 mg/kg/day to 60 mg/15 mg/kg/day given in three divided doses.
Elderly
No dose adjustment is considered necessary.

Renal impairment

Dose adjustments are based on the maximum recommended level of amoxicillin.
No adjustment in dose is required in patients with creatinine clearance (CrCl) greater than 30 ml/min.

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. 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 .
Transient hepatitis and cholestatic jaundice has been reported, hence, KETACLAV 625 should be used with caution in patients with evidence of hepatic dysfunction.
Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe reactions when treated with cephalosporins.
Allergic reactions may occur, usually manifesting as pruritic skin rash, an erythematous skin reaction, urticaria, angiodema, anaphylaxis or eosinophilia - Coomb's test may become positive. In this event, withdrawal of KETACLAV 625 and the administration of antihistamine will suffice in most cases. Should a serious anaphylactic reaction occur, KETACLAV 625 should be discontinued and the patient treated with the usual agents: adrenalin, corticosteroids and antihistamines.
Treatment with KETACLAV 625 may give rise to a maculopapular rash during therapy or within a few days after completion. The incidence of maculopapular rash is especially high in patients suffering from infectious mononucleosis and hence should be avoided.
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.

4.5 Interaction with other medicinal products and other forms of interaction

Oral anticoagulants

Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are cases of increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalised

ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary

Methotrexate

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. The change in pre-dose level may not accurately represent changes in overall MPA exposure.

Therefore, a change in the dose of mycophenolate mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment

4.6 Pregnancy and lactation

Amoxicillin is excreted into human milk in small amounts and is considered compatible with breast-feeding. Clavulanate has not been detected in human milk. Adverse effects in the nursing infant are unlikely. The manufacturer recommends caution when amoxicillin-clavulanate is administered to a nursing woman.

Amoxicillin and clavulanic acid is acceptable to use during breastfeeding. Limited information indicates that serious reactions in infants are very uncommon during the use of amoxicillin-clavulanic acid during nursing, with restlessness, diarrhea and rash occurring occasionally. If amoxicillin-clavulanic acid is required by the mother, it is not a reason to discontinue breastfeeding. Monitor the infant for these reactions during nursing.

4.7 Effects on the ability to drive and use machines

Do not drive vehicle and also do not operate machinery.

4.8 Undesirable effects

Amoxicillin

Sensitivity reactions are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever or urticaria. The hypersensitivity reactions reported are erythematous maculopapular rashes, urticaria, fever and joint pains. Anaphylactic shock may occur.

Gastrointestinal

Nausea, heartburn, vomiting and diarrhoea. Pseudomembranous colitis has been reported.

Liver

Hepatotoxicity, hepatitis, cholestatic jaundice may occur. A moderate rise in serum glutamic oxalacetic transaminase (SGOT) has been noted, but the significance of this finding is unknown.

Hemic and Lymphatic Systems
Anaemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and granulocytopenia have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.
Central Nervous System
Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioural changes, and/or dizziness have also been reported. Depression, seizures, or hallucinations.

Clavulanic acid:
Gastro-intestinal: Nausea and diarrhoea
Liver: Cholestatic jaundice and hepatitis

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 PARTICULARS

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.

5.2 Pharmacokinetic properties

The pharmacokinetics of amoxicillin and clavulanic acid are closely allied and neither are adversely affected by the presence of food in the stomach, and are stable in the presence of gastric acid. The oral bioavailability of amoxicillin and potassium clavulante is approximately 90% and 75% respectively.
Peak serum levels of both occur about 1-2 hour after oral administration. Clavulanic acid has about the same plasma elimination half-life (1 hour) as that of amoxicillin (1,3 hours). KETACLAV 625 is eliminated primarily unchanged through the renal route (glomerular filtration and tubular secretion). Approximately 50-78% of amoxicillin and 25-40% of clavulanic acid are excreted unchanged in urine within the first 6 hrs. after administration.

5.3 Preclinical Safety

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Microcrystalline Cellulose	BP
Croscarmellose Sodium	BP
Colloidal anhydrous silica	BP
Sodium Starch Glycolate	BP
Magnesium Stearate	BP
Silicon Dioxide	USP
Sodium Lauryl Sulphate	BP
Ethyl Cellulose	BP
Diethyl Phthalate	BP
Purified Talc	BP
Isopropyl Alcohol	BP
Dichloromethane	BP
Hypromellose	BP
Titanium Dioxide	BP

6.2 Incompatibilities

NA

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30°C. Protect from light, heat & moisture.
KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

1 x 10 Alu-Alu Blister pack in a printed carton along with package insert.

6.6 Special precautions for disposal and other handling

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.

7. MARKETING AUTHORISATION HOLDER

Saga LABORATORIES
Ahmedabad
Gujarat, India.
E-mail: info@sagalabs.com
URL: www.sagalabs.com

8. MARKETING AUTHORISATION NUMBER(S)

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