

## CLAVAMOX

AMOXICILLIN AND CLAVULANATE POTASSIUM TABLETS USP  
AMOXICILLIN & POTASSIUM CLAVULANATE ORAL SUSPENSION BP  
TABLET COMPOSITION : Each film coated tablet contains:

SUSPENSION COMPOSITION : Each 5ml of reconstituted suspension contains:

### PHARMACODYNAMIC PROPERTIES

Mode 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 peptidoglycal 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 of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a beta-lactam structurally related to penicillin. 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 clvulanic 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.

### 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 on 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 time to the peak plasma concentration ( $T_{max}$ ) in each case is approximately one hour. Amoxicillin and clavulanic acid serum concentrate 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 0.3-0.4 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 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 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.

**INDICATIONS:** Amoxicillin and Clavulanate Potassium tablets are indicated for the treatment of the following infections in adults and children

**Lower Respiratory Infections:** Caused by B-lactamase-producing strains of *H. influenzae* and *M. catarrhalis*

**Upper Respiratory tract infection e.g., Otitis Media:** Caused by B-lactamase-producing strains of *H. influenzae* and *M. catarrhalis*.

**Sinusitis:** Caused by B-lactamase-producing strains of *H. influenzae* and *M. catarrhalis*

Skin and Skin Structure Infections: Caused by B-lactamase-producing strains of *S. aureus*, *E. coli* & *Klebsiella* spp.

Urinary Tract Infections: Caused by B-lactamase-producing strains of *E. coli* & *Klebsiella* spp., and *Enterobacter* spp.

Bone and Joint Infection e.g., osteomyelitis

Dosage & Administration:

The dose of CLAVAMOX 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.

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.

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

If it is considered that a higher daily dose of amoxicillin is required, it is recommended that another preparation of CLAVAMOX 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 with CLAVAMOX tablets, suspension or pediatric sachets.

The table below presents the received dose (mg/kg body weight) in children weighing 25 kg to 40 kg upon administering a single 500/125 mg tablet.

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.

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

Method of administration: CLAVAMOX is for oral use. Administer at the start of a meal to minimise potential gastrointestinal intolerance and optimise absorption of amoxicillin/clavulanic acid.

**CONTRAINDICATION:** In patients with a history of hypersensitivity to beta-lactams, e.g. penicillins and cephalosporins. Safety in pregnancy has not been established. There is limited information on the use of Amoxicillin and Clavulanate Potassium in human pregnancy. Use should be avoided in pregnancy unless considered essential by the physician. Amoxicillin and

Clavulanate Potassium is contra-indicated in patients with a previous history of Amoxicillin and Clavulanate Potassium associated jaundice/hepatic dysfunction.

**WARNING AND PRECAUTIONS:** 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 penicillin. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity, who have experienced severe reactions when treated with cephalosporins. Before initiating therapy with any penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens, if an allergic reaction occurs, amoxicillin and clavulanate potassium should be discontinued and the appropriate therapy instituted: adrenaline, corticosteroids and antihistamines.

CLAVAMOX 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.

Transient hepatitis and cholestatic jaundice has been reported. CLAVAMOX should be used with caution in patients with evidence of hepatic dysfunction. In patients with renal impairment, dosage should be adjusted according to the degree of impairment. CLAVAMOX should not be used in patients with a glomerular filtration rate of less than 30 ml/minute. Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

**DRUG INTERACTIONS:** Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Its use may result in increased and prolonged blood levels of amoxicillin but does not delay renal excretion of the clavulanic acid.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. There are no data on the concomitant use of CLAVAMOX and allopurinol. As with other broad spectrum antibiotics, CLAVAMOX may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives. In the literature there are rare cases of increased international normalized ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalized ratio should be carefully monitored with the addition or withdrawal of CLAVAMOX.

**PREGNANCY AND LACTATION:** Reproduction studies in animals (mice and rats) with orally and parenterally administered CLAVAMOX have shown no teratogenic effect. In a single study in woman with preterm, premature rupture of the foetal membrane (pPROM), it was reported that prophylactic treatment with CLAVAMOX may be associated with an increased risk of necrotizing enterocolitis in neonates. As with all medicines, use should be avoided in pregnancy, especially during the first trimester, unless considered essential by the physician. CLAVAMOX may be administered during the period of lactation. With the exception of the risk of sensitisation, associated with the excretion of trace quantities in breast milk, there are no detrimental effects for the infant.

**Effect on Ability to Drive and Use Machines:** Adverse effects on the ability to drive or operate machinery have not been observed. **Adverse Reactions:** Data from large clinical trials were used to determine the frequency of very common to rare 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.

**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 Warning and Precautions ). CLAVAMOX can be removed from the circulations by hemolysis

**INCOMPATIBILITIES :** None known.

**SHELF LIFE:** The expiry date is indicated on the packaging.

**SPECIAL PRECAUTIONS FOR STORAGE:** CLAVAMOX oral presentations should be stored in a dry place 25°C or below. Once reconstituted, CLAVAMOX suspension must be stored in a refrigerator ( but not frozen) and used within 7 days.

**PRESENTATION:** Tablet Pack Size & Pack Style ( 2 x 7 / Alu-Alu )- 7 Tablets packed in one Alu-Alu Blister. Such 2 Alu-Alu Blisters packed in unit printed duplex board carton along with its package insert. Such carton are packed in export worthy shippers. These shippers are sealed with BOPP Tape.

Suspension - 100 ml: 100 ml Clear glass bottle with PP Cap and measuring cup in a unit printed duplex board carton along with its Package Insert.

**STORAGE:** Must be stored in a dry place below 25°C