Amclamed

Amoxicillin and Clavulanic Acid

Qualitative and quantitative composition:
Each film coated tablet contains: Amoxicillin Trihydrate USP Eq. to Amoxicillin 500mg and Diluted Potassium Clavulanate BP Eq. to Clavulanic Acid 125mg
Each 5 ml of reconstituted suspension contains: Amoxicillin Trihydrate BP Eq. to Amoxicillin 200mg and Diluted Potassium Clavulanate BP Eq. to Clavulanic Acid 28.5mg
Pharmaceutical form: Tablet and Oral powder for suspension
Pharmacology
Pharmacotherapeutics Group: Combination of penicillins including beta-lactamase inhibitors,
ATC Code: J01CR02.
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 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 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.
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 approximately70% 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 fluid, 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/hr in healthy subjects. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted
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 proportionality 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 β-lactamase-producing strains of H. influenzae and M. catarrhalis
- **Upper Respiratory tract infection** e.g., Otitis Media: Caused by β-lactamase-producing strains of H.influenzae and M. catarrhalis.

Sinusitis: Caused by β-lactamase-producing strains of H. influenza and M. catarrhalis
Skin and Skin Structure Infections: Caused byβ-lactamase-producing strains of S. aureus, E. coli & Klebsiella spp.
Urinary Tract Infections: Caused by β-lactamase-producing strains of E. coli & Klebsiella spp., and Enterobacter spp.
Bone and Joint Infection e.g., osteomyelitis

Dosage & Administration:
The dose of AMCLAMED 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.

		Weight	Dosage
Amclamed	Adults & Children	More than 40kg	One 500 mg/125mg dose taken three times a day.i.e total daily dose of 1500mg Amoxicillin/375mg Clavulanic acid
Amclamed	Children	Less than 40kg	20mg/5 mg/kg/day to 60mg / 15mg/ kg/day given in three divided doses i.e. the maximum daily dose of 2400mg Amoxicillin / 600mg Clavulanic acid

The use of alternative presentation of AMCLAMED (e.g., those that provide higher doses of amoxicillin and/or different ration of amoxicillin to clavulanic acid) should be considered as necessary.
If it is considered that higher daily dose of amoxicillin is required, it is recommended that another preparation of AMCLAMED 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 infection (e.g. osteomyelitis) require longer periods of treatment with AMCLAMED tablets, suspension of paediatric sachets.
The table below presents the received dose (mg/kg body weight) in children weighing 25kg to 40kg upon administering a single 500/125mg tablet.

Body Wight (Kg)	40	35	30	25	Single dose recommended [mg/kg body weight] (see above)
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		
	Age	Weight	
AMCLAMED Suspension & Paediatric Sachets	6 Years or below	Less than 25 kg	
AMCLAMED 4:1 formulations higher than 40 mg/10 mg/kg per day	Under 2 Years	Higher than 40	No clinical data found.

Elderly No dose adjustment is considered necessary.
Renal impairment Dose adjustment 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.
Adults and children ≥ 40kg

Cr Cl: 10-30 ml/min	500 mg/125 mg twice daily
Cr Cl<10 ml/min	500 mg/125 mg once daily
Haemodialysis	500mg/125mg every 24 hours, plus 500 mg/125 mg during dialysis, to be repeated at the end of dialysis (as serum concentrations of both Amoxicillin and Clavulanic acid are decreased)
Cr Cl: 10-30 ml/min	15 mg/3.75 mg/kg twice daily (maximum 500 mg/125 mg twice daily).
Cr Cl<10 ml/min	15 mg/3.75 mg/kg as a single daily dose (maximum 500 mg/125 mg).
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.
Method of administration: AMCLAMED is for oral use. Administer at the start of a meal to minimize potential gastrointestinal intolerance and optimize 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) reaction 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 reaction 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.
AMCLAMED 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. AMCLAMED 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. AMCLAMED 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 AMCLAMED and allopurinol. As with other broad spectrum antibiotics, AMCLAMED 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 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 Amclamed
Pregnancy and Lactation:
Reproduction studies in animals (mice and rats) with orally and parenterally administered AMCLAMED have shown no teratogenic effect. In a single study in woman with preterm, premature rupture of the foetal membrane it was reported that prophylactic treatment with AMCLAMED 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. AMCLAMED 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 requencies 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.

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 haemolytic anaemia.Prolongation of bleeding time and prothrombin time Immune system disorders.
Very rare	Angioneurotic oedema, 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 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-lactam class antibiotics, but significance of these findings is unknown.
Very rare	Hepatitis and cholestatic janudice.

Skin and subcutaneous tissue disorders

Uncommon	Skin rash, pruritus, urticaria
Rare	Erythema multiforme
Very rare	Stevens-Johnson 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)

Overdose:
Gastrointestinal symptoms and disturbance of the fluid and electrolyte imbalances 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). AMCLAMED can be removed from the circulations by hematolysis.
Incompatibilities: None known.
Shelf Life: The expiry date is indicated on the packaging.
Special Precautions for Storage: AMCLAMED oral presentations should be Stored below 30°C in a dry & dark place. Once reconstituted, AMCLAMED suspension must be stored in a refrigerator 2-8°C (but not frozen) and used within 7 days.
Nature and contents of container:
Tablet Pack Size & Pack Style (1 x 10 / Alu-Alu)-Tablets packed in Alu-Alu Blister. Such 1 Blister 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: 70 ml Transparent Glass Bottle with PP Cap and measuring cup in a unit printed duplex board carton along with its Package Insert.
Storage: Stored below 30°C in a dry & dark place. Keep the medicine out of reach of children.
Legal category:
Prescription only medicine, (POM)

Manufactured for:
Dawa Limited
Plot No. 7879/8, Baba Dogo Road, Ruaraka.
P. O. Box 16633 – 00620, Nairobi, Kenya

Manufactured by:
Medicef Pharma, Plot No. 28, 29 & 48,
Phase-1, EPIP, Jharmajri, Baddi, District Solan 173205 (H.P.), India.

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