Amoxi-Clav 312.5mg/5ml

(Amoxicillin + Clavulanic acid)

Each 5mL of the reconstituted suspension contains:
Amoxicillin Trihydrate BP
Eq. to Amoxicillin ..... 250 mg
Diluted Potassium Clavulanate BP
Eq. to Clavulanic Acid ..... 62.5 mg
Excipients ..... q.s.

PHARMACEUTICAL FORM
Powder for Oral suspension: White coloured powder gives a off white coloured suspension after reconstitution.

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 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 dose 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 1/kg for Amoxicillin and around 0.2 1/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 party 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 Liters/hour 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 hour after administration of single 125 mg/31.25mg suspension. 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 those 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/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 suspension 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 Infections e.g., osteomyelitis

Dosage & Administration:
Infections due to beta-lactamase-producing strains (where amoxicillin alone not appropriate) including respiratory-tract infections, bone and joint infections, genito-urinary and abdominal infections, cellulitis,animal bites (doses for 125/31.25mg suspension)
Acute sinusites (doses for 125/31.25 suspension)
BY MOUTH USING ORAL SUSPENTION
1. The Child 1–11 months: 0.25 mL/kilogram 3 times a day for 5 days
2. Child 1–5 years: 5 mL 3 times a day for 5 days, alternatively 0.25 mL/kilogram 3 times a day for 5 days

The dose of **Amoxi-Clav156.25mg/5ml (Amoxicillin + Clavulanic acid) E** that is selected to treat an individual infection should be taken 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

Renal impairment : Risk of crystalluria with high doses (particularly during parenteral therapy).

1. With oral use in adults 125mg/31.25mg suspension: if eGFR 10–30 mL/minute/1.73m2, one 125mg/31.25mg strength suspension every 12 hours; if eGFR less than 10 mL/minute/1.73m2, one 125mg/31.25 strength suspension every 24 hours.

2. With oral use in children amoxicillin & clavulanic acid 125mg/31.25mg suspension, use normal dose every 12 hours if estimated glomerular filtration rate 10–30 mL/minute/1.73m2. Use the normal dose recommended for mild or moderate infections every 12 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73m2. amoxicillin & clavulanic acid 125mg/31.25mg suspension: avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73m2.

Hepatic impairment: Dose with caution and monitor hepatic function at regular intervals.
Method of administration: Amoxi-Clav156.25mg/5ml (Amoxicillin + Clavulanic acid) is for oral use. Administer at the start of a meal to minimise potential gastrointestinal intolerance and optimise absorption of Amoxicillin/Clavulanic Acid.

Directions for reconstitution.

Shake the bottle to loose powder. Boil the water and allow it to cool. Slowly add cooled water up to the mark on the bottle. Shake vigorously. Adjust the volume up to the mark by adding more water, If necessary . This makes 100ml of the suspension.

CONTRAINDICATIONS: In patients with a history to 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 penicillin associated jaundice/hepatic dysfunction.

WARNING AND PRECAUTIONS: Serious and occasionally fatal hypersensitivity (Anaphylactic) reaction have been reported in patients on Amoxicillin & Potassium Clavulanate 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 to be instituted such as : adrenaline, corticosteroids and antihistamines.

Amoxi-Clav 156.25mg/5ml (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. Transient hepatitis and cholestatic jaundice has been reported. **Amoxi-Clav 156.25mg/5ml (Amoxicillin + Clavulanic acid)** 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. **Amoxi-Clav 156.25mg/5ml (Amoxicillin + Clavulanic acid)** 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: Probenecid decreases the renal tubular secretion of Amoxicillin. Concurrent use with **Amoxi-Clav156.25mg/5ml (Amoxicillin + Clavulanic acid)** 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 **Amoxi-Clav 156.25mg/5ml (Amoxicillin + Clavulanic acid)** and Allopurinol administered concurrently.
In common, with other broad-spectrum antibiotics, **Amoxi-Clav 156.25mg/5ml (Amoxicillin + Clavulanic acid)** may reduce the efficacy of oral contraceptives.

PREGNANCY AND LACTATION: Reproduction studies in animals (mice and rats) with orally and parenterally administered **Amoxi-Clav 156.25mg/5ml (Amoxicillin + Clavulanic acid)** 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 **Amoxi-Clav 156.25mg/5ml (Amoxicillin + Clavulanic acid)** 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. **Amoxi-Clav 156.25mg/5ml (Amoxicillin + Clavulanic acid)** 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 in infants.

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.

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 Amoxi-Clav156.25mg/5ml (Amoxicillin + Clavulanic acid) 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 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)

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). **Amoxi-Clav 312.5mg/5ml (Amoxicillin + Clavulanic acid)** 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:
Powder for Oral suspension: '
Do not store above 25°C. Keep the container tightly closed in order to protect from moisture. Store in the original container.
Once reconstituted, **Amoxi-Clav 312.5mg/5ml (Amoxicillin + Clavulanic acid)** Suspension must be stored in refrigerator (2°C to 8°C) and used within 7days (Do not freeze).

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

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