AMCLAV™
[Co-amoxiclav]

AMCLAV-DS™
[Co-amoxiclav]

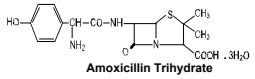
AMCLAV-PLUS™
[Co-amoxiclav]

ایمکلیو
ایمکلیو-ڈی ایس
ایمکلیو-پلس

375mg, 625mg, 1g Tablets
156.25mg/5mL, 312.5mg/5mL, 457mg/5mL Suspension,
62.5mg/mL Drops

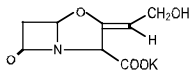
DESCRIPTION

AMCLAV (Co-amoxiclav) is an oral antibacterial combination consisting of the semisynthetic antibiotic amoxicillin and the β-lactamase inhibitor, Clavulanate potassium (the potassium salt of Clavulanic acid). Amoxicillin is an analog of ampicillin, derived from the basic penicillin nucleus, 6-aminopenicillanic acid. The amoxicillin molecular formula is $C_{16}H_{19}N_3O_5S{\cdot}3H_2O$. Chemically, amoxicillin is (2S,5R,6R)-6-[(R)(-)-2-Amino-2-(p-hydroxyphenyl) acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2carboxylic acid trihydrate and may be represented structurally as:



Amoxicillin Trihydrate

Clavulanic acid is produced by the fermentation of Streptomyces clavuligerus. It is a β-lactam structurally related to the penicillins and possesses the ability to inactivate a wide variety of β-lactamases by blocking the active sites of these enzymes. Clavulanic acid is particularly active against the clinicallyimportant plasmid-mediated β-lactamases frequently responsible for transferred drug resistance to penicillins and cephalosporins. The clavulanate potassium molecular formula is $C_8H_8KNO_5$. Chemically, Clavulanate potassium is potassium (Z) (2R,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]-heptane-2-carboxylate, and may be represented structurally as:



Clavulanate Potassium

QUALITATIVE AND QUANTITATIVE COMPOSITION

AMCLAV (Co-amoxiclav) is available for oral administration as:

1. AMCLAV Tablets 375mg
   Each film-coated tablet contains:
   Amoxicillin USP…250mg
   (as amoxicillin trihydrate)
   Clavulanic acid…125mg
   (as clavulanate potassium USP)

2. AMCLAV Tablets 625mg
   Each film-coated tablet contains:
   Amoxicillin USP…500mg
   (as amoxicillin trihydrate)
   Clavulanic acid…125mg
   (as clavulanate potassium USP)

3. AMCLAV Tablets 1g
   Each film-coated tablet contains:
   Amoxicillin USP…875mg
   (as amoxicillin trihydrate)
   Clavulanic acid…125mg
   (as clavulanate potassium USP)

4. AMCLAV Suspension 156.25mg/5mL
   Each reconstituted 5mL contains:
   Amoxicillin USP… 125mg
   (as amoxicillin trihydrate)
   Clavulanic acid…31.25mg
   (as clavulanate potassium USP)

5. AMCLAV-DS Suspension 312.5mg/5mL
   Each reconstituted 5mL contains:
   Amoxicillin USP… 250mg
   (as amoxicillin trihydrate)
   Clavulanic acid…62.5mg
   (as clavulanate potassium USP)

6. AMCLAV-PLUS Suspension 457mg/5mL
   Each reconstituted 5mL contains:
   Amoxicillin USP… 400mg
   (as amoxicillin trihydrate)
   Clavulanic acid…57mg
   (as clavulanate potassium USP)

7. AMCLAV Drops 62.5mg/mL
   Each reconstituted mL contains:
   Amoxicillin USP…50mg
   (as amoxicillin trihydrate)
   Clavulanic acid…12.5mg
   (as clavulanate potassium USP)

CLINICAL PHARMACOLOGY

Mechanism of Action

Amoxicillin is a semisynthetic antibiotic with a broad spectrum of antibacterial activity against many gram-positive andgram-negativemicroorganisms. Amoxicillin is, however, susceptible to degradation by β-lactamases, and therefore, the spectrum of activity does not include organisms which produce these enzymes.

Clavulanic acid is a β-lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range of β-lactamase enzymes commonly found in microorganisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid-mediated β-lactamases frequently responsible for transferred drug resistance. It isgenerally less effective against chromosomally-mediated type 1 β-lactamases.

The formulation of amoxicillin and clavulanic acid in amoxicillin/clavulanate potassium protects amoxicillin from degradation by β-lactamase enzymes and effectively extends the antibiotic spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin, other penicillins and cephalosporins. Thus, amoxicillin/clavulanate potassium possesses the distinctive properties of a broad-spectrum antibiotic and a β-lactamase inhibitor.

Microbiology

Co-amoxiclav is bactericidal to a wide range of organisms including:

Gram-Positive aerobes:
*Bacillus anthracis
Corynebacterium species
*Enterococcus faecalis
*Enterococcus faecium
Listeria monocytogenes
Nocardia asteroides
*Staphylococcus aureus
*Coagulase negative staphylococci (including *Staphylococcus epidermidis)
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes
Streptococcus species
Streptococcus viridians

Gram-Negative aerobes:
Bordetella pertussis
Brucella species
*Escherichia coli
Gardnerella vaginalis
*Haemophilus influenzae
Helicobacter pylori
*Klebsiella species
Legionella species
*Moraxella catarrhalis (Branhamella catarrhalis)
*Neisseria gonorrhoeae
*Neisseria meningitidis
Pasteurella multocida
*Proteus mirabilis
*Proteus vulgaris
*Salmonella species
*Shigella species
Vibrio cholerae
*Yersinia enterocolitica

Gram-Positive anaerobes:
Clostridium species
Peptococcus species
Peptostreptococcus species

Gram-Negative anaerobes:
*Bacteroides species (including Bacteroides fragilis)
*Fusobacterium species
Others:
Borrelia burgdorferi
Chlamydiae
Leptospira icterohaemorrhagiae
*Some members of these species of bacteria produce beta-lactamase, rendering them insensitive to amoxicillin

Pharmacokinetics

Absorption / Distribution:

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/clavulanate potassium is optimisedwhen taken at the start of a meal. Neither amoxicillin nor clavulanic acid is highly protein bound.

Metabolism / Excretion:

Clavulanic acid is extensively metabolised to 2,5-dihydro-4-(2-hydroxyethyl)-5-oxo-1H-pyrrole-3-carboxylic acid and 1-amino-4-hydroxy-butane-2-one.

The major route of elimination for amoxicillin is via the kidneys. It is partly excreted in the urine as penicilloic acid in quantities equivalent to 10-25% of the initial dose, whereas for clavulanate it is by both renal andnon-renal mechanisms. Its metabolite iseliminated inurine and feces as carbon dioxide in expired air. Approximately 60-70% of the amoxicillin and approximately 40-65% of the clavulanic acid are excreted unchanged in urine during the first 6 hours after administration of amoxicillin/clavulanate potassium tablets.

THERAPEUTIC INDICATIONS

AMCLAV (Co-amoxiclav) is indicated for the short term treatment of bacterial infections such as:
- Upper Respiratory Tract Infections (including ENT) e.g., tonsillitis, sinusitis, otitis media.
- Lower Respiratory Tract Infections e.g., acute exacerbations of chronic bronchitis, lobar and broncho-pneumonia.
- Genito-urinary Tract Infections e.g., cystitis, urethritis, pyelonephritis, female genital infections.
- Skin and Soft Tissue Infections e.g., boils, abscesses, cellulitis and wound infection.
- Bone and Joint Infections e.g., osteomyelitis.
- Other Infections e.g., septic abortion, puerperal sepsis, intra-abdominal sepsis, septicaemia, peritonitis, post-surgical infections.
  AMCLAV (Co-amoxiclav) is also indicated for prophylaxis against infection which may be associated with major surgical procedures such as gastro-intestinal, pelvic, head and neck, cardiac, renal, joint replacement and biliary tract surgery.

Mixed infections caused by amoxicillin susceptible organism in conjunction with AMCLAV (Co-amoxiclav) -susceptible beta-lactamase-producing organisms may therefore be treated by AMCLAV (Co-amoxiclav).

DOSAGE AND ADMINISTRATION

Dosage depends on the age, weight and renal function of the patient and severity of the infection. AMCLAV (Co-amoxiclav) should be taken at the start of a meal to enhance the absorption of amoxicillin and to minimize the potential for gastrointestinal intolerance. Two AMCLAV 375mg tablets should not be substituted for one AMCLAV 625mg tablet since they are not equivalent.

Adults

Mild to moderate infections
1 AMCLAV 375mg tablet taken three times daily.
1 AMCLAV 625mg tablet taken two or three times daily.

1 AMCLAV 1g tablet taken twice daily.
Severe infections (Including chronic and recurrent urinary tract infections and those of the lower respiratory tract).
1 to 2 AMCLAV 625mg tablet given three times daily.
1 AMCLAV 1g tablet given two or three times daily.

Children up to 12 years
The usual recommended daily dosage is 25mg/kg/day in divided doses every eight hours.
Under 1 year:
25mg/kg/day (for example a 7.5kg child would require 2mL AMCLAV 156.25mg syrup three times daily)
1-6 Years (10-15kg):
5mL AMCLAV 156.25mg suspension three times a day.
Over 6 years (18-40kg):
5mL AMCLAV-DS 312.5mg suspension thee times a day or 5mL AMCLAV-PLUS 475mg suspension two times a day.

Children weighing 40kg and over should be dosed according to the adult recommendations.

The lower dose is recommended for infections such as skin and soft tissue and recurrent tonsillitis. The higher dose is recommended for infections such as otitis media, sinusitis, lower respiratory tract infections and urinary tract infections.

Infants
Every Eight hours in divided doses
AMCLAV 62.5mg/mL drops
Recommended dose
25 mg/kg/day
In serious infections dose may be doubled up to 50 mg/kg/day

AMCLAV (Co-amoxiclav) Drops should be administered using the supplied dropper. The dropper has markings which correspond to the required volume of the dose. The dose should be withdrawn to corresponding volume marked on the dropper. A similar dose should be administered once every eight hours. For information, the volumes of AMCLAV (Co-amoxiclav) Drops which correspond to the weight markings are shown below:

Weight (kg)	Volume (mL) of AMCLAV Drops	Weight (kg)	Volume (mL) of AMCLAV Drops
1	0.13	6	0.80
1.5	0.20	6.5	0.87
2	0.27	7	0.93
2.5	0.33	7.5	1.00
3	0.40	8	1.07
3.5	0.47	8.5	1.14
4	0.53	9	1.20
4.5	0.60	9.5	1.27
5	0.67	10	1.34
5.5	0.73		

Duration of therapy should be appropriate to the indication and should not be extended beyond 14 days without review.

Renal Insufficiency
Adults
Creatinine Clearance greater than 30mL/min
No adjustment necessary
Creatinine Clearance 10 to 30mL/min
1 tablet of AMCLAV 625mg taken twice daily or 1 to 2 tablets of AMCLAV 375mg, depending upon severity of infection, taken twice daily.
Creatinine Clearance less than 10mL/min
1 tablet of AMCLAV 625mg given once daily or 1 to 2 tablets of AMCLAV 375mg , depending upon severity of infection, taken once daily.

Children
Creatinine Clearance greater than 30mL/min
No adjustment necessary
Creatinine Clearance 10 to 30mL/min
15mg/3.75mg/kg taken twice daily.
Creatinine Clearance less than 10ml/min
15mg/3.75mg/kg taken as a single daily dose.

Infants
Creatinine Clearance greater than 30mL/min:
No adjustment necessary.
Creatinine Clearance 10 to 30mL/min:
The recommended dose mentioned in table above, given twice daily instead of three times per day*.
Creatinine Clearance less than 10mL/min:
The recommended dose mentioned in table above, given once daily instead of three times per day*.

*In more serious cases this dose may be doubled.

Hemodialysis
Adults
1 tablet of AMCLAV 625mg or 2 tablets of AMCLAV 375mg taken every 24 hours, plus one dose during dialysis, to be repeated at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased).
The AMCLAV 1g should only be used in patients with a creatinine clearance of more than 30mL/min.

Children
15mg/3.75mg/kg/day given as a single daily dose. Prior to haemodialysis one additional dose of 15mg/3.75mg/kg should be administered. In order to restore circulating drug levels, another dose of 15mg/3.75mg/kg should be administered after hemodialysis.

Hepatic Insufficiency
Caution should be taken while dosing and monitoring of hepatic function at regular interval is very necessary.

Direction for reconstitution:
Add a little amount of previously boiled and cooled water. Invert bottle and shake until powder is dispersed. Then add more water upto the mark on the label.
The reconstituted suspension can be used within 7 days when stored in refrigerator.

ADVERSE REACTIONS
Very Common: Diarrhea

Common: Mucocutaneous candidiasis, nausea, vomiting.
Nausea is more often associated with higher oral dosages. If gastrointestinal reactions are evident, they may be reduced by taking Co-amoxiclav at the start of the meal.

Uncommon: Dizziness, headache, Skin rash, pruritus, urticaria.

Rare: Reversible Leucopenia (including neutropenia) and thrombocytopenia, Erythema multiforme.

Very Rare: Reversible agranulocytosis and haemolytic anaemia. Prolongation of bleeding time and prothrombin time, Angioneurotic oedema, anaphylaxis, serum sickness-like syndrome, hypersensitivity vasculitis. Antibiotic associated colitis(including pseudomembranous colitis and hemorrhagic colitis). Superficial tooth discoloration which can be removed usually by brushing. Hepatitis and cholestatic jaundice usually associated with prolonged treatment predominantly in males and elderly. Steven-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative-dermatitis, acute generalised exanthemous pustulosis (AGEP). Interstitial nephritis and crystalluria.

CONTRAINDICATIONS
Co-amoxiclav is contraindicated in patients with;
- a history of hypersensitivity to beta-lactams, e.g., penicillins and cephalosporins.
- a previous history of amoxicillin-clavulanate-associated jaundice/hepatic dysfunction.

WARNINGS AND PRECAUTIONS
- Before initiating therapy with co-amoxiclav, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens.
- If an allergic reaction occurs, co-amoxiclav therapy should be discontinued and appropriate alternative therapy instituted. Serious anaphylactoid reactions require immediate emergency treatment with adrenaline. Oxygen, intravenous steroids and airway management, including intubation may also be required.
- Co-amoxiclav 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.
- Prolonged use may also occasionally result in overgrowth of non- susceptible organisms.
- In general co-amoxiclav is well tolerated and possesses the characteristic low toxicity of the penicillin group of antibiotics. Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy.
- Abnormal prolongation of prothrombin time (increased INR) has been reported rarely in patients receiving amoxicillin-clavulanate and oral anticoagulants. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.
- Co-amoxiclav should be used with caution in patients with evidence of hepatic dysfunction.
- In patients with renal insufficency, dosage should be adjusted according to the degree of impairment.
- In patients with reduced urine output crystalluria has been observed very rarely, predominantly with parenteral therapy. During administration of high doses of amoxicillin it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria.

Pregnancy
Co-amoxiclav should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
Co-amoxiclav may be administered during the period of lactation. With the exception of the risk of sensitization, associated with the excretion of trace quantities in breast milk, there are no detrimental effects for the breast-fed infant.

DRUG INTERACTIONS
- Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use with Co-amoxiclav may result in increased and prolonged blood levels of amoxicillin, but not of clavulanic acid.
- Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.
- In common with other antibiotics, Co-amoxiclav may affect the gut flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral contraceptives.

STORAGE
Store at 25°C (Excursions permitted between 15°C to 30°C).
Protect from sunlight & moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
1. AMCLAV (Co-amoxiclav) Tablets375mg are available in bottle of 6's.
2. AMCLAV (Co-amoxiclav) Tablets 625mg are available in bottle of 6s.
3. AMCLAV (Co-amoxiclav) Tablets 1g are available in bottle of 6's.
4. AMCLAV (Co-amoxiclav) Suspension 156.25mg/5mL is available in bottle of 60mL.
5. AMCLAV-DS (Co-amoxiclav) Suspension 312.5mg/5mL is available in bottle of 60mL.
6. AMCLAV-PLUS (Co-amoxiclav) Suspension 457mg/5mL is available in bottle of 70mL.
7. AMCLAV (Co-amoxiclav) Drops 62.5mg/mL is available in bottle of 20mL.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
CSH Pharmaceuticals (Pvt.) Ltd.
32-KM, Ferozepur Road, Lahore.

Manufactured for:
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www.getzpharma.com
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