Co-Amoxiclav

AmoClav®

228.5 mg/5 mL Powder for Suspension
457 mg/5 mL Powder for Suspension

ANTIBACTERIAL

FORMULATION

Co-amoxiclav (AmoClav®) 228.5 mg/5 mL suspension
After reconstitution, each 5 mL suspension contains:
Amoxicillin (as trihydrate),-- ..... 200 mg
Clavulanic acid (as potassium clavulanate),-- ..... 28.5 mg

Co-amoxiclav (AmoClav®) 457 mg/5 mL suspension
After reconstitution, each 5 mL suspension contains:
Amoxicillin (as trihydrate),-- ..... 400 mg
Clavulanic acid (as potassium clavulanate),-- ..... 57 mg

PRODUCT DESCRIPTIONS

Co-amoxiclav (AmoClav®) 228.5 mg/5 mL or 457 mg/5 mL is a white-cream colored, raspberry-flavored homogeneous powder for suspension.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Amoxicillin (an aminopenicillin antibiotic) and potassium clavulanate (a β-lactamase inhibitor) [Co-amoxiclav] is usually bactericidal in action. Concurrent administration of clavulanic acid does not alter the mechanism of action of amoxicillin. However, because clavulanic acid has a high affinity for and binds to certain β-lactamases that generally inactivate amoxicillin by hydrolyzing its β-lactam ring, concurrent administration of the drug with amoxicillin results in synergistic bactericidal effect which expands amoxicillin's spectrum of activity against many strains of β-lactamase-producing bacteria resistant to amoxicillin alone.

ANTIMICROBIAL SPECTRUM OF ACTIVITY

In vitro and clinical studies have demonstrated the susceptibility of the following microorganisms to Co-amoxiclav:

COMMONLY SUSCEPTIBLE SPECIES	
Aerobic Gram-positive Microorganisms	*Bacillus anthracis* *Enterococcus faecalis* *Listeria monocytogenes* *Nocardia asteroides* *Streptococcus pyogenes*†* *Streptococcus agalactiae*†* *Streptococcus spp. (other β-hemolytic)*†* *Staphylococcus aureus (methicillin susceptible)** *Staphylococcus saprophyticus (methicillin susceptible)* *Coagulase negative staphylococcus (methicillin susceptible)*
Aerobic Gram-negative Microorganisms	*Bordetella pertussis* *Haemophilus influenzae** *Haemophilus parainfluenzae* *Helicobacter pylori* *Moraxella catarrhalis** *Neisseria gonorrhoeae* *Pasteurella multocida* *Vibrio cholera*
Other Microorganisms	*Borrelia burgdorferi* *Leptospira ictterohaemorrhagiae* *Treponema pallidum*
Anaerobic Gram-positive Microorganisms	*Clostridium spp.* *Peptocostreptoccus niger* *Peptostreptococcus magnus* *Peptostreptococcus spp.*
Anaerobic Gram-negative Microorganisms	*Bacteroides fragilis* *Bacteroides spp.* *Capnocytophaga spp.* *Eikenella corrodens* *Fusobacterium nucleatum* *Fusobacterium spp.* *Porphyromonas spp.* *Prevotella spp.*

*where clinical efficacy of Co-amoxiclav has been demonstrated in clinical trials
†organisms that do not produce beta-lactamase. If an isolate is susceptible to amoxicillin, it can be considered susceptible to Co-amoxiclav.

SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM	
Aerobic Gram-positive Microorganisms	*Corynebacterium spp.* *Enterococcus faecium* *Streptococcus pneumonia *†* *Viridancs group streptococcus*
Aerobic Gram-negative Microorganisms	*Escherichia coli** *Klebsiella oxytoca* *Klebsiella pneumoniae** *Klebsiella spp.* *Proteus mirabilis* *Proteus vulgaris* *Proteus spp.* *Salmonella spp.* *Shigella spp.*

*where clinical efficacy of Co-amoxiclav has been demonstrated in clinical trials
†organisms that do not produce beta-lactamase. If an isolate is susceptible to amoxicillin, it can be considered susceptible to Co-amoxiclav.

INHERENTLY RESISTANT ORGANISMS	
Aerobic Gram-negative Microorganisms	*Acinetobacter spp.* *Citrobacter freundii* *Enterobacter spp.* *Hafnia alvei* *Legionella pneumophilia* *Morganella morganii* *Providencia spp.* *Pseudomonas spp.* *Serratia spp.* *Stenotrophomas maltophilia* *Yersinia enterolitica*
Other Microorganisms	*Chlamydia pneumoniae* *Chlamydia psittaci* *Chlamydia spp.* *Coxiella burnetti* *Mycoplasma spp.*

PHARMACOKINETICS

In a study in children 2 to 5 years old with urinary tract infections who received a single oral dose of 125 mg of amoxicillin and 31.75 mg of clavulanic acid suspension, the C_{max} of amoxicillin were 9.4, 9.7, and 6.5 mcg/mL and of clavulanic acid were 2.1, 4.4, and 2.5 mcg/mL at 30, 60, and 90 minutes, respectively, after the dose.

In a study in fasting children who received a single amoxicillin dose of 35 mg/kg given as Co-amoxiclav oral suspension, concentrations of amoxicillin and of clavulanic acid in middle ear effusions averaged 3 and 0.5 mcg/mL, respectively, 2 hours after the dose.

When a single 5 mL oral dose of Co-amoxiclav 457 mg/5 mL suspension was administered in healthy male and female subjects (fasted state), pharmacokinetic parameters reached were: C_{max} 5.789 mcg/mL, T_{max} 1.164 hours, $AUC_{0\text{-}t}$ 12.21 mcg/mL•hr and $AUC_{0\text{-}\infty}$ 12.855 mcg/mL•hr for amoxicillin, and C_{max} 1.379 mcg/mL, T_{max} 1.039 hours, $AUC_{0\text{-}t}$ 2.492 mcg/mL•hr and $AUC_{0\text{-}\infty}$ 2.727 mcg/mL•hr for clavulanic acid.

Therapeutic concentrations of both amoxicillin and clavulanic acid have been found in the gall bladder, abdominal tissue, skin, fat, and muscle tissues; the synovial and peritoneal fluids, bile and pus. Animal studies show no evidence that either component may accumulate in any organ.

Neither amoxicillin nor clavulanic acid is highly protein-bound; studies show that about 13% to 25% of total plasma drug concentration of each compound is protein-bound.

Both Co-amoxiclav components readily cross the placenta. Only small amounts of amoxicillin and clavulanic acid are distributed in human milk.

Serum concentrations of amoxicillin and clavulanic acid both decline in a biphasic manner and their $t_{1/2}$ are similar. Approximately 50 to 73% of amoxicillin and 25 to 45% of clavulanic acid are excreted unchanged in urine within 6 to 8 hours following oral administration of a single dose of Co-amoxiclav in adults with normal renal function.

In a study in children 2 to 15 years old, the elimination $t_{1/2}$ of amoxicillin and clavulanic acid averaged 1.2 and 0.8 hours, respectively.

INDICATIONS

For the treatment of the following infections caused by susceptible microorganisms:
- **Upper respiratory tract infections (including ENT infections):** Tonsillitis, sinusitis, otitis media
- **Lower respiratory tract infections:** Acute and chronic bronchitis, pneumonia, lung abscess
- **Genito-urinary tract and abdominal infections:** Cystitis, urethritis, pyelonephritis, female genital infections, septic abortion, pelvic or puerperal sepsis, intra-abdominal sepsis
- **Skin and skin structure infections:** Furuncle and abscess, cellulitis, wound infections
- **Bone and joint infections:** Osteomyelitis
- **Dental infection:** Dentoalveolar abscess
- **Other infections:** Septicemia, peritonitis, post-surgical infections
- Step down treatment for infections due to susceptible organisms, initially given antimicrobial therapy, particularly parenteral Co-amoxiclav.

DOSAGE AND ADMINISTRATION

- Administer Co-amoxiclav at the start of a meal to minimize potential gastrointestinal intolerance and to optimize absorption.
- Drink plenty of water to ensure proper state of hydration and adequate urinary output.
- Treatment should not exceed 14 days without first re-evaluating the patient.

Usual Oral Dosage in Children up to 12 years old:

Use the measuring spoon provided with the product.
Co-amoxiclav is dosed based on the amoxicillin component and is given in divided doses every 12 hours.
- Children below 1 year old: 30 mg/kg body weight/day
- For Mild to Moderate Infections: 25 mg/kg body weight/day
- For Severe Infections: 45 mg/kg body weight/day

Age	Weight	Mild to Moderate Infections		Severe Infections	
		Co-amoxiclav 228.5 mg per 5 mL	**Co-amoxiclav 457 mg per 5 mL**	**Co-amoxiclav 228.5 mg per 5 mL**	**Co-amoxiclav 457 mg per 5 mL**
Less than 1 year	Less than 10 kg	2.5 mL (1/2 teaspoonful)	-	2.5 mL (1/2 teaspoonful)	-
1 to 6 years	10 to 18 kg	2.5 to 5 mL (1/2 to 1 teaspoonful)	2.5 mL (1/2 teaspoonful)	5 to 10 mL (1 to 2 teaspoonsful)	2.5 to 5 mL (1/2 to 1 teaspoonful)
6 to 12 years	18 to 40 kg	5 to 10 mL (1 to 2 teaspoonsful)	2.5 to 5 mL (1/2 to 1 teaspoonful)	10 to 20 mL (2 to 4 teaspoonsful)	5 to 10 mL (1 to 2 teaspoonsful)

- Dose in children weighing over 40 kg and children over 12 years old is based on adult dosing recommendations.
- Or, as prescribed by a physician.

Dosage in Children up to 12 years old with Renal Impairment:

Creatinine Clearance	Recommended Oral Dose
>30 mL/min	No dosage adjustment necessary
10 to 30 mL/min	15 mg/kg body weight every 12 hours
<10 mL/min	15 mg/kg body weight once daily

- In the majority of cases, treatment with parenteral Co-amoxiclav, where available, may be preferred.

Dosage in Children up to 12 years old on Hemodialysis: 15 mg/kg body weight once daily. Patients should receive an additional dose of 15 mg/kg body weight both during and at the end of dialysis.

Dosage in Children up to 12 years old with Hepatic Impairment: Dose with caution and monitor hepatic function regularly.

DIRECTIONS FOR RECONSTITUTION

Co-amoxiclav Powder for Suspension	Volume of Distilled Water to be added	Directions
228.5 mg per 5 mL (70 mL)	58 mL	First tap the bottle several times to loosen the powder before reconstitution. Then add the required amount of distilled water in two portions and shake vigorously until all contents are evenly suspended.
457 mg per 5 mL (70 mL)	59 mL	
457 mg per 5 mL (35 mL)	29 mL	
Shake well before taking each dose. Once reconstituted, the suspension must be stored in a refrigerator (2°C to 8°C). Discard any unused portion after 7 days		

CONTRAINDICATIONS

- Known hypersensitivity to penicillin or any ingredient in this product
- History of severe immediate hypersensitivity reaction (e.g., anaphylaxis or Stevens-Johnson syndrome) to another β-lactam antibiotic (e.g. a cephalosphorin, carbapenem or monobactam)
- Patients with a previous history of cholestatic jaundice/hepatic impairment associated with Co-amoxiclav or penicillin
- Patients with glandular fever or lymphatic lymphoma should not be given Co-amoxiclav as the amoxicillin component is likely to cause a maculopapular rash
- Patients with infectious mononucleosis either suspected or confirmed

WARNINGS AND PRECAUTIONS

• ***Hypersensitivity Reactions:*** Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Careful inquiry should be made concerning previous hypersensitivity to penicillins, cephalosporins, or other drugs before initiating therapy with Co-amoxiclav. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be instituted.

• ***Clostridium difficile-associated disease (CDAD):*** This has been reported with the use of nearly all antibacterial agents, including Co-amoxiclav, and may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agents. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

• ***Hepatic Dysfunction:*** Hepatic dysfunction, including hepatitis and cholestatic jaundice has been associated with the use of Co-amoxiclav. Hepatic toxicity is usually reversible; however, deaths have been reported. Hepatic function should be monitored at regular intervals in patients with hepatic impairment.

• In patients with renal impairment, the dose of Co-amoxiclav should be adjusted based on the degree of impairment **[See Dosage and Administration]**.

• During administration of high doses of amoxicillin, it is recommended to maintain adequate fluid intake and urinary output in order to reduce the possibility of crystalluria associated with amoxicillin therapy.

• Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly with Co-amoxiclav since prolongation of prothrombin time has been reported rarely in patients receiving Co-amoxiclav.

• Although Co-amoxiclav has a low toxicity profile, the renal, hepatic, and hematopoietic status of patients undergoing prolonged treatment with the drug should be evaluated periodically.

• As with other antibacterial drugs, long term or repeated use may result in overgrowth of non-susceptible organisms, including fungi.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

The carcinogenic potential of Co-amoxiclav has not been evaluated in long-term animal studies.

The mutagenic potential of the drug has been investigated *in vitro* using Ames test, a human lymphocyte cytogenic assay, a yeast test and a mouse lymphoma forward mutation assay, and *in vivo* using mouse micronucleus tests and a dominant lethal test. Results were negative for all tests except for the *in vitro* mouse lymphoma assay where weak activity was found at very high, cytotoxic concentrations.

Oral doses of Co-amoxiclav up to 1,200 mg/kg/day (5.7 times the maximum human dose) was found to have no effect on fertility and reproductive performance in rats, dosed with a 2:1 ratio formulation of amoxicillin:clavulanic acid.

Reproduction studies in mice and rats using up to 10 times the usual human dose have not revealed evidence of impaired fertility or harm to the fetus.

Effects on Ability to Drive and Use Machines: No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g., allergic reactions, dizziness and convulsions), which may influence the ability to drive and use machines.

INTERACTIONS WITH OTHER MEDICAMENTS

DRUGS	NATURE OF INTERACTION
Probenecid	Decreased renal tubular secretion of amoxicillin resulting in increased and prolonged serum amoxicillin concentrations, but not of clavulanic acid. Concomitant use is not recommended.
Allopurinol	Increased incidence of skin rashes, particularly in hyperuricemic patients. It is not known whether this potentiation of amoxicillin rashes is due to allopurinol or the hyperuricemia in these patients.
Methotrexate	Decreased renal clearance of methotrexate and subsequent increase in methotrexate toxicity
Oral Contraceptives	Co-amoxiclav may reduce the efficacy of combined oral contraceptives by altering the gut flora and result in lower estrogen absorption. It may also lead to increased incidence of breakthrough bleeding or pregnancy on rare occasions.
Oral Anticoagulants (Acenocoumarol or Warfarin)	Abnormal prolongation of prothrombin time (increased International Normalized Ratio (INR)) has been reported in patients receiving amoxicillin and oral anticoagulants. Appropriate monitoring should be undertaken when these drugs should be used concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.
Disulfiram	Co-amoxiclav should not be used in patients receiving disulfiram (although there is no established rationale/evidence to date that concomitant use would result to a disulfiram-like reaction).
Mycophenolate mofetil	Reduction in pre-dose concentration of the active metabolite mycophenolic acid (MPA) of approximately 50% has been reported following commencement of oral Co-amoxiclav. The change in pre-dose level may not accurately represent changes in overall MPA exposure. Close monitoring should be performed during concomitant administration of these drugs.

Interference with Laboratory Tests

• High urine concentrations of ampicillin may result in false-positive reactions when testing for urinary glucose using cupric sulfate (e.g., Clinitest®, Benedict's Solution). Since this effect may also occur with amoxicillin, glucose oxidase methods (e.g., Clinistix®) should be used when urinary glucose determinations are indicated in patients receiving Co-amoxiclav.

• Although not reported to date with Co-amoxiclav, positive direct antiglobulin (Coombs') test results have been reported in patients who received ticarcillin and clavulanic acid and appear to be caused by clavulanic acid. This reaction may interfere with hematologic studies or transfusion cross-matching procedures and therefore should be considered in patients receiving Co-amoxiclav.

• Following administration of amoxicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone, and estradiol has been noted.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

Pregnancy: (Pregnancy Category B). There are no adequate or controlled studies in pregnant women and safe use in pregnancy has not been definitely established. However, oral Co-amoxiclav has been administered to pregnant women, particularly in the treatment of urinary tract infections, without evidence of adverse effects to the fetus.

In a single study in women with preterm, premature rupture of the fetal membrane (pPROM), it was reported that prophylactic treatment with Co-amoxiclav may be associated with an increased risk of necrotizing enterocolitis in neonates. As with all medicines, use should be avoided in pregnancy unless considered essential by the physician.

Lactation: Co-amoxiclav is distributed in human milk and may cause diarrhea, fungal infection of the mucous membrane and sensitization in the breastfed infant. Caution should be exercised if Co-amoxiclav is to be administered to a nursing mother.

Use in children: Children weighing over 40 kg should be dosed based on recommended dosing in adult patients.

Use in elderly patients: Since elderly patients have increased risk of renal impairment, dose adjustment and renal function monitoring may be necessary.

Renal Impairment: Dosage adjustments are based on the maximum recommended level of amoxicillin. No adjustment in dose is required in patients with creatinine clearance greater than 30 mL/min.

Hepatic Impairment: Dose with caution; monitor hepatic function at regular intervals for both adults and children.

UNDESIRABLE EFFECTS

Dermatologic and Hypersensitivity Reactions: acute generalized exanthematous pustulosis (AGEP), anaphylaxis, angioedema, angioneurotic edema, bullous exfoliative-dermatitis, edema, erythematous maculopapular rash, erythema multiforme, exfoliative dermatitis (including toxic epidermal necrolysis), fever, hypersensitivity vasculitis, pruritus, serum sickness-like syndrome (urticarial or skin rash accompanied by arthritis arthralgia, myalgia, and frequently fever), skin rash, Stevens-Johnson syndrome and urticaria.

Gastrointestinal Effects: Abdominal cramps, abdominal discomfort, acid stomach, anorexia, black "hairy" tongue, constipation, diarrhea/loose stools, *Clostridium difficile*-associated diarrhea and colitis (antibiotic-associated hemorrhagic colitis and pseudomembranous colitis), colic pain, dyspepsia, enterocolitis, flatulence, indigestion, intestinal candidiasis, nausea, gastritis, glossitis, mucocutaneous candidiasis, stomatitis and vomiting.

Hematologic Effects: Anemia (including hemolytic anemia), basophilia, eosinophilia, lymphocytopenia, prolonged bleeding time and prothrombin time, reversible agranulocytosis, reversible leukopenia (including neutropenia), slight increase in platelets, thrombocytopenia, thrombocytopenic purpura, and thrombocytosis.

Nervous System Effects: Agitation, aseptic meningitis, anxiety, behavioral changes, confusion, dizziness, headache, insomnia, reversible hyperactivity and convulsions particularly in patients with impaired renal functions or those receiving high doses

Hepatic Effects: A moderate rise in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT), serum bilirubin and/or alkaline phosphatase, lactic dehydrogenase, hepatic cholestasis, hepatitis, cholestatic jaundice, acute hepatic dysfunction

Renal and Genitourinary Effects: Acute interstitial nephritis, crystalluria, hematuria, overgrowth of non-susceptible organisms and vaginitis

Other Effects: Bad taste, malaises and superficial tooth discoloration (brown, yellow, or gray staining)

OVERDOSE AND TREATMENT

Clinical features of overdosage with Co-amoxiclav may include gastrointestinal symptoms, fluid and electrolyte imbalance. Amoxicillin crystalluria, leading to renal failure, has also been observed in some cases. Convulsions may occur in patients with impaired renal function or those receiving high doses.

Children (Additional Statement)
A prospective study of 51 pediatric patients at a poison control center suggested that overdosages of less than 250 mg/kg of amoxicillin are not associated with significant clinical symptoms and do not require gastric emptying.

Symptomatic treatment is recommended. Co-amoxiclav can be removed by hemodialysis.

STORAGE CONDITIONS

- Store in a dry place at temperatures not exceeding 25°C.
- Keep the product out of sight and reach of children.

AVAILABILITY

Co-amoxiclav (AmoClav®) 228.5 mg/5 mL Powder for Suspension (DR-XY33485)
– in amber bottle of 70 mL
Co-amoxiclav (AmoClav®) 457 mg/5 mL Powder for Suspension (DR-XY33488)
– in amber bottles of 35mL and 70mL

DATE OF FIRST AUTHORIZATION (DR-XY33485): April 2010
DATE OF FIRST AUTHORIZATION (DR-XY33488): April 2010
DATE OF REVISION OF PACKAGE INSERT: July 2015

CAUTION

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

ADVERSE DRUG REACTION REPORTING STATEMENT

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

Manufactured by Bilim Ilac Sanayii Ve Ticaret A.S.
Cerkezkoy Organize Sanayi Bolgesi
Karaagac Mahallesi 5. Sokak No: 6
Kapakli/Tekirdag-Turkey
Imported and Distributed by **UNILAB, Inc.**
No. 66 United Street, Mandaluyong City
Metro Manila, Philippines

12017774

Reg. IPOPHIL
PED152090IN03