pharmaniaga®

Co-Amoxiclav

Tablet
Suspension

COMPOSITION

Pharmaniaga Co-Amoxiclav Tablet 625 mg
Each film coated tablet contains Amoxicillin Trihydrate equivalent to Amoxicillin 500 mg and Potassium Clavulanate equivalent to Clavulanic Acid 125 mg.

Pharmaniaga Co-Amoxiclav Suspension 228 mg
Each 5 mL contains Amoxicillin Trihydrate equivalent to Amoxicillin 200 mg and Potassium Clavulanate equivalent to Clavulanic Acid 28.50 mg.

DESCRIPTION

Pharmaniaga Co-Amoxiclav Tablet 625 mg
White to off white oblong shaped film coated tablet with plain one side and word "RMB" on the other side.

Pharmaniaga Co-Amoxiclav Suspension 228 mg
Powder:
Off white to yellowish granules.

Reconstituted oral suspension:
Off white to yellowish fruit flavoured suspension

PHARMACODYNAMICS

Amoxicillin / Clavulanic acid is an antibiotic agent with a broad spectrum of activity against the commonly occuring bacterial pathogens. The β-lactamase inhibitory action of Clavulanic acid extends the spectrum of Amoxicillin to embrace a wider range of organisms, including many resistant to other β-lactam antibiotics.

Resistance to many antibiotics is caused by bacterial enzymes which destroy the antibiotic before it can act on the pathogen. The Clavulanic acid anticipates this defense mechanism by blocking the β-lactamase enzymes, thus rendering the organisms sensitive to Amoxicillin's rapid bactericidal effect at concentrations readily attainable in the body. Clavulanic acid by itself has little antibacterial activity; however, in association with Amoxicillin it produces an antibiotic agent of broad spectrum with wide application in hospital and general practice.

Amoxicillin/Clavulanic acid is bactericidal to a wide range of organisms categorised as follows according to their in vitro susceptibility to Amoxicillin/Clavulanic acid.

Commonly susceptible species:

Gram-positive Aerobes	*Bacillus anthracis, Enterococcus faecalis, Listeria monocytogenes, Nocardia asteroids, †Streptococcus pyogenes, †Streptococcus agalactiae, †Streptococcus spp.* (other Beta-hemolytic), *Staphylococcus aureus* (methicillin susceptible), *Staphylococcus saprophyticus* (methicillin susceptible), Coagulase negative staphylococcus (methicillin susceptible).
Gram-negative Aerobes	*Bordetella pertussis, Haemophilus influenzae, Haemophilus parainfluenzae, Helicobacter pylori, Moraxella catarrhalis, Neisseria gonorrhoeae, Pasteurella multocida, Vibrio cholerea.*
Other	*Borrelia burgdorferi, Leptospira icterohaemorrhagiae, Treponema pallidum.*
Gram-positive Anaerobes	*Clostridium spp., Peptococcus niger, Peptostreptococcus magnus, Peptostreptococcus micros, Peptostreptococcus spp.*
Gram-negative Anaerobes	*Bacteroides fragilis, Bacteroides spp., Capnocytophaga spp., Eikenella corrodens, Fusobacterium nucleatum, Fusobacterium spp., Porphyromonas spp., Prevotella spp.*

Species for which acquires resistance may be a problem:

Gram-positive Aerobes	*Corynebacterium spp., Enterococcus faecium, †Streptococcus pneumoniae,* and Viridans group streptococcus.
Gram-negative Aerobes	*Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Klebsiella spp., Proteus mirabilis, Proteus vulgaris, Proteus spp., Salmonella spp., Shigella spp.*

Inherently resistant organisms:

Gram-negative Aerobes	*Acinetobacter spp., Citrobacter freundii, Enterobacter spp., Hafnia alvei, Legionella pneumophila, Morganella morganii, Providencia spp., Pseudomonas spp., Serratia spp., Stenotrophomas maltophilia, Yersinia enterolitica.*
Other	*Chlamydia pneumoniae, Chlamydia psittaci, Chlamydia spp., Coxiella burnetti, Mycoplasma spp.*

†Organisms that do not produce beta-lactamase. If an isolate is susceptible it can be considered susceptible to this product.

PHARMACOKINETICS

The pharmacokinetics of the two components of Amoxicillin/Clavulanic Acid are closely matched. Peak serum levels of both occur about 1 hour after oral administration. Absorption of Amoxicillin/Clavulanic is optimised at the start of a meal. Doubling the dosage of Amoxicillin/Clavulanic Acid approximately doubles the serum levels achieved. Both Amoxicillin/Clavulanic Acid have low levels of serum binding; about 70% remains free in the serum.

INDICATION

It is indicated for the treatment of the following infections:
a) Upper & lower respiratory tract infections - sinusitis, otitis media, bronchitis.

b) Skin and soft tissue infections - boils, abscesses, cellulitis, wound infections.

c) Genitourinary tract infections - cystitis, urethritis, pyelonephritis.

d) Bone & joint infections - osteomyelitis.

DOSAGE AND ADMINISTRATION

Pharmaniaga Co-Amoxiclav Tablet 625mg
Adults and children > 12 years :
Mild to moderate infections : 1 tablet (625 mg) 2 times daily.
Not recommended for children of 12 years and under.

Renal Impairment :
Adults : Mild Impairment (creatinine clearance > 30 mL/min):
No change in dosage.
Moderate Impairment (creatinine clearance 10-30 mL/min):
1 tab (625 mg) 2 times daily.
Severe Impairment (creatinine clearance < 10 mL/min):
1 tab (625 mg) 24 hourly.

Duration of therapy should be appropriate to the indication and should not exceed 14 days without review. Therapy can be started parenterally and continued with an oral preparation.

Pharmaniaga Co-Amoxiclav Suspension 228 mg
The usual recommended daily dosage is :

- 25/ 3.6 mg/ kg/ day in mild to moderate infections (upper respiratory tract infections e.g recurrent tonsillitis, lower respiratory infections and skin and soft tissue infections).
- 45/ 6.4 mg/ kg/ day for the treatment of more serious infections (upper respiratory tract infections e.g. otitis media and sinusitis, lower respiratory tract infections e.g. bronchopneumonia and urinary tract infections).

Children over 2 years		
25/3.6 mg/kg/day	2-6 years (13-21 kg)	5 mL Co-Amoxiclav Suspension 228 mg 2 times daily.
	7-12 years (22-40 kg)	10 mL Co-Amoxiclav Suspension 228 mg 2 times daily.
45/6.4 mg/kg/day	2-6 years (13-21 kg)	10 mL Co-Amoxiclav Suspension 228 mg 2 times daily.

Note : Duration of therapy should be appropriate to the indication and should not exceed 14 days without review. Therapy can be started parenterally and continued with an oral preparation.

Children <2 months: There is insufficient experience with Co-Amoxiclav Suspension to make dosage recommendations for children <2 months.

Infants with Immature Kidney Function: For infants with immature renal function, Co-Amoxiclav Suspension are not recommended.

Renal Impairment: For children with a GFR of >30 mL/min, no adjustment in dosage is required. For children with a GFR of <30 mL/min, Co-Amoxiclav suspension is not recommended.

Hepatic Impairment: Dose with caution, monitor hepatic function at regular intervals. There is, as yet, insufficient evidence on which to base a dosage recommendation.

Route of Administration: Oral

INSTRUCTION FOR USE

Pharmaniaga Co-Amoxiclav Tablet 625mg
Tablets should be swallowed whole without chewing. To minimise potential gastrointestinal intolerance, administer at the start of a meal. The absorption of Co-Amoxiclav is optimised when taken at the start of a meal.

Store the remaining tablets in original packaging after open.

Pharmaniaga Co-Amoxiclav Suspension 228mg
Reconstitution: Shake the bottle to loosen the powder. Add freshly boiled and cooled water and shake well. Make up to the required volume as stated on the label. Use reconstituted suspension within 7 days. Keep in the refrigerator. Complete the prescribed course.

CONTRAINDICATIONS

It is contraindicated in patients with a history of allergic reactions to any penicillin or beta-lactamase inhibitors. It is also contraindicated in patients with a previous history of Amoxicillin with Clavulanic acid or Penicillin - associated jaundice/hepatic dysfunction. Attention should be paid to possible cross-sensitivity with other β-lactam antibiotics.

ADVERSE EFFECTS

Infections 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 sickness-like syndrome and hypersensitivity vasculitis.

Nervous system disorders
Uncommon: Dizziness and headache.
Very rare: Reversible hyperactivity and convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Gastrointestinal disorders
Adults
Very common: Diarrhoea.
Common: Nausea and vomiting.

Children
Common: Diarrhoea, nausea and vomiting.

All populations
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 a meal.
Uncommon: Indigestion.
Very rare: Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) and black hairy tongue.

Hepatobiliary disorders
Uncommon: A moderate rise in AST and/or ALT has been noted in patients treated with beta-lactam class antibiotics, but the significance of these findings is unknown.
Very rare: Hepatitis and cholestatic jaundice. These events have been noted with other penicillins and cephalosporins.

Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children. Signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until several weeks after treatment has ceased. These are usually reversible. Hepatic events may be severe and in extremely rare circumstances, deaths have been reported. These have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have the potential for hepatic effects.

Skin and subcutaneous tissue disorders
Uncommon: Skin rash, pruritus and urticaria.
Rare: Erythema multiforme.
Very rare: Stevens-Johnson syndrome and toxic epidermal necrolysis, bullous exfoliative-dermatitis, acute generalised exanthemous pustulosis (AGEP), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).
If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued.

Renal and urinary disorders
Very rare: Interstitial nephritis and crystalluria.

WARNINGS AND PRECAUTIONS
Before initiating therapy with Co-Amoxiclav careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens.

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients receiving therapy with beta-lactams. Before initiating therapy with this product, careful inquiry should be made concerning previous hypersensitivity reaction to penicillins, cephalosporins, carbapenems or other beta-lactam agents. If an allergic reaction occurs, this product must be discontinued immediately and appropriate alternative therapy instituted.

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.

Pseudomembranous colitis has been reported with the use of antibiotics and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhoea during or after antibiotic use. If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further.

Abnormal prolongation of prothrombin time (increased INR) has been reported rarely in patients receiving Co-Amoxiclav 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. Changes in liver function tests have been observed in some patients receiving Co-Amoxiclav. The clinical significance of these changes is uncertain. Co-Amoxiclav should be used with caution in patients with evidence of hepatic dysfunction.

Cholestatic jaundice, which may be severe, but is usually reversible, has been reported rarely. Signs and symptoms may not become apparent for up to six weeks after treatment has ceased.

In patients with renal impairment, Co-Amoxiclav dosage should be adjusted as recommended in the Dosage and Administration section. In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the 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.

For suspension only, Co-Amoxiclav suspension contain aspartame and therefore should be used with caution in patients with phenylketonuria.

INTERACTION WITH OTHER MEDICAMENTS
Probenecid
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.

Allopurinol
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 Co-Amoxiclav and allopurinol.

Oral contraceptives
In common with other antibiotics, Co-Amoxiclav may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

Oral anticoagulants
In the literature there are rare cases of increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of Co-Amoxiclav.

Mycophenolate mofetil
In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid (MPA) of approximately 50% has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure. Close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

Coombs test
The presence of clavulanic acid in Co-Amoxiclav may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

Methotrexate
Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

PREGNANCY AND LACTATION
As with all medicines, use should be avoided in pregnancy, especially during the first trimester, unless considered essential by the physician.

Co-Amoxiclav 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.

OVERDOSE AND TREATMENT
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. Convulsions may occur in patients with impaired renal function or in those receiving high doses. Co-Amoxiclav can be removed from the circulation by haemodialysis.

STORAGE CONDITIONS
Pharmaniaga Co-Amoxiclav Tablet 625 mg
Store below 30°C.
Protect from light and moisture.

Pharmaniaga Co-Amoxiclav Suspension 228 mg
Store below 30°C.
Keep bottle tightly closed.
Protect from light and moisture.
Reconstituted suspension should be stored in a refrigerator (2-8°C) and used within 7 days.

SHELF LIFE
Product should not be used beyond the expiry date imprinted on the product packaging.

PRESENTATION
Pharmaniaga Co-Amoxiclav Tablet 625 mg.
(MAL 20013767AZ)
i. Packed in blister of 7 tablets in carton box (10 x 7's).
ii. Packed in blister of 10 tablets in carton box (10 x 10's).

Pharmaniaga Co-Amoxiclav Suspension 228 mg.
(MAL 20021372AZ)
70mL in 120mL Amber glass bottle.

Date of Revision : 8th Nov 2021

PRODUCT REGISTRATION HOLDER / MANUFACTURER:
IDAMAN PHARMA MANUFACTURING SDN BHD (200401023395)
Lot 120, Taman Farmaseutikal, 32610 Bandar Seri Iskandar,
Perak Darul Ridzuan, Malaysia.