Natrapharm

Co-amoxiclav

Natravox®

Rx

156.25mg per 5mL Powder for suspension;
228.5mg per 5mL powder for suspension;
312.5mg per 5mL powder for suspension;
457mg per 5mL powder for suspension;
642.9mg 5mL powder for suspension;
375mg film-coated tablet;
625mg film-coated tablet
Antibacterial (Penicillin)

FORMULATION:
156.25mg per 5ml powder for suspension - Each 5ml contains:
Amoxicillin (as trihydrate), USP.....125mg
Clavulanic Acid (as Potassium clavulanate).....31 .25mg

228.5mg per 5ml powder for suspension - Each 5ml contains:
Amoxicillin (as trihydrate), USP.....200mg
Clavulanic Acid (as Potassium clavulanate).....28.5mg

312.5mg per 5ml powder for suspension - Each 5ml contains:
Amoxicillin (as trihydrate), USP.....250mg
Clavulanic Acid (as Potassium clavulanate).....62.5mg

457mg per 5ml powder for suspension - Each 5ml contains:
Amoxicillin (as trihydrate), USP.....400mg
Clavulanic Acid (as Potassium clavulanate).....57mg

642.9 per 5ml powder for suspension - Each 5ml contains:
Amoxicillin (as trihydrate), USP.....600mg
Clavulanic Acid (as Potassium clavulanate).....42.9mg

375mg film-coated tablet - Each tablet contains:
Amoxicillin (as trihydrate), USP.....250mg
Clavulanic Acid (as Potassium clavulanate).....125mg

625mg film-coated tablet - Each tablet contains:
Amoxicillin (as trihydrate), USP.....500mg
Clavulanic Acid (as Potassium clavulanate).....125mg

Product Description:
(Co-amoxiclav) Natravox Powder for Suspension
White to off-white to yellowish-white powder. White to off-white to yellowish-white suspension. Vanilla Caramel Flavored. Sweet characteristic taste.

(Co-amoxiclav) Natravox Film-coated tablet
White to off-white film-coated, biconvex, oval shape and plain on both sides tablet.

Indications:
For the treatment of the infections caused by susceptible organisms such as upper and lower respiratory tract infections, genito-urinary tract infections and skin and soft tissue infections.

-Upper Respiratory Tract infections (including ENT) - sinusitis, otitis media, recurrent tonsillitis. These infections are often caused by *Streptococcus pneumoniae*, *Haemophilus influenzae, Moraxella catarrhalis* and Streptococcus pyogenes.

-Lower Respiratory Tract Infections acute exacerbations of chronic bronchitis, bronchopneumonia, urinary-tract infections often caused *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis.*

-Genito-urinary Tract and Abdominal Infections in particular cystitis (especially when recurrent or complicated, but not prostatitis) septic abortion, pelvic or puerperal sepsis, and intra-abdominal sepsis. These infections are often caused by *Enterobacteriaceae* (mainly *Escherichia coli*), *Staphylococcus saprophyticus, Enterococcus* species.

Skin and Soft Tissues Infections in particular cellulites, animal bites and severe dental abscess with spreading cellulites caused by *Staphylococcus aureus, Streptococcus pyogenes* and *Bacteriodes species.*

Pharmacodynamics:
Co-amoxiclav is an oral antibacterial combination consisting of amoxicillin (as trihydrate) and the beta-lactamase inhibitor, clavulanic acid (as potassium clavulanate).

Amoxicillin is the 4-hydroxy analogue of ampicillin. It is a semisynthetic antibiotic with a broad spectrum activity against many gram-positive and gram-negative microorganisms. Amoxicillin is inactivated by beta lactamases and complete cross-resistance has been reported between amoxicillin and ampicillin.

The spectrum of activity of amoxicillin may be extended by use with a beta-lactamase inhibitor like clavulanic acid. As well as reversing resistance to amoxicillin in beta-lactamase producing strains of species otherwise sensitive, clavulanic acid has also been reported to enhance the activity of amoxicillin against several species not generally considered sensitive. These have included: *Bacteroides, Legionella and Nocardia spp. Haemophilus influenzae, Moraxella catarrhalis* and *Pseudomonas pseudomallei.*

Clavulanic acid has a beta-lactam structure resembling that of penicillin nucleus, except that the fused thiazolidine ring of the penicillins is replaced by an oxazolidine ring. In general, clavulanic acid has only weak antibacterial activity. It is potent progressive inhibitor of plasmid-mediated and some chromosomal beta-lactamases produced by Gram-negative bacteria including *Haemophilus ducreyi, H. influenzae, Neisseria gonorrhoeae, Moraxella catarrhalis* (*Branhamella catarrhhalis), Bacteroides fragilis* and some *Enterobacteriacese.* It is also an inhibitor of the beta-lactamases produced by *Staphylococcus aureus.* Clavulanic acid can permeate bacterial cell walls and can therefore inactivate both extracellular enzymes and those that are bound to the cell. Its mode of action depends on the particular enzyme inhibited, but it generally acts as a competitive, and often irreversible, inhibitor. Clavulanic acid consequently enhances the activity of penicillin and cephalosporin antibacterials against many resistant strains of bacteria. However, it is generally less effective against chromosomally medicated type 1 beta-lactamases: therefore, many *Citrobacter, Enterobacter, Morganells and Serratia spp.* And *Pseudomonas aeruginosa* remain resistant. Some plasmid-mediated extended-spectrum beta lactamases in Klebsiella pneumoniae, some other Enterobactriaceae, and Ps. aeruginosa are also not inhibited by beta-lactamases inhibitors.

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

Gram-positive:
Aerobes: Enterococcus faecalis, Enterococcus faecium, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus viridans, Staphylococcus aureus, Coagulase negative staphylococci (including Staphylococcus epidermidis), Corynebacterium species, Bacillus anthracis, Listeria monocytogenes Anerobes: Clostridium species, Peptococcus species, Peptostreptococcus

Gram negative:
Aerobes: Haemophilus influenzae, Moraxella catarrhalis, (Branhamella catarhalis) Escherichia coli, Proteus mirabilis, Proteus vulgaris, Klebsiella species, Salmonella species, Neisseria gonorrhoeae, Neisseria meningitidis, Vibrio cholerae, Pasteurella multocida Anaerobes: Bacteroides species, including B. fragilis

Pharmacokinetics
Amoxicillin and clavulanate potassium are well absorbed from the gastrointestinal tract after oral administration. Approximately 50% to 70% of the amoxicillin and approximately 25% to 40% of the clavulanic acid are excreted unchanged in urine during the first 6 hours after administration of 10 mL 250mg/5mL co-amoxiclav suspension.

Neither component of co-amoxiclav is highly protein-bound; clavulanic acid has been found to be approximately 25% bound to human serum and amoxicillin 18% bound.

Amoxicillin diffuses readily into most body tissues and fluids with the exception of the brain and spinal fluid. The results of experiments involving the administration of clavulanic acid to animals suggest that this compound, like amoxicillin, is well distributed in body tissues.

Side Effects
Amoxicillin/clavulanate potassium is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were diarrhea/loose stools nausea, skin rashes and urticaria ,vomiting and vaginitis . The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: Abdominal discomfort, flatulence, and headache.

The following adverse reactions have been reported for ampicillin-class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, mucocutaneous candidiasis, enterocolitis, and hemorrhagic/pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment.

Hypersensitivity Reactions: Skin rashes, pruritus, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson syndrome), acute generalized exanthematous pustulosis, hypersensitivity vasculitis, and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis) have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin.

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin-class antibiotics, but the significance of these findings is unknown. Hepatic dysfunction, including hepatitis and cholestatic jaundice, increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with amoxicillin/clavulanate potassium.
Renal:Interstitial nephritis and hematuria have been reported rarely. Crystalluria has also been reported.

Hemic and Lymphatic System: Anemia, including hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with amoxicillin/clavulanate potassium. There have been reports of increased prothrombin time in patients receiving amoxicillin/clavulanate potassium and anticoagulant therapy concomitantly.

Central Nervous System: Agitation, anxiety, behavioral changes, confusion, convulsions, dizziness, insomnia, and reversible hyperactivity have been reported rarely.

Miscellaneous: Tooth discoloration (brown, yellow, or gray staining) has been rarely reported. Most reports occurred in pediatric patients. Discoloration was reduced or eliminated with brushing or dental cleaning in most cases.

Drug interactions:
Probenicid decreases the renal tubular secretion of amoxicillin. Concurrent use with co-amoxiclav may result in increased and prolonged blood levels of amoxicillin. In common with other broad-spectrum antibiotics, co-amoxiclav may reduce the efficacy of oral contraceptives.

Contraindications:
Co-amoxiclav is contraindicated in patients with a history of allergic reactions to any penicillin. It is also contraindicated in patients with a previous history of amoxicillin-potassium clavulanate-associated cholestatic jaundice/hepatic dysfunction.

Adverse effects and Precautions:
Hepatitis and cholestatic jaundice have been reported with the combination amoxicillin and clavulanic acid. Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis and exfoliative dermatitis have also been attributed occasionally to the use of amoxicillin with clavulanic acid.

Overdosage
Cases of overdosages are usually asymptomatic. If encountered, gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. They may be treated symptomatically with attention to the water electrolyte balance. Co-amoxiclav can be removed from the circulation by haemodialysis.
During the administration of high doses of co-amoxiclav, adequate fluid intake and urinary output should be maintained to minimize the possibility of amoxicillin crystalluria.

Pregnancy and lactation
There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Ampicillin class antibiotics are excreted in the milk; therefore, caution should be exercised when co-amoxiclav is administered to a nursing mother.

Dosage and administration
Suspension: Due to differing content of clavulanic acid, not all formulations are interchangeable

Directions for mixing oral suspension:
Prepare the suspension at the time of dispensing:

For 35mL suspension: 457 mg per 5mL suspension
Tap bottle until all the powder flows freely. Add 30mL water and shake vigorously until the powder is evenly suspended.

For 50mL suspension: 642.9mg per 5mL suspension
Tap bottle until all the powder flows freely. Add 41 mL water and shake vigorously until the powder is evenly suspended.

For 60mL suspension: 156.25mg per 5mL suspension
312.5mg per 5mL suspension
Tap bottle until all the powder flows freely. Add 50 mL water and shake vigorously until the powder is evenly

For 70mL suspension: 228.5mg per 5mL suspension
457mg per 5mL suspension
642.9mg per 5mL suspension
Tap bottle until all the powder flows freely. Add 58 mL water and shake vigorously until the powder is evenly suspended.

For 100mL suspension: 642.9mg per 5mL suspension
Tap bottle until all the powder flows freely. Add 83 mL water and shake vigorously until the powder is evenly

Description of mixed suspension: White to off-white to yellowish white in color

NOTE: ONCE RECONSTITUTED, STORE NATRAVOX SUSPENSION IN A REFRIGERATOR (2^{o}C - 8^{o}C BUT NOT FROZEN) AND USED WITHIN SEVEN (7) DAYS. SHAKE THE RECONSTITUTED SUSPENSION BEFORE USING. DISCARD AFTER.

Pediatric Patients:
Based on the amoxicillin component, Natravox suspension should be dosed as follows:

A: *156.25mg per 5mL powder for suspension*
312.5mg per 5mL powder for suspension
Neonates and infants aged less than 3 months: 30mg/kg/day divided every 12 hours (125mg/5mL suspension is recommended)
Patients ages 3 months and older
Severe infections, otitis media, lower respiratory tract infections: 40mg/kg/day every 8 hour
Less severe infections: 20mg/kg/day every 8 hour

B. *228.5mg per 5mL powder for suspension*
457 mg per 5mL powder for suspension

Patients ages 3 months and older
Severe infections, otitis media, lower respiratory tract infections: 45mg/kg/day every 12 hour
Less severe infections: 25mg/kg/day every 8 hour
Treatment duration for otitis media is 10 days

C. *642.9mg per 5mL powder for suspension*

Patients ages 3 months and older
90mg/kg/day divided every 12 hours, administered for 10 days

Tablets
Tablets should be swallowed whole without chewing. To minimize potential gastrointestinal intolerance, administer at the start of a meal. The absorption of co-amoxiclav is optimized when taken at the start of a meal. Duration of therapy should be appropriate to the indication and should not exceed 14 days without review.

Since both 375mg and 625mg Natravox tablets contain the same amount of clavulanic acid, two 375mg Natravox tablets are not equivalent to one 625mg Natravox tablet. Therefore two 375mg Natravox tablet should not be substituted for one 625mg Natravox tablet.

Tablets are not recommended in children of 12 years and under

Usual adult dose:
Mild to moderate infections: 375mg tablet three times a day or 625mg tablet twice a day
Severe infections: 625mg tablet thrice a day or one lg tablet twice a day
Dental infections: 375mg three times a day for 5 days or 625mg tablet twice a day for five days.

Or as prescribed by the physician.

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

Availability:
Co-amoxiclav 156.25 per 5mL Powder for Suspension-Amber Glass Bottle x 60mL (Box of 1 's)
Co-amoxiclav 228.5mg per 5mL Powder for Suspension-Amber Glass Bottle x 70mL (Box of 1 's)
Co-amoxiclav 312.5 per 5mL Powder for Suspension-Amber Glass Bottle x 60mL (Box of 1 's)
Co-amoxiclav 457mg per 5mL Powder for Suspension-Amber Glass Bottle x 35mL & 70mL (Box of 1 's)
Co-amoxiclav 642.9mg/5mL Powder for oral suspension- Type III Amber Glass Bottle with Measuring cup x 50mL, 70mL and 100mL (Box of I's)
Co-amoxiclav 375mg Film-coated tablet- Blister pack x 8's in aluminum pouch (Box of 48's)
Co-amoxiclav 625mg Film-coated tablet —Blister pack x 8's (Box of 40's)

Also Available
Co-amoxiclav 600mg Powder for Injection (IV)- Clear, Colorless, USP Type I Glass vial (Box of I's)
Co-amoxiclav 1.2g Powder for Injection (IV)- Clear, Colorless, USP Type I Glass vial, Box of I's

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

STORE THE DRY SUSPENSION AND TABLETS IN DRY PLACE
STORE AT TEMPERATURES NOT EXCEEDING 25^{o}C

Registration Number: 156.25mg/5mL (DR-XY34785), 228.5mg/5mL (DR-XY34776), 312.5mg/5mL (DR-XY34778), 457mg/5mL (DR-XY34777, 642.9mg/5mL (DR-XY36416), 375mg (DR-XY28251), 625mg (DR-XY28249)

Date of First Authorization: 156.25mg/5mL, 228.5mg/5mL, 312.5mg/5mL, 457mg/5mL (August 2008), 642.9mg/5mL (August 2009), 375mg, 625mg (January 2003)

Revision Date: January 2022

Manufactured for
Natrapharm, Inc.
The Patriot Building
Km. 18, West Service Road,
South Luzon Expressway,
Parañaque City

by Lloyd Laboratories, Inc.
No. 10 Lloyd Avenue,
First Bulacan Industrial City
City of Malolos, Bulacan

NTNXSALLOOI IN2201