For the use of only a Registered Medical Practitioner or a Hospital or a Laboratory

Not to be sold by retail without the prescription of a Registered Medical Practitioner

Prescribing Information

1. Generic Name

Amoxycillin and Potassium Clavulanate Tablets IP
(Brand Name: BLUMOX®-CA 375 mg / 625 mg Tablets)

2. Qualitative and Quantitative Composition

BLUMOX-CA 375 mg Tablets
Each film coated tablets contains:
Amoxycillin Trihydrate IP equivalent to Amoxycillin …….…..……. 250 mg.
Diluted Potassium Clavulanate IP equivalent to Clavulanic Acid ….……. 125 mg.
Excipients…….q.s.
Colour: Titanium Dioxide IP

BLUMOX-CA 625 mg Tablets
Each film coated tablets contains:
Amoxycillin Trihydrate IP equivalent to Amoxycillin ……. 500 mg.
Diluted Potassium Clavulanate IP equivalent to Clavulanic Acid ….…….. 125 mg.
Excipients……..q.s.
Colour: Titanium Dioxide IP

3. Dosage Form and Strength

Dosage Form: Tablets.
Dosage Strength: Amoxycillin 250 mg / 500 mg with clavulanic acid 125 mg / 125 mg per tablets of BLUMOX-CA 375 mg and BLUMOX-CA 625 mg respectively.

4. Clinical Particulars

4.1 Therapeutic Indication

BLUMOX-CA Tablets are indicated in the treatment of following infections when caused by susceptible bacteria in adults and children:

- Acute bacterial sinusitis.
- Acute otitis media.
- Acute exacerbations of chronic bronchitis.
- Community acquired pneumonia.
- Cystitis.
- Pyelonephritis.
- Skin and soft tissue infections in particular cellulitis, animal bites.
- Severe dental abscess with spreading cellulitis.

- Bone and joint infections, in particular osteomyelitis.

4.2Posology and Method of Administration

For oral administration.

Dosage in adults and children above 12 years of age (or weighing ≥ 40 kg).

- **Usual Dose**: 1 tablet of BLUMOX-CA 375 mg to be given thrice daily. Or, 1 tablet of BLUMOX-CA 625 mg to be given twice daily.
- **Severe Infections and Infections of the Respiratory Tract:** 1 tablet of BLUMOX-CA 625 mg to be given thrice daily.

Or, as prescribed by the physician.

The duration of therapy depends on type and severity of infection. Treatment should not be extended beyond 14 days without review. BLUMOX-CA Tablets may be taken without regard to meals. However, absorption of clavulanate potassium is enhanced when it is administered at the start of a meal. To minimize the potential for gastrointestinal intolerance, BLUMOX-CA Tablets should be taken at the start of a meal.

4.3Contraindications

BLUMOX-CA Tablets are contraindicated in the following:

- Hypersensitivity to amoxycillin, clavulanic acid, penicillin class of drugs, or any excipient of the formulation.
- History of a severe immediate hypersensitivity reaction (e.g., anaphylaxis) to another beta-lactam agent (e.g., a cephalosporin, carbapenem or monobactam).
- History of jaundice/hepatic impairment due to amoxycillin/clavulanic acid.

4.4Special Warnings and Precautions for Use

Hypersensitivity Reactions: Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam antibacterials, including amoxycillin/clavulanic acid. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. Before initiating therapy with amoxycillin/clavulanic acid, careful inquiry should be made regarding previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, amoxycillin/clavulanic acid should be discontinued and appropriate therapy instituted.

Hepatic Dysfunction: Hepatic dysfunction, including hepatitis and cholestatic jaundice has been associated with the use of amoxycillin/clavulanic acid. Hepatic function should be monitored at regular intervals in patients with hepatic impairment.

***Clostridium Difficile*-Associated Diarrhea (CDAD):** CDAD has been reported with use of nearly all antibacterial agents, including amoxycillin/clavulanic acid, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*. If CDAD is suspected or confirmed, ongoing antibacterial use not directed against *C. difficile* may need to be discontinued. Appropriate fluid

and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Skin Rash in Patients with Mononucleosis: A high percentage of patients with mononucleosis who receive amoxycillin develop an erythematous skin rash. Thus, amoxycillin/clavulanic acid should not be administered to patients with mononucleosis.

Potential for Microbial Overgrowth: The possibility of super infections with fungal or bacterial pathogens should be considered during therapy. If super infection occurs, amoxycillin/ potassium clavulanate should be discontinued and appropriate therapy instituted.

Development of Drug-Resistant Bacteria: Prescribing amoxycillin/clavulanic acid in the absence of a proven or strongly suspected bacterial infection is unlikely to provide any benefit to the patient, and increases the risk of the development of drug-resistant bacteria.

4.5Drug Interactions

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

Probenecid: Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxycillin, but does not delay renal excretion of clavulanic acid. Concurrent use may result in increased and prolonged blood concentrations of amoxycillin.

Oral Anticoagulants: Abnormal prolongation of prothrombin time has been reported in patients receiving amoxycillin 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.

Oral Contraceptives: Amoxycillin/clavulanic acid may affect intestinal flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral estrogen/progesterone contraceptives.

4.6Use in Special Populations

Pregnant Women

Pregnancy Category B. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Limited data on the use of amoxycillin/clavulanic acid during pregnancy in humans do not indicate an increased risk of congenital malformations. 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.

Lactating Women

Amoxycillin has been shown to be excreted in human milk. Amoxycillin/clavulanic acid use by nursing mothers may lead to sensitization of infants. Caution should be exercised when amoxycillin/clavulanic acid is administered to a nursing woman.

Paediatric Patients

This formulation is not intended for use in children as there is no feasibility of dosage adjustments. Amoxycillin/clavulanic acid combination is safe for use in children. But, due to higher dosage strength, BLUMOX-CA Tablets are not recommended for use in children. It is advised that children below 12 years of age or weighing less than 40 kg should use paediatric formulations of amoxycillin/clavulanic acid combination.

Geriatric Patients

Usually, no dose adjustment is considered necessary in elderly patients with normal renal function. However, this drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Renal Impairment Patients

The total serum clearance of amoxycillin/clavulanic acid decreases proportionately with decreasing renal function. Amoxycillin is primarily eliminated by the kidney and dosage adjustment is usually required in patients with severe renal impairment (GFR < 30 ml/min).

Hepatic Impairment Patients

Dosage should be used with caution and hepatic function monitored at regular intervals.

4.7Effect 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, convulsions), which may influence the ability to drive and use machines.

4.8Undesirable Effects

Clinical Trials Experience

The most frequently reported adverse reactions are diarrhea/loose stools, nausea, skin rashes and urticaria, vomiting, and vaginitis. The overall incidence of adverse reactions, and in particular diarrhea, increases with increase in doses. Other less frequently reported adverse reactions include abdominal discomfort, flatulence, and headache.

Post-Marketing Experience

Gastrointestinal: Indigestion, gastritis, stomatitis, glossitis, black hairy tongue, mucocutaneous candidiasis, enterocolitis, and hemorrhagic/pseudomembranous colitis.

Hypersensitivity Reactions: Pruritus, angioedema, serum sickness–like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia, and frequently fever), erythema multiforme, Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), hypersensitivity vasculitis, and cases of exfoliative dermatitis (including toxic epidermal necrolysis) have been reported.

Liver: Hepatic dysfunction, including hepatitis and cholestatic jaundice, increases in serum transaminases (AST and/or ALT), serum bilirubin, and/or alkaline phosphatase, has been reported with amoxycillin/clavulanic acid.
Renal: Interstitial nephritis, hematuria, and crystalluria have been reported.
Hemic and Lymphatic Systems: Anemia, including hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, thrombocytosis and agranulocytosis has been reported. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.
Central Nervous System: Agitation, anxiety, behavioral changes, confusion, convulsions, dizziness, insomnia, and reversible hyperactivity have been reported.
Miscellaneous: Tooth discoloration (brown, yellow, or gray staining) has been reported. Most reports occurred in paediatric patients. Discoloration was reduced or eliminated with brushing or dental cleaning in most cases.

4.9Overdose

Symptoms: Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Convulsions may occur in patients with impaired renal function or in those receiving high doses. Interstitial nephritis resulting in oliguric renal failure has been reported in patients after overdose with amoxycillin/clavulanic acid. Crystalluria, in some cases leading to renal failure, has also been reported after amoxycillin/clavulanic acid overdose in adult and paediatric patients.
Treatment: In case of overdose, adequate fluid intake and diuresis should be maintained to reduce the risk of amoxycillin/clavulanic acid crystalluria. Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance. Renal impairment appears to be reversible with cessation of drug administration. Amoxycillin/clavulanic acid can be removed from the circulation by haemodialysis.

5. Pharmacological Properties

5.1 Mechanism of Action

Amoxycillin is a penicillin class of beta-lactam antibiotics. Amoxycillin is semi-synthetic penicillin 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 peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.
Amoxycillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore, the spectrum of activity of amoxycillin alone does not include organisms which produce these enzymes.
Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxycillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.
The formulation of amoxycillin and clavulanic acid protects amoxycillin from degradation by some beta-lactamase enzymes and extends the antibiotic spectrum of amoxycillin to include many bacteria normally resistant to amoxycillin.

5.2Pharmacodynamic Properties

Amoxycillin/clavulanic acid has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections:

Gram-Positive Bacteria

- *Staphylococcus aureus.*

Gram-Negative Bacteria

- *Enterobacter* species.
- *Escherichia coli.*
- *Haemophilus influenza.*
- *Klebsiella* species.
- *Moraxella catarrhalis.*

The following *in vitro* data are available, but their clinical significance is unknown. At least 90% of the following bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for amoxycillin/clavulanic acid. However, the efficacy of amoxycillin/clavulanic acid in treating clinical infections due to these bacteria has not been established in adequate and well-controlled clinical trials.

Gram-Positive Bacteria

- *Enterococcus faecalis.*
- *Staphylococcus epidermidis.*
- *Staphylococcus saprophyticus.*
- *Streptococcus pneumoniae.*
- *Streptococcus pyogenes.*
- *Streptococcus viridans* group.

Gram-Negative Bacteria

- *Eikenella corrodens.*
- *Proteus mirabilis.*

Anaerobic Bacteria

- *Bacteroides* species including *Bacteroides fragilis.*
- *Fusobacterium* species.
- *Peptostreptococcus* species.

5.3Pharmacokinetic Properties

Absorption: Amoxycillin 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 amoxycillin/clavulanic acid is optimized when taken at the start

of a meal. Following oral administration, amoxycillin and clavulanic acid are approximately 70% bioavailable. The plasma profiles of both components are similar and the time to peak plasma concentration (Tmax) in each case is approximately 1 hour.

Distribution: About 25% of total plasma clavulanic acid and 18% of total plasma amoxycillin is bound to protein. The apparent volume of distribution is around 0.3 to 0.4 l/kg for amoxycillin and around 0.2 l/kg for clavulanic acid.

Metabolism: Small amount of amoxycillin is metabolized to inactive penicilloic acid. The inactive metabolites excreted in the urine in quantities equivalent to up to 10 to 25% of the initial dose. Clavulanic acid is extensively metabolized and eliminated in urine and faeces as a carbon dioxide in expired air.

Excretion: The major route of elimination for amoxycillin is via the kidney, whereas clavulanic acid is excreted by both renal and non-renal mechanisms. Amoxycillin/clavulanic acid has a mean elimination half-life of approximately 1 hour. Approximately 60 to 70% of the amoxycillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h. Various studies have found the urinary excretion to be 50 to 85% for amoxycillin and between 27 to 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.

6. Nonclinical Properties

6.1 Animal Toxicology

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity and toxicity to reproduction.

Repeat dose toxicity studies performed in dogs with amoxycillin/clavulanic acid demonstrate gastric irritancy and vomiting, and discoloured tongue.

Carcinogenicity studies have not been conducted with amoxycillin/clavulanic acid.

7. Description

BLUMOX-CA 375 Tablets are White oval shaped, biconvex film coated tablets plain on both sides.

BLUMOX-CA 625 Tablets are White oval shaped, biconvex film coated tablets plain on both sides.

BLUMOX-CA 375 Tablets contain 250 mg of amoxycillin with 125 mg of clavulanic acid whereas BLUMOX-CA 625 Tablets contains 500 mg of amoxycillin with 125 mg of clavulanic acid for oral administration in adults and adolescents.

BLUMOX-CA is an oral antibacterial combination consisting of amoxycillin and the beta lactamase inhibitor, potassium clavulanate (the potassium salt of clavulanic acid).

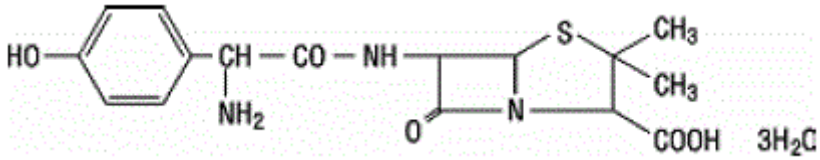
Amoxycillin Trihydrate

Amoxycillin is a semisynthetic antibiotic with a broad spectrum of bactericidal activity against many Gram-positive and Gram-negative microorganisms.

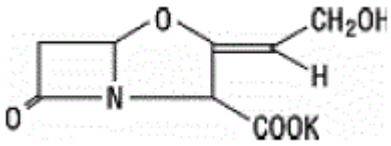
Amoxycillin trihydrate is crystalline and off-white in color.

Molecular Weight: 419.45 g/mol.

Molecular Formula: C16H19N3O5S•3H2O.
Chemical Name: (2S,5,R,6,R)-6-[(,R)-(-)-2-amino-2-(p-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate.
Structural Formula:



Potassium Clavulanate
Clavulanic acid is a beta-lactamase inhibitor structurally related to the penicillins and possesses the ability to inactivate some beta lactamases by blocking the active sites of these enzymes. Potassium clavulanate is a white or almost white crystalline powder.
Molecular Weight: 237.25 g/mol.
Molecular Formula: C8H8KNO5.
Chemical Name: Potassium (Z)(2R,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]-heptane-2-carboxylate.
Structural Formula:



Inactive ingredients (excipients) of BLUMOX-CA 375 mg Tablets contain Crospovidone, Colloidal Silicon Dioxide, Magnesium Stearate, Hydroxy Propyl Cellulose, Inst moist Shiled, Methylene Chloride, Isopropyl Alcohol, Titanium Dioxide, Carnauba Wax, Bees Wax & Carbon Tetra Chloride.

Inactive ingredients (excipients) of BLUMOX-CA 625 Tablets contain Crospovidone, Colloidal Silicon Dioxide, Magnesium Stearate, Hydroxy Propyl Cellulose, Inst moist Shiled, Methylene Chloride, Isopropyl Alcohol, Titanium Dioxide, Carnauba Wax, Bees Wax & Carbon Tetra Chloride.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life

18 Months

8.3Packaging Information

10 tablets per strip.

8.4Storage and Handling Instructions

Store protected from light and moisture at temperature not exceeding 25°C.
Keep out of the reach of children.

9. Patient Counseling Information

Administration Instructions

- Patients should be counseled that antibacterial drugs should only be used to treat bacterial infections. Not to use this medicine to treat infections caused by viruses.
- Patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may decrease the effectiveness of the treatment and increase the likelihood that bacteria will develop resistance to the antibiotic and may not be treatable by amoxycillin-clavulanic acid combination therapy or other antibacterial drugs in the future.
- Advise patients that diarrhea is a common problem caused by antibacterial drugs which usually ends when the antibacterial drug is discontinued.
- Sometimes after starting treatment with antibacterial drugs, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibacterial drug. If this occurs, patients should contact their Doctor as soon as possible.
- BLUMOX-CA Tablet contains a penicillin class of drug that can cause allergic reactions in some individuals. If patient has history of allergic reaction to any penicillin class of drug in the past, BLUMOX-CA Tablets should be strictly avoided.
- Patients should be advised to take BLUMOX-CA Tablets with a meal or snack so as to reduce the possibility of gastrointestinal upset.

10. Details of Manufacturer

Twenty First CentuaryPharmaceutical Pvt Ltd. Unit-II: Khasra No 282, NalheriDehviran, Puhana, Iqbalpur Road, Roorkee- 247 668, Dist. Haridwar, Uttarakhand.

11. Details of Permission or License Number with Date

Mfg. Lic. No. 11/UA/SC / P- 2010, Date of FDA product permission 18/02/2015

12. Date of Revision

March 2021.

Marketed by:
BLUE CROSS LABORATORIES PVT LTD.
A-12, M.I.D.C., NASHIK-422 010.
Regd. Off.: Peninsula Chambers, G. K. Marg, Mumbai-400 013.