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 Injection IP

(Brand Name: BLUMOX ® - CA 1.2 g Injection)

2. Qualitative and Quantitative Composition

Each combipack contains:

a) Amoxycillin and Potassium Clavulanate Injection IP

Each vial contains:

Amoxycillin Sodium IP (Sterile) equivalent to Amoxycillin …… 1000 mg

Potassium Clavulanate IP (Sterile) equivalent to Clavulanic Acid ……. 200 mg

b) One Ampoule of

Sterile Water for Injection IP ……. 20 ml

3. Dosage Form and Strength

Dosage Form: Injection.

Dosage Strength: Amoxycillin 1000 mg with Clavulanic Acid 200 mg per vial.

4. Clinical Particulars

4.1 Therapeutic Indication

BLUMOX-CA Injection is indicated for the treatment of the following infections when caused by susceptible bacteria in adults and children:

- Severe infections of the ear, nose and throat (such as acute otitis media, mastoiditis, peritonsillar infections, epiglottitis, and sinusitis when accompanied by severe systemic signs and symptoms)
- Acute exacerbations of chronic bronchitis (AECB)
- Community acquired pneumonia (CAP)
- Cystitis
- Pyelonephritis
- Skin and soft tissue infections (SSTIs) such as cellulitis, animal bites, severe dental abscess with spreading cellulitis
- Bone and joint infections such as osteomyelitis
- Intra-abdominal infections
- Female genital infections

- Surgical prophylaxis

4.2Posology and Method of Administration

For intravenous (I.V.) use only.

Doses are expressed in terms of amoxycillin/clavulanic acid content.

Adults and Children ≥ 40 kg

Usual Recommended Dose: 1000 mg/ 200 mg (amoxycillin/clavulanic acid) every 8 hours.

For Surgical Prophylaxis: For procedures less than 1 hour in duration, the recommended dose is 1000 mg/200 mg to 2000 mg/200 mg given at induction of anesthesia (doses of 2000 mg/200 mg can be achieved by using an alternative intravenous formulation).

For procedures greater than 1 hour in duration, the recommended dose is 1000 mg/200 mg to 2000 mg/200 mg given at induction of anesthesia, with up to 3 doses of 1000 mg/200 mg in 24 hours.

BLUMOX-CA Injection provides a total daily dose of 3000 mg amoxycillin and 600 mg clavulanic acid when administered in usual recommended dosage. If a higher daily dose of the drug is required, only amoxycillin should be administered separately to avoid unnecessarily high daily doses of clavulanic acid.

Children < 40 kg

Recommended doses are:

- **Children over 3 months:** 25 mg/5 mg per kg every 8 hours.
- **Children aged less than 3 months or weighing less than 4 kg:** 25 mg/5 mg per kg every 12 hours.

Or, as prescribed by the physician.

Elderly: No dose adjustment is considered necessary.

Hepatic Impairment: Dose with caution and monitor hepatic function at regular intervals.

Renal Impairment: No dose adjustment is required in patients with creatinine clearance (CrCl) greater than 30 ml/min. In patients with renal impairment, the dose should be adjusted according to the degree of impairment as follows:

Adults and Children ≥ 40 kg

CrCl: 10-30 ml/min	Initial dose of 1000 mg/200 mg and then 500 mg/100 mg given twice daily
CrCl < 10 ml /min	Initial dose of 1000 mg/200 mg and then 500 mg/100 mg given every 24 hours
Haemodialysis	Initial dose of 1000 mg/200 mg and then followed by 500 mg/100 mg every 24 hours, plus a dose of 500 mg/100 mg at the end of dialysis

Children < 40 kg

CrCl: 10-30 ml/min	25 mg/5 mg per kg given every 12 hours
CrCl < 10 ml /min	25 mg/5 mg per kg given every 24 hours

Haemodialysis	25 mg/5 mg per kg given every 24 hours, plus a dose of 12.5 mg/2.5 mg per kg at the end of dialysis

The duration of therapy depends on type/site of infection, severity of infection, and response of the patient to the drug therapy. Treatment should not be extended beyond 14 days without review.

Method of Administration

BLUMOX-CA Injection may be administered either by slow I.V. injection over a period of 3 to 4 min directly into a vein or by I.V. infusion over 30 to 40 min. This injection is not suitable for intramuscular administration.

Children aged less than 3 months should be administered by I.V. infusion only.

Directions for Reconstitution and Dilution

Dissolve the powdered content in 20 ml of sterile water for injection (SWFI). The reconstitution/dilution is to be made under aseptic conditions. Reconstituted solutions are normally colourless or a pale straw colour. The reconstituted solution for injection is for single use only. The reconstituted solution should be used or diluted immediately, within 20 minutes. The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from visible solid particles. Any unused medicinal product or waste material should be disposed immediately.

Compatible Diluents

For administration as intravenous infusion, reconstituted solution should be added with 100 ml of compatible diluents. After dilution, solution is stable for 2 to 3 hours at room temperature (25°C) as stated in the below table.

Intravenous Infusion	**Stability Period at 25°C**
Water for Injection	3 hours
0.9% w/v Sodium Chloride Intravenous Infusion (9 mg/ml)	3 hours
Compound Sodium Chloride Injection 1959 (Ringer's)	2 hours
Compound Sodium Lactate Intravenous Infusion (Ringer-Lactate: Hartmann's)	2 hours
0.3% w/v Potassium Chloride and 0.9% w/v Sodium Chloride Intravenous Infusion (3 mg/ml and 9 mg/ml)	2 hours

Reconstituted solutions may be added to pre-refrigerated infusion bags containing either water for injection or sodium chloride infusion (0.9% w/v), which may be stored for up to 8 hours at 5 °C. Thereafter, the infusion should be administered immediately after reaching room temperature.

4.3Contraindications

BLUMOX-CA injection is 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

Test Dose: Before therapy with BLUMOX-CA injection is instituted, a test dose is recommended to ascertain possibility of hypersensitivity to ingredients of BLUMOX-CA Injection. Serious acute hypersensitivity reactions may require the use of subcutaneous epinephrine and other emergency measures.

Hypersensitivity/Anaphylactic Reactions: Before initiating therapy with amoxycillin/ clavulanic acid, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other beta-lactam agents. Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. If an allergic reaction occurs, amoxycillin/clavulanic acid therapy should be discontinued and appropriate alternative therapy instituted.

Hepatic Impairment: Amoxycillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment. 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. In all populations, 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.

Renal Impairment: In patients with renal impairment, the dose 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 amoxycillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxycillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

***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 a morbilliform skin rash. Thus, amoxycillin/clavulanic acid should not be administered to patients with mononucleosis.

Concomitant use of allopurinol during treatment with amoxycillin can increase the likelihood of allergic skin reactions.

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

Acute Generalised Exanthemous Pustulosis (AGEP): Occurrence at the treatment initiation of a feverish generalised erythema associated with pustules may be a symptom of acute generalised exanthemous pustulosis (AGEP). This reaction requires amoxycillin/clavulanic acid discontinuation, and contraindicates any subsequent administration of amoxycillin.

General: Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy.

This product contains sodium and potassium. This is to be taken into consideration by patients on a controlled sodium/potassium diet.

4.5Drug Interactions

Oral Anticoagulants: Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are cases of increased international normalised ratio (INR) in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxycillin. If co-administration is necessary, the prothrombin time or INR should be carefully monitored with the addition or withdrawal of amoxycillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary.

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. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxycillin, but not of clavulanic acid.

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 amoxycillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure. Therefore, a change in

the dose of mycophenolate mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

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. Use should be avoided during pregnancy, unless considered essential by the physician.

Lactating Women

Both substances are excreted into breast milk. Effect of clavulanic acid on the breast-fed infant is not known. Diarrhoea and fungal infection of the mucous membranes are possible in the breast-fed infant, so nursing may have to be discontinued. Amoxycillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician.

Paediatric Patients

BLUMOX-CA Injection can be administered in pediatric population. Dosage should be given as specified in the 'Posology and Method of Administration' section.

Geriatric Patients

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.

4.7Effect on Ability to Drive and Use Machines

Studies have not been available for effects of amoxycillin/clavulanic acid therapy on ability to drive and use machines. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines. If these effects are observed, patients should not drive or operate machinery.

4.8Undesirable Effects

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, mucocutaneous candidiasis, enterocolitis, and hemorrhagic/pseudomembranous colitis.

Immune: Hypersensitivity reactions, anaphylactic/anaphylactoid reactions (including shock), angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia, and frequently fever), hypersensitivity vasculitis.
Skin and Appendages: Rashes, pruritus, urticaria, erythema multiforme, Steven Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN), Drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthemous pustulosis (AGEP), and exfoliative dermatitis.
Liver: Increases in serum transaminases (AST and/or ALT), serum bilirubin, and/or alkaline phosphatase, hepatitis, and cholestatic jaundice.
Renal: Interstitial nephritis, hematuria and crystalluria
Hemic and Lymphatic Systems: Anemia, including hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with penicillins.
Central Nervous System: Agitation, anxiety, behavioral changes, aseptic meningitis, confusion, convulsions, dizziness, insomnia, and reversible hyperactivity have been reported rarely.
Miscellaneous: Tooth discoloration (brown, yellow, or gray staining) has been rarely reported. Discoloration was reduced or eliminated with brushing or dental cleaning in most cases.

4.9Overdose

Gastrointestinal symptoms and disturbance of fluid and electrolyte balance may be evident. Amoxycillin 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. Amoxycillin has been reported to precipitate in bladder catheters, predominantly after intravenous administration of large doses. A regular check of patency should be maintained.
Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance. Amoxycillin/clavulanic acid can be removed from the circulation by haemodialysis.

5. Pharmacological Properties

5.1 Mechanism of Action

Amoxycillin is a semisynthetic penicillin class of beta-lactam antibiotic. Amoxycillin produces bactericidal activity against Gram-positive and Gram-negative bacteria. Amoxycillin inhibits 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. Clavulanic acid is a beta-lactam structurally related to penicillins. Clavulanic acid alone does not exert a clinically useful antibacterial effect. Clavulanic acid inactivates plasmid-mediated beta-lactamase enzymes which are responsible for producing antimicrobial resistance.

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 combination therapy exerts antibacterial effect (bactericidal). Following is the antimicrobial spectrum of amoxycillin/clavulanic acid therapy:

Commonly susceptible species

Aerobic Gram-positive Microorganisms

- *Enterococcus faecalis*
- *Gardnerella vaginalis*
- *Staphylococcus aureus* (methicillin-susceptible)
- *Streptococcus agalactiae*
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes* and other *beta-haemolytic streptococci*
- *Streptococcus viridans* group

Aerobic Gram-negative Microorganisms

- *Actinobacillus actinomycetemcomitans*
- *Capnocytophaga spp.*
- *Eikenella corrodens*
- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- *Neisseria gonorrhoeae*
- *Pasteurella multocida*

Anaerobic Microorganisms

- *Bacteroides fragilis*
- *Fusobacterium nucleatum*
- *Prevotella spp.*

Species for which acquired resistance may be a problem

Aerobic Gram-positive Microorganisms

- *Enterococcus faecium*

Aerobic Gram-negative Microorganisms

- *Escherichia coli*
- *Klebsiella oxytoca*
- *Klebsiella pneumoniae*

- *Proteus mirabilis*
- *Proteus vulgaris*

Inherently resistant organisms

Aerobic Gram-negative Microorganisms

- *Acinetobacter sp.*
- *Citrobacter freundii*
- *Enterobacter sp.*
- *Legionella pneumophila*
- *Morganella morganii*
- *Providencia spp.*
- *Pseudomonas sp.*
- *Serratia sp.*
- *Stenotrophomonas maltophilia*

Other Microorganisms

- *Chlamydia trachomatis*
- *Chlamydophila pneumoniae*
- *Chlamydophila psittaci*
- *Coxiella burnetti*
- *Mycoplasma pneumoniae*

5.3Pharmacokinetic Properties

Absorption: Amoxycillin is well absorbed by the oral and parenteral routes. After administration of 1000/200 mg of amoxycillin/clavulanic acid by I.V. bolus injection, mean peak serum concentrations of amoxycillin and clavulanic acid were 105.4 μg/ml and 28.5 μg/ml respectively.

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 0.3-0.4 l/kg for amoxycillin and around 0.2 l/kg for clavulanic acid. Following intravenous administration, both amoxycillin and clavulanic acid have been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxycillin does not adequately distribute into the cerebrospinal fluid. Amoxycillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanic acid can also be detected in breast milk.

Metabolism: Amoxycillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10 to 25% of the initial dose. Clavulanic acid is extensively metabolized in man, and eliminated in urine and faeces and as carbon dioxide in expired air.

Elimination: The major route of elimination for amoxycillin is via the kidney, whereas for clavulanic acid it is by both renal and non-renal mechanisms.

Amoxycillin/clavulanic acid has a mean elimination half-life of approximately 1 hour and a mean total clearance of approximately 25 l/h in healthy subjects. 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 hours after the administration of a single 500/100 mg or a single 1000/200 mg bolus intravenous injection. 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 Injection is white to off white color powder filled in 20 ml clear colorless glass vials.

Each vial contains 1000 mg of amoxycillin with 200 mg of clavulanic acid for I.V. injection.

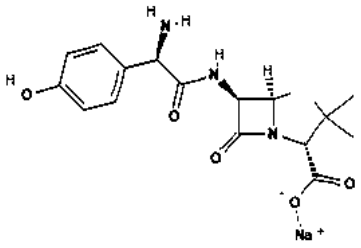
Amoxycillin Sodium

Molecular Weight: 387.4g/mol.

Molecular Formula: C16H18N3NaO5S.

Chemical Name: sodium;(2S,5R,6R)-6-[[(2R)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate.

Structural formula:



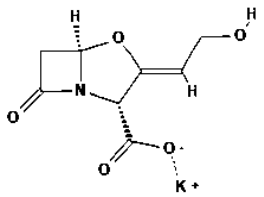
Potassium Clavulanate

Molecular Weight: 237.25 g/mol.

Molecular Formula: C8H8KNO5.

Chemical Name: potassium;(2R,3Z,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo [3.2.0] heptane-2-carboxylate.

Structural Formula:



8. Pharmaceutical Particulars

8.1 Incompatibilities

BLUMOX-CA injection should not be mixed with blood products, other proteinaceous fluids such as protein hydrolysates, or with intravenous lipid emulsions. If prescribed concomitantly with an aminoglycoside, the antibiotics should not be mixed in the same syringe, intravenous fluid container or giving set because loss of activity of the aminoglycoside can occur under these conditions. For dilution, reconstituted solutions should not be mixed with infusions containing glucose, dextran or bicarbonate.

8.2 Shelf-life

18 months.

After reconstitution and/or dilution, to avoid microbiological contamination, the solution should be used immediately. Unused/remaining portion of the solution, if any, should be discarded.

8.3 Packaging Information

Combipack of one glass vial and one 20 ml ampoule of sterile water for injection.

8.4 Storage 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

- Instruct patient to store medication as advised and not to expose the vial to moisture or direct light.
- 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 antibiotic.
- Counsel patients that diarrhea is a common problem caused by antibacterials, and it usually ends when the therapy is discontinued.

- Reconstituted solution should be used or diluted immediately within 20 minutes. Any unused medicinal product should be disposed immediately.

10.Details of Manufacturer

Aqua Vitoe Laboratories,
Plot No 4, Vill. Kunjhal, Near Jharmajri,
Baddi, Distt. Solan – 173205 (H.P.), India.

11. Details of Permission or License Number with Date

DCG(I) approval date: 07/08/1990.
Manufacturing license No. MB/07/536 dated 04/06/2016.

12. Date of Revision

November 2022.

Marketed by:
BLUE CROSS LABORATORIES PVT LTD.
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