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 Cloxacillin Capsules
(Brand Name: BLUMOX® -PLUS Capsules)

2. Qualitative and Quantitative Composition

Each hard gelatin capsule contains:
Amoxycillin Trihydrate IP equivalent to Amoxycillin …… 250 mg.
Cloxacillin Sodium IP equivalent to Cloxacillin ……. 250 mg.
Excipients…….q.s.
Colours used in capsule shell: Ponceau 4R, Carmoisine, Tartrazine& Titanium Dioxide IP, Methyl Paraben& Propyl Paraben used as antimicrobial Preservative.

3. Dosage Form and Strength

Dosage Form: Capsules.
Dosage Strength: Amoxycillin 250 mg with cloxacillin 250 mg per capsule.

4. Clinical Particulars

4.1 Therapeutic Indication

BLUMOX-PLUS Capsules are indicated for the treatment of respiratory tract infections, skin and skin structure infections and other bacterial infections due to beta-lactamse producing organisms. This product may not be effective against the "methicillin-resistant" strains of Staphylococcus.

4.2Posology and Method of Administration

For oral administration.
Adults: Usual dose is 1 to 2 capsules to be administered 3 times daily.
BLUMOX-PLUS Capsules to be administered preferably half to one hour before meals. Swallow capsule whole with water; do not open, crush or chew. The duration of therapy should be determined by the type of infection and the response of the patient.
Or, as prescribed by the physician.

4.3Contraindications

BLUMOX-PLUS Capsules are contraindicated in the following:

- Known or suspected hypersensitivity to amoxycillin or to cloxacillin or to any component of the formulation.
- History of allergic reaction to any beta-lactam antibiotic.

4.4Special Warnings and Precautions for Use

Amoxycillin

Anaphylactic Reactions: Before initiating therapy with amoxycillin, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins and cephalosporins. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of hypersensitivity to beta-lactam antibiotics.

Clostridium Difficile **Associated Diarrhea (CDAD):** CDAD has been reported with use of nearly all antibacterial agents, including amoxycillin, and may range in severity from mild diarrhea to fatal colitis. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

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

Skin Reactions: The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (AEGP). This reaction requires amoxycillin discontinuation and contra-indicates any subsequent administration. Amoxycillin 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 amoxycillin.

Overgrowth of Non-Susceptible Microorganisms: Prolonged use may also occasionally result in overgrowth of non-susceptible organisms.

Crystalluria: In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the 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.

Renal Impairment: In patients with renal impairment, the rate of excretion of amoxycillin will be reduced depending on the degree of impairment and it may be necessary to reduce the total daily dose of amoxycillin (in line with degree of renal impairment).

Use in Children: Precautions should be taken in premature children and during the neonatal period; renal, hepatic and hematological functions should be monitored.

Cloxacillin

Hypersensitivity: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients receiving penicillin therapy. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens. Careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. If an allergic or anaphylactic reaction occurs, discontinue treatment and administer the usual agents, e.g. antihistamines, pressor amines, corticosteroids.

Superinfection: Candidiasis and other super infections may occur, especially in debilitated and malnourished patients, or those with low resistance to infection due to corticosteroids, immunosuppressive agents or irradiation. If super infection occurs, institute appropriate measures.

Prolonged Therapy: During long-term therapy, renal, hepatic and hematopoietic functions should be checked periodically. Cloxacillin should be administered with caution to such patients and frequent evaluation of organ system function is recommended.

Central Nervous System (CNS) Effects: The passage of any penicillin from blood into brain is facilitated by inflamed meninges and during cardiopulmonary bypass. In the presence of such factors, particularly in renal failure when high serum concentrations can be attained, CNS adverse effects including myclonia, convulsive seizures and depressed consciousness can be expected. Although this complication has not been reported with cloxacillin, it should be anticipated.

4.5Drug Interactions

Amoxycillin

Probenecid: Probenecid decreases the renal tubular secretion of amoxycillin. Concurrent use with amoxycillin may result in increased and prolonged blood levels of amoxycillin.

Oral Contraceptives: As with other antibiotics, amoxycillin may affect the gut flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral contraceptives.

Allopurinol: Concurrent administration of allopurinol during treatment with amoxycillin can increase the likelihood of allergic skin reactions.

Oral Anticoagulants: In the literature there are rare cases of increased international normalized 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.

Cloxacillin

Probenecid: As with other penicillins, concurrent administration of probenecid enhances the serum concentration of cloxacillin.

Warfarin: Both increase and decrease in effectiveness of warfarin has been reported when warfarin is combined with cloxacillin. International normalized ratio (INR) should be checked more frequently after initiating cloxacillin. INR can increase within days of cloxacillin initiation. The increased frequency of INR testing should continue even after discontinuation of cloxacillin; as required, warfarin dosage to be adjusted until it become stable.

Methotrexate: Penicillin-type antibiotics may reduce the renal clearance of methotrexate causing hematological or gastrointestinal toxicity. Complete blood counts should be checked weekly and monitoring of gastrointestinal toxicity (e.g., mouth sores, nausea) should be assessed daily.

Sulphonamides and Aspirin: Sulphonamides and acetylsalicylic acid/aspirin inhibit serum protein binding of cloxacillin *in vitro*. This may result in increased levels of free cloxacillin in serum *in vivo*.

Allopurinol: Concurrent administration of allopurinol with cloxacillin can increase the likelihood of allergic skin reactions.

4.6Use in Special Populations

Pregnant Women

Amoxycillin: Pregnancy Category B; Cloxacillin: Pregnancy Category B. For amoxycillin, animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Limited data on the use of amoxycillin during pregnancy in humans do not indicate an increased risk of congenital malformations. There was no evidence of harm to the fetus due to cloxacillin. For this combination product, there are, however, no adequate and well-controlled studies available in pregnant women. As animal reproduction studies are not always predictive of human response, BLUMOX-PLUS Capsules should be used during pregnancy only if clearly needed.

Lactating Women

Penicillins have been shown to be excreted in human milk. Usually penicillin class of drugs can be given during lactation. However, the use of penicillins by nursing mothers may lead to sensitization of infants. Thus, caution should be exercised when BLUMOX-PLUS Capsules are administered to a nursing woman.

Paediatric Patients

Within recommended dosage, both, amoxycillin and cloxacillin can be used in children. With this formulation, dosage adjustment is not feasible in paediatric patients. Thus, due to its higher dosage strength, BLUMOX-PLUS Capsules are not indicated for use in children.

Geriatric Patients

Usually, no dose adjustment is considered necessary in elderly patients with normal renal and hepatic function. Amoxycillin is known to be substantially excreted by the kidney, and the risk of toxic 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

For both, amoxycillin and cloxacillin, no dosage adjustment is usually required in patients with mild to moderate renal impairment. However, amoxycillin is primarily eliminated by the kidney, and thus, dosage adjustment is necessary in patients with severe renal impairment. In patients with creatinine clearance <10 ml/min and in hemodialysis patients, longer dosing interval (once or twice daily dosing) and a reduction in total daily dose should be considered.

Hepatic Impairment Patients

In patients with hepatic impairment, BLUMOX-PLUS Capsules should be prescribed with caution; it is recommended to reduce the dosage frequency depending on the severity of the condition. Also, it has been suggested to monitor the hepatic function 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

Amoxycillin

The most common adverse reactions reported with amoxycillin are diarrhea, rash, vomiting, and nausea. Other less frequently or rarely reported adverse events in clinical trials and post-marketing data include following:

Mucocutaneous candidiasis; Reversible leucopenia (including severe neutropenia or agranulocytosis), reversible thrombocytopenia and haemolytic anaemia; Prolongation of bleeding time and prothrombin time; Severe allergic reactions, including angioneurotic oedema, anaphylaxis, serum sickness and hypersensitivity vasculitis; Hyperkinesia, dizziness and convulsions; Antibiotic-associated colitis (including pseudomembraneous colitis and haemorrhagic colitis); Black hairy tongue; Superficial tooth discoloration; Hepatitis and cholestatic jaundice; A moderate rise in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT); Urticaria and pruritus; Skin reactions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous and exfoliative dermatitis and acute generalised exanthematous pustulosis (AGEP); Interstitial nephritis; Crystalluria.

Cloxacillin

Gastrointestinal disturbances, such as nausea, vomiting, epigastric discomfort, flatulence and loose stools, have been reported in some patients. Rarely, mild leukopenia has occurred. Mildly elevated serum glutamic oxaloacetic transaminase (SGOT) levels (<100 units) have been reported in a few patients for whom pre-therapeutic determinations were not made. Fever, anaphylaxis and allergic reactions (rash, urticaria) including wheezing and sneezing, have occasionally been encountered. Acute generalised exanthematous pustulosis (AGEP); Eosoinophilia, with or without overt allergic manifestations, has been detected in some patients during therapy.

4.9Overdose

Amoxycillin

Symptoms: Gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident and should be treated symptomatically with attention to the water/electrolyte balance. Crystalluria, in some cases leading to renal failure, has also been reported after amoxycillin overdose in adult and pediatric patients.

Treatment: In case of overdose, adequate fluid intake and diuresis should be maintained to reduce the risk of amoxycillin crystalluria. Renal impairment appears to be reversible with cessation of drug administration. High blood levels may occur more readily in patients with impaired renal function because of decreased renal clearance of amoxycillin. Amoxycillin may be removed from circulation by hemodialysis.

Cloxacillin

Symptoms: When penicillin reaches a certain (as yet undetermined) concentration in the cerebrospinal fluid (CSF), neurotoxic symptoms may occur consisting of myoclonia, convulsive seizures, and depressed consciousness. Unless administration of the drug is stopped or its dosage reduced, the syndrome may progress to coma and death. Penicillin does not normally cross the blood-brain barrier to any substantial extent, but when massive doses are used (several grams a day) in the presence of inflamed meninges and/or impaired renal function, or in elderly patients, the drug may cause the above- mentioned toxic reactions.

Treatment: Stop administration of cloxacillin therapy temporarily and promote excretion (e.g., dialysis). Toxic serum levels and the lethal serum level of cloxacillin in man are not known.

5. Pharmacological Properties

5.1 Mechanism of Action

Amoxycillin

Amoxycillin is a penicillin class of beta-lactam antibiotics. Amoxycillin acts through the inhibition of cell wall biosynthesis during the stage of active multiplication that leads to the death of the bacteria - bactericidal action. 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 bacterial cell lysis and death.

Cloxacillin

Cloxacillin is a narrow-spectrum antibiotic of the isoxazolyl penicillin group. Cloxacillin is not inactivated by staphylococcal beta-lactamases. Cloxacillin displays less intrinsic antibacterial activity. Cloxacillin exerts a bactericidal action against susceptible microorganisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptides.

5.2Pharmacodynamic Properties

Amoxycillin

Amoxycillin has been shown to be active against most isolates of the bacteria mentioned below, both *in vitro* and in clinical infections.

Gram-Positive Bacteria

- *Enterococcus faecalis.*
- *Staphylococcus species.*
- *Streptococcus pneumoniae.*
- *Alpha and beta-hemolytic streptococci.*

Gram-Negative Bacteria

- *Escherichia coli.*

- *Haemophilus influenza.*
- *Neisseria gonorrhoeae.*
- *Proteus mirabilis.*
- *Helicobacter pylori.*

Cloxacillin

Cloxacillin demonstrates activity against strains of beta-hemolytic streptococci, pneumococci, penicillin G sensitive staphylococci and, due to its resistance to penicillinase, penicillin G resistant (beta-lactamase producing) staphylococci.

The average minimal inhibitory concentration (MIC) of cloxacillin for these organisms is as follows:

Gram+ve Bacteria	**MIC (mcg/ml)**
Streptococcus pneumoniae	0.2
Staphylococcus aureus (non-penicillinase producing)	0.2
Staphylococcus aureus (penicillinase producing)	0.4
Streptococcus pyogenes	0.05

5.3Pharmacokinetic Properties

Amoxycillin

Absorption: The absolute bioavailability of amoxycillin depends on the dose and ranges between 75 and 90%. In the dose range between 250 mg and 750 mg the bioavailability is linearly proportional to the dose. At higher doses the extent of absorption decreases. The absorption is not affected by concomitant food intake.

Distribution: Protein binding for amoxycillin is approximately 17%. Therapeutic drug levels are rapidly achieved in serum, lung tissue, bronchial secretions, middle ear fluid, bile and urine. Amoxycillin crosses the placenta and a small percentage is excreted into the breast milk.

Metabolism and Excretion: The main route of excretion of amoxycillin is the kidney. About 60 to 80% of oral dose of amoxycillin are excreted in unchanged active form in the urine within 6 hours of administration, and a small fraction is excreted in the bile. Approximately 7 to 25% of the administered dose is metabolised to inactive penicilloic acid. The serum half-life in patients with normal renal function is approximately 1 to 1.5 hour. In patients with end-stage renal failure the half-life ranges between 5 to 20 hours.

Cloxacillin

Absorption: Cloxacillin is rapidly but incompletely absorbed from the gastrointestinal tract after oral administration. Cloxacillin is stable in an acid medium and is approximately 50% absorbed orally. After an oral dose of 500 mg cloxacillin, a peak serum level of about 8 µg/ml is reached in about 1 hour. Food in the stomach or small intestine reduces absorption and peak serum levels are approximately 50% of those obtained after fasting. As with other penicillins, concurrent administration of probenecid enhances the serum concentration.

Distribution: Once absorbed, approximately 94% of cloxacillin is bound to plasma proteins.
Metabolism and Excretion: After oral administration, roughly 20% of the dose is excreted in the urine, together with one or more active metabolites. The elimination half-life of cloxacillin is about 30 minutes.

6. Nonclinical Properties

6.1 Animal Toxicology

Amoxycillin

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development. Carcinogenicity studies have not been conducted with amoxycillin.

Cloxacillin

Acute Toxicity: Cloxacillin sodium shares the lack of toxicity of other penicillins. It has been administered to mice, rats, dogs, cats and rabbits by various routes. Studies on the acute toxicity of cloxacillin sodium have shown that it has a very low acute toxicity whether given orally or parenterally. Studies on newborn rats also show low toxicity. The oral LD50 in mice was more than 5,000 mg/kg and 1,200 mg/kg by intravenous injection.
Subacute Toxicity: Cloxacillin sodium in doses of 100 mg and 500 mg/kg was administered orally and subcutaneously to two groups of 12 male rats each over a period of 12 weeks. No haematological, biochemical, histological or organ weight abnormalities were observed. Sodium cloxacillin was administered in doses of 500 mg and 2000 mg/kg twice daily to two groups of 3 dogs each for a period of 4 weeks. No haematological, biochemical or histological abnormalities were noted.
Teratogenicity: No evidence of teratogenicity was reported in a study of sodium cloxacillin given intramuscularly to female rabbits. Six pregnant rabbits were administered 250 mg/kg cloxacillin from the 8^{th} day to the 16^{th} of pregnancy. The animals given cloxacillin had no abortions and delivered normal sized litters with no fetal abnormalities.

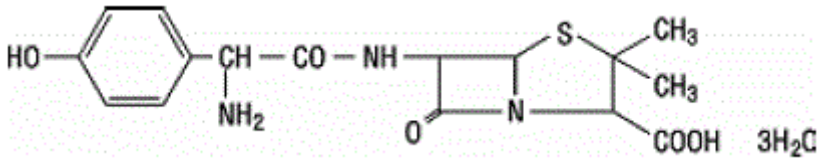
7. Description

BLUMOX-PLUS Capsules are e Red cap & yellow body, Size "0" snapfit hard gelatin capsules filled with white granular powder.
BLUMOX-PLUS Capsule contains 250 mg of amoxycillin and 250 mg of cloxacillin for oral administration in adults.

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:



Cloxacillin Sodium

Cloxacillin sodium is the sodium salt of cloxaclliin. Cloxacillin is a semisynthetic beta-lactamase resistant penicillin antibiotic with antibacterial activity.

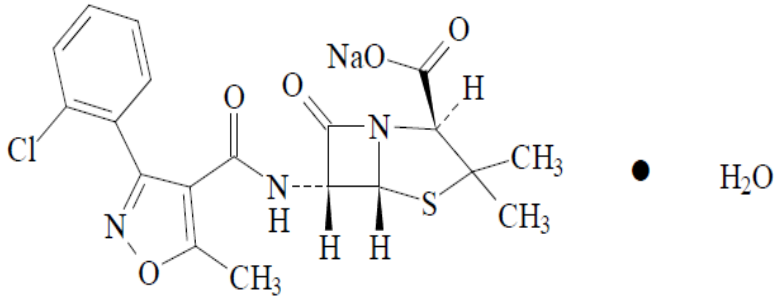
Cloxacillin sodium (monohydrate) is a white, odourless, crystalline powder.

Molecular Weight: 475.88 g/mol.

Molecular Formula: C19H17ClN3NaO5S•H2O.

Chemical Name: Sodium; (2S,5R,6R)-6-[[3-(2-chlorophenyl)-5-methyl-1,2-oxazole-4-carbonyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate; monohydrate.

Structural Formula:



Inactive ingredients (excipients) of BLUMOX-PLUS Capsule contain Magnesium Stearate, Sodium Starch Glycolate, Talc,& Hard Gelatin Capsule Shell.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life

18 Months

8.3Packaging Information

Strip of 15 capsules.

8.4Storage and Handling Instructions

Store protected from light and moisture at temperature not exceeding 30°C.

Keep out of 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.
- 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-PLUS Capsules contains amoxycillin which is a penicillin class of drug that can cause allergic reactions in some individuals. If patient has past history of allergic reaction to any penicillin class of drug, BLUMOX-PLUS Capsules should be strictly avoided.

10. Details of Manufacturer

Malik LifesciencesPvt Ltd. Plot No.16, Vardhman Industrial Estate, N H 58, Haridwar - 247667, Uttarakhand.

11. Details of Permission or License Number with Date

Mfg. Lic. No.: 48/UA/SC/P - 2013 Date of FDA Product Permission: 23/01/2018

12. Date of Revision

February 2022.

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.