pharmaniaga®

XACIL

Powder for solution for Injection or infusion 500mg

Composition:
Each vial contains:
Cloxacillin Sodium equivalent to 500mg Cloxacillin

Description:
Cloxacillin Sodium is a sterile powder supplied in an airtight container.
Before reconstitution: It is a white or almost white, crystalline powder.

After reconstitution: The solutions are clear and colourless; any opalescence produced is not more pronounced than that of reference suspension 1; any colour produced is not more intense than that of reference solution yellow or yellow green. If the solution does not comply with the requirement, stop use it immediately.

Pharmacodynamics
Pharmacotherapeutic group: Beta-lact amase resistant penicillins

ATC code: J01CF02 – Cloxacillin

Mechanism of action
Cloxacillin belongs to a group of isoxazolyl penicillins combining activity against beta-lactamase-producing staphylococci with acid stability. Cloxacillin inhibits bacterial cell wall synthesis. The effect is bactericidal. Cloxacillin exerts a bacterial action against susceptible microorganisms during the stage of active multiplication. Cloxacillin displays less intrinsic antibacterial activity and a narrower spectrum than penicillin G.

Antibacterial spectrum

Commonly susceptible species	• *Staphylococcus aureus* and, including beta-lactamase-producing strains • Streptococci • Pneumococci
Species for which acquired resistance may be a problem	• Coagulase-negative staphylococci
Inherently resistant species	• Methicillin-resistant staphylococci • Enterococci • Gram-negative bacteria *Clostridium difficile*

Resistance is common (approximately 40%) in coagulase-negative staphylococci due to methicillin resistance. Streptococci and pneumococci are more sensitive to benzylpenicillin and phenoxymethylpenicillin (penicillin V) compared to cloxacillin.

Mechanism of resistance
Resistance against isoxazolyl penicillins (methicillin resistance) is caused by the production of an altered penicillin-binding protein in bacteria. Cross resistance occurs within the beta-lactam group (penicillins and cephalosporins). In general, methicillin-resistant staphylococci show low sensitivity to all beta-lactam antibiotics.

Pharmacokinetics
Absorption
Absorption is more complete when intramuscular injection is administered, and maximum plasma concentration of approximately 15 ug/ml is reached 30 minutes after a dose of 500 mg. Protein binding: 92%

Distribution
Provides good concentration in synovial fluid, urine and gall bladder. Therapeutic serum concentration level of approximately 1 µg/ml (2.1 µmol/l) is kept for about 4 hours.

Biotransformation
Half-life in serum is approximately 30 minutes.

Elimination
Within 6 hours 30 – 50% of the oral dose is excreted in the urine. 10% is secreted as active metabolites in the urine

Indications:
Cloxacillin is indicated for the treatment of :-

- Skin and soft tissue infections caused by pneumococci.
- Upper and lower respiratory tract infection.
- Consideration should be given to official guidance on the appropriate use of antibacterial agent.

Dosage and Administration:
Parenteral drug products should be inspected visually for particulate matter and discoloration, prior to administration whenever solution and container permit.

The recommended dosages are given below. In severe, stubborn infections, a higher dosage may be administered.

Adults:
Intramuscular Use:
250 mg every 4-6 hours.

Intravenous Use:
500 mg every 4-6 hours, administered into a vein either directly or via a drip-tube over a period of 3-4min.
More rapid administration may result in convulsive seizures.

Infants and Children:
In infants up to 2 years of age, one-quarter of the adult dosage.
In children 2-10 years of age, half the adult dosage.

Renal Insufficiency:
In the presence of severe renal impairment (creatinine clearance <10ml/min) a reduction in dose or extension of dose interval should be considered

Instruction for Use
Reconstitution
For Intravenous doses (IV):
500 mg reconstitute with 4.8 ml WFI (to make 5.0 ml 100 mg/ml solution)

For Intramuscular doses (IM):
500 mg reconstitute with 1.7 ml WFI (to make 2.0 ml 250 mg/ml solution)

Further Dilution:
IV Infusion:
Dilute 1 vial to 125-250 ml diluent.

Continuous IV Infusion:
Dose >500 mg can be diluted with 500 mL diluent.

Maximum concentration 2 mg/ml.

Administration & Infusion Rate:
IM
Slow IV bolus injection: Administer the reconstituted solution over at least 3 – 5 minutes.
IV infusion: Administer over 60 minutes.
Continuous Infusion: Administer over 6 – 12 hours.

Compatible diluents for dilution:
This product is compatible with the following infusion solutions:
• Sterile water for injection
• 0.9% sodium chloride
• 5% dextrose

Route of Administration
The recommended route of administration is by intravenous and intramuscular injection.

Contraindications
Hypersensitivity to the active substance, other penicillins and to cephalosporins.

Warnings and Precautions
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 Cloxacillin, careful inquiry should be made concerning previous hypersensitivity reactions 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.

Prescribing this medication in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

Special precaution should be given to patients with asthma and history of seizure disorder.

Diarrhoea/pseudomembranous colitis caused by *Clostridium difficile* may occur. Therefore, patients suffering from diarrhoea must be closely followed.

Administration of high parenteral doses to patients with significantly reduced renal function or with injury to the blood-brain barrier can cause neurological complications in a form of spasms. If such symptoms appear, the dose must be decreased.

This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially "sodium-free".

Rapid intravenous administration of large doses of cloxacillin may cause hyperkalaemia, dysrhythmias and cardiac arrest, particularly in patients with impaired renal function.

During long-term therapy, renal, hepatic and haematopoietic functions should be checked periodically.

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 concentration can be attained, central nervous system adverse effects including myoclonia, convulsive seizures and depressed consciousness can be expected. Although this complication has not been reported with cloxacillin, it should be anticipated.

Candidiasis and other superinfections may occur, especially in debilitated and malnourished patients, or those with low resistance to infection due to corticosteroids, immunosuppressors or irradiation. If superinfection occurs, institute appropriate measures.

Experience in premature and newborn infants is limited. Cautious administration of the drug to such patients and frequent evaluation of organ system function is recommended.

Interaction with Other Medicaments
The administration of probenecid with Cloxacillin results in higher serum peak concentrations and prolongs serum concentrations of cloxacillin.

Concurrent use with allopurinol may increase the possibility of skin rash, especially in hyperuricemic patients.

Antidiarrheals, antiperistalstic (for example, opiates and diphenoxylate and atropine): Penicillins may cause pseudomembranous colitis which may result in severe water diarrhoea. Concurrent of

subsequent administration of antiperistaltic antidiarrheals is not recommended since they may delay the removal of toxins from the colon, thereby, prolonging and/or worsening the diarrhoea.

Chloramphenicol or erythromycin or sulphonamides or tetracyclines may interfere with the bactericidal effect of penicillins in the treatment of meningitis or other situations where a rapid bactericidal effect is necessary. It is best to avoid concurrent therapy. Chloramphenicol and cloxacillin are sometimes administered concurrently in paediatric patients.

Concurrent use with oral contraceptives may decrease the effectiveness of oral contraceptives. Stimulation of oestrogen metabolism or reduction in enterohepatic circulation of oestrogen can cause menstrual irregularities, intermenstrual bleeding and unplanned pregnancies. Patient should be advised to use an alternate method of contraception while taking any of these penicillins.

Probenecid may decrease renal tubular secretion of penicillins when used concurrently.

Pregnancy and Lactation
Pregnancy
FDA Pregnancy Category B. No evidence of impaired fertility or harm to the foetus.

Breastfeeding
Penicillins are distributed into breast milk, some in low concentrations. Although significant problems in humans have not been documented, the use of penicillins by nursing mothers may lead to sensitization, diarrhoea, candidiasis, and skin rash in the infant.

Adverse effects
It may be expected the most common untoward reactions will be related to sensitivity. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and cephalosporins and in those with a history of allergy, asthma, hay fever or urticaria. All degrees of hypersensitivity, including fatal anaphylaxis, have been reported with penicillin.

System Organ Class	Adverse reactions
Infections/infestations	Pseudomembranous colitis
Blood and lymphatic system	Eosinophilia
	Agranulocytosis, leucopenia, thrombocytopenia, anaemia, thrombocytopenic purpura, neutropenia 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. Thrombophlebitis has occurred during the course of intravenous therapy. Mildly elevated serum glutamic oxaloacetic transaminase (SGOT) level (less than 100 units) have been reported.
Immune system	Anaphylactic reactions Allergic reactions (rash, urticaria) including wheezing and sneezing have been reported.
Vascular	Thrombophlebitis (with intravenous injection)
Gastrointestinal	Nausea, diarrhoea, vomiting, epigastric discomfort, flatulence and loose stools have been noted in some patients.
Hepatobiliary	Cholestatic effect on the liver
Skin and subcutaneous tissue	Exanthema Urticaria
Renal and urinary	Kidney damage with increased creatinine

Overdose and Treatment
Toxicity
Large doses are usually well tolerated. However, parenteral administration of high doses has produced toxic symptoms with, for example, reduced renal function and a defect in the blood-brain barrier. Acute reactions are mainly due to hypersensitisation.

Symptoms
Toxic reactions; nausea, vomiting, diarrhoea, electrolyte disorders, decreased level of consciousness, muscle fasciculations, myoclonus, spasms, coma, haemolytic reactions, renal failure, acidosis.

In rare cases an anaphylactic reaction can occur within 20-40 minutes.

Treatment
Treatment is likely needed only in patients with severely impaired renal function, since patients with normal kidneys excrete penicillins at a fast rate. No specific treatment can be recommended.

Symptomatic treatment
In difficult cases: hemoperfusion or haemodialysis.

In anaphylactic reaction: Adrenaline 0.1-0.5 mg slowly intravenously. Hydrocortisone 200 mg intravenously, possibly promethazine 25 mg intravenously. Fluid. Acidosis correction.

Effects on ability to drive and use machine
This product has no or negligible influence on the ability to drive and use machines.

Incompatibilities
No known incompatibilities with other diluents reported.

This medicinal product must not be mixed with other medicinal products except compatible IV solution mentioned

Storage Condition
Unopened vial:
Store at temperature below 30°C in a dry place.

Opened vial:
From a microbiological point of view, unless the method of opening/reconstitution/ dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

i) **Reconstituted solution in vial**
Chemical and physical in-use stability has been demonstrated for up to 48 hours when stored at 2-8°C and 24 hours when stored at room temperature (30°C).

Diluent	Stability period
After reconstitution with Sterile Water for Injection	24 hours below 30°C 48 hours at 2-8°C

ii) **Diluted reconstituted solution, for infusion**
Chemical and physical in-use stability has been demonstrated as below for the suitable diluents:

Diluent	Stability period
After dilution with 0.9% sodium chloride	24 hours below 30°C 48 hours at 2-8°C
After dilution with 5% dextrose	12 hours below 30°C 48 hours at 2-8°C

Shelf Life:
3 years from date of manufacture.

Dosage form and Packaging available:
This product is available in glass vials. The product is packed in a carton with 1 & 10 vials.

Product Registration Holder:
PHARMANIAGA MARKETING SDN BHD
No.7, Lorong Keluli 1B, Kawasan Perindustrian Bukit Raja Selatan, Seksyen 7, 40000 Shah Alam, Selangor Darul Ehsan, Malaysia

Manufacturer:
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Date of Revision: 22 January 2025