1.4 Product Information

1. Name of the Product

Cloxacillin Sodium for Injection 500mg

2. Pharmaceutical Form:

Sterile Powder for Injection

3. Qualitative/Quantitative Composition:

Each vial contains Cloxacillin sodium 546mg equivalent to cloxacillin 500mg

4. Clinical Particulars

4.1 Therapeutic indications

Cloxacillin is indicated for the treatment of all staphylococcal infections occurring in hospitals or general practice, particularly where the infection is severe and where treatment must be initiated before the results of sensitivity tests are available. Cloxacillin is of particular value in treating mixed Gram-positive infections, e.g. infected burns where the presence of a penicillinase-producing staphylococci may inactivate other penicillins before they can exert any effect on the otherwise sensitive organisms. Cloxacillin is indicated in the following:

Pneumonia	Tonsillitis and pharyngitis
Osteomyelitis	Infected burns
Wound infections	Acute and sub-acute endocarditis
Boils and carbuncles	Staphylococcal enteritis
Abscesses and cellulitis	Staphylococcal meningitis
Otitis media	Staphylococcal urinary tract infection

4.2 Posology and method of administration

Dosage and administration

ROUTE	DOSAGE (for adults)	ADMINISTRATION
Intramuscular injection	250 mg - 500 mg six hourly	The contents of each vial should be dissolved in 1,5 mL of Water for Injections BP
Intravenous injection	500 mg four to six hourly	500 mg of Cloxacillin to be dissolved in 10 mL - 20 mL of Water for Injections BP
Intravenous	Up to 3 g daily	Cloxacillin is compatible with the commonly used

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infusion	depending on severity of infection.	the intravenous fluids and may be added to the drip bottle or, the preferably, injected directly into the drip tube over a period of two or three minutes

Dosage for children: Under two years: Quarter adult dose.

Two to ten years: Half adult dose.

Note: In severe infections the dosage may safely be increased.

As with other penicillins, concomitant administration of probenecid to patients with normal renal function raises the serum level of Cloxacillin two to five fold and the duration of inhibitory serum concentrations is prolonged to at least six hours. Probenecid may be given either as six hourly 0,5 g doses, or as twice daily 1 g doses. Such combinations are valuable in the treatment of conditions which may require higher Cloxacillin blood levels, e.g. osteomyelitis and bacterial endocarditis.

4.3 Contraindications

Allergy to penicillins is an absolute contra-indication to the use of Cloxacillin

4.4 Special warnings and special precautions for use

Allergic reactions may occur presenting as a pruritic skin rash, an erythematous skin reaction or urticaria. In this event, withdrawal of Cloxacillin and administration of an antihistamine will suffice in most cases. Should a serious anaphylactic reaction occur, Cloxacillin should be discontinued and the patient treated with the usual agents (adrenaline, corticosteroids and antihistamines). The use of this antibiotic may lead to the appearance of resistant strains of organisms and sensitivity testing should, therefore, be carried out wherever possible to ensure the appropriateness of therapy.

4.5 Interaction with other FPPs and other forms of interaction

Drug Interactions

Cloxacillin/Fusidic Acid: May diminish the therapeutic effect of cloxacillin. Therefore, administer cloxacillin at least 2 hours before fusidic acid.

Cloxacillin/Methotrexate: Serum methotrexate concentrations may be elevated, increasing the risk of toxicity. Thus, monitor for methotrexate toxicity. Measure methotrexate concentrations twice a week for at least the first 2 weeks in patients receiving low-dose oral methotrexate. May need a

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dosage adjustment for methotrexate during therapy with cloxacillin. Avoid cloxacillin immediately before and during IV methotrexate treatment.

Cloxacillin/Warfarin: Effects of warfarin may be increased, resulting in an increased risk of bleeding; therefore UNR should be closely monitored upon addition and withdrawal of cloxacillin. UNR should also be reassessed periodically during therapy since an adjustment in the warfarin dose may be necessary to maintain an effective level of anticoagulation.

Penicillins/Aminoglycosides: Concurrent therapy with penicillins has resulted in inactivation of aminoglycosides. Therefore, do not mix parenteral aminoglycosides and penicillins in the same IV solution. Monitor aminoglycoside serum concentrations and renal function and adjust dose accordingly. Penicillins and aminoglycosides are often used together to achieve synergistic action.

Penicillins/Live Typhoid Vaccine: Penicillins may interfere with the immunologic response to the vaccine. Therefore, administer oral live typhoid vaccine at least 24 hours from the last dose of the antibiotic.

Penicillins/Oral Contraceptives: Antibacterial agents may suppress intestinal flora that provide hydrolytic enzymes essential for enterohepatic recirculation of estrogens resulting in decreased contraceptive effectives. There is a possibility of contraceptive failure. Concurrent use may therefore warrant an additional form of birth control to avoid slight increased risk of pregnancy.

Penicillins/Chloramphenicol/Erythromycin/Tetracyclines/Sulfonamides: Pharmacologic and therapeutic action of penicillins could be reduced. Since bacteriostatic drugs may interfere with the bactericidal effect of penicillins in the treatment of meningitis or other conditions where a rapid bactericidal effect is necessary, it is best to avoid concurrent therapy.

Penicillins/Probenecid: Probenecid may decrease renal tubular secretion of penicillin-type drugs, resulting in increased blood levels of cloxacillin . Thus there may be an increase in the effect of cloxacillin; this effect has been utilized clinically to prolong the excretion and enhance the efficacy of penicillins.

Drug/Food Interactions (for oral cloxacillin): Food decreases the extent of absorption of cloxacillin and therefore may reduce its antimicrobial effectiveness. Administer cloxacillin on an empty stomach 1 hour before of 2 hours after meals to enhance its absorption.

Diagnostic Interference

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Treatment with penicillins may result in false positive reactions when testing for the presence of glucose in urine using Clinitest, Benedict's Solution or Fehling's Solution. Tests based on enzymatic glucose oxidase reactions such as Clinistix or Tes-Tape are not affected.

4.6 Pregnancy and lactation

Use in Pregnancy

Safety for use in pregnancy has not been established.

Use in Breastfeeding

Since penicillins are excreted in breast milk, administration of this drug to nursing mothers may lead to sensitization, diarrhea, candidiasis and skin rash in infants. Therefore, having taken into account the importance of the drug to the mother, either discontinue nursing or discontinue the drug.

4.7 Effects on ability to drive and use machines

Not reported.

4.8 Undesirable effects

Adverse Reactions

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. These reactions are more likely to occur in individuals who have previously demonstrated hypersensitivity to pencillins and in those with a history of allergy, asthma, hay fever, or urticaria.

In common with other □ -lactam antibiotics, angioedema and anaphylaxis may occur.

The following adverse reactions have been reported as being associated with the use of penicillins.

Hypersensitivity

Anaphylaxis is the most serious potential adverse reaction to a penicillin drug. It is usually associated with the administration of parenteral rather than oral dosage forms. Serious anaphylactoid reactions require immediate emergency treatment with adrenaline. Oxygen, intravenous steroids and airway management including intubation, should also be administered as indicated.

Erythematous maculopapular rashes, urticaria, and occasional cases of exfoliative dermatitis,

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erythema multiforme and Stevens-Johnson syndrome have been reported. Laryngeal edema and serum sickness-like reactions including chills, fever, serum sickness, edema and arthralgia have also been reported. Such reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to penicillin therapy.

Gastrointestinal

Glossitis, stomatitis, glossitis, black "hairy" tongue, nausea, vomiting, enterocolitis, pseudomembranous colitis and diarrhea have been observed.

4.9 Overdose

Overdosage of penicillin drugs may cause neuromuscular hyperirritability or convulsive seizures. Discontinue medication, treat symptomatically, and institute supportive measures as required. In patients with renal function impairment, the antibiotic may be removed from the circulation by hemodialysis, not by peritoneal dialysis.

5. Pharmacological Propert

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Penicillins

ATC code: J01CF02 - cloxacillin ; Belongs to the class of beta-lactamase resistant penicillins. Used in the systemic treatment of infections.

Mechanism of action

Antimicrobial Action: Inhibits bacterial cell wall synthesis. Cloxacillin is bactericidal with a mode of action similar to that of benzylpenicillin, but is resistant to staphylococcal penicillinase. It is active against penicillinase-producing and non-penicillinase-producing staphylococci, with minimum inhibitory concentrations in the range of 0.25-0.5 mcg/mL. Its activity against streptococcal eg, Streptococcus pneumoniae and Streptococcus pyogenes is less than that of benzylpenicillin, but sufficient to be useful when these organisms are present with penicillin-resistant staphylococci. Cloxacillin is virtually ineffective against Enterococcus faecalis.

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Cloxacillin exerts a bacterial action against susceptible microorganisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptides.

Cloxacillin demonstrates activity against strains of beta-hemolytic streptococci, pneumococci, penicillin G sensitive staphylococci and, due to its resistance to penicillinase, penicillin G resistant (β-lactamase producing) staphylococci. Cloxacillin displays less intrinsic antibacterial activity and a narrower spectrum than penicillin G

5.2 Pharmacokinetic properties

Pharmacokinetics:

Cloxacillin sodium is incompletely absorbed from the gastrointestinal tract; absorption is more complete when given by IM injection and peak plasma concentrations of about 15 mcg/mL have been observed 30 min after a dose of 500 mg. Doubling the dose can double the plasma concentration. About 94% of cloxacillin in the circulation is bound to plasma proteins. Cloxacillin has been reported to have a plasma half-life of 0.5-1 hr. The half-life is prolonged in neonates. Cloxacillin crosses the placenta and is excreted in breast milk. There is little diffusion into the CSF except when the meninges are inflamed. Therapeutic concentrations can be achieved in pleural and synovial fluids and in bone.

Cloxacillin is metabolized to a limited extent and the unchanged drug and metabolites are excreted in the urine by glomerular filtration and renal tubular secretion.

Plasma concentrations are enhanced if probenecid is given concomitantly. Reduced concentrations in patients with cystic fibrosis have been attributed to enhanced nonrenal clearance of cloxacillin.

5.3 Preclinical safety data

Not application.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

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36 months.

6.4 Special precautions for storage

Unopened: Store in well-closed containers not exceeding 30℃

Reconstituted: Cloxacillin Sodium for Injection should preferably be freshly prepared but will retain their anti-bacterial potency for 24 hours at room temperature (23℃), or for four days in a refrigerator (5℃).

INTRAVENOUS FLUID	STABILITY PERIOD OF Cloxacillin AT 23℃
Normal saline	24 hours
5% dextrose	24 hours
Dextrose saline	24 hours
M/6 sodium lactate	6 hours
Ringer's solution	24 hours
1,4% sodium bicarbonate	6 hours
Dextran 40 injection in normal saline	24 hours
Dextran 40 injection in 5% dextrose	24 hours

6.5 Nature and contents of container

10ml molded glass vials, non flip-off cap

50vials/tray/box, 20boxes/carton

6.6 Instructions for use and handling

Cloxacillin vials are not suitable for multi-dose use. Any residual Cloxacillin solution should be discarded

7. Marketing authorisation holder:

Reyoung Pharmaceutical Co., Ltd.

No. 1, Ruiyang Road, Yiyuan County, Shandong Province, China

8. Marketing authorisation number(s):

Lu 20160062

9. Date of first authorisation/renewal of the authorisation:

Feb. 25, 2007

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10. Date of revision of the text

Feb. 12, 2016

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