SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cloxacillin-Medo 500 mg, powder for solution for injection or infusion

Cloxacillin-Medo 1gr, powder for solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500mg or 1g of cloxacillin dry powder for solution for injection or infusion (as cloxacillin sodium).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion

A white or almost white crystalline powder.

4. CLINICAL PATICULARS

4.1. Therapeutic indications

Cloxacillin is indicated for the treatment of sensitive staphylococcal infections: respiratory infections, otorhinolaryngologic infections, renal infections, urogenital infections, neuro-meningeal infections, bone and joint infections, endocarditis, and treatment of skin infections caused by sensitive staphylococci and/or streptococci. Cloxacillin is also indicated as preventive treatment of postoperative infections in neurosurgery.

4.2. Posology and method of administration

Posology

Dosage in patients with normal renal and hepatic function:

Treatment of infections:

Adults: 6 to 12 g / day, divided into 4-6 daily administrations

Paediatric population: 100 to 200 mg / kg / day divided into 4-6 daily administrations, without exceeding 12 g / day.

Prevention of postoperative infections in adults:

the antibioprophylaxis must be of short duration, usually limited to the intraoperative period, 24 hours, but never more than 48 hours:
- 2 g IV with induction of anesthesia,
- thereafter 1 g IV every 2 hours in case of prolonged intervention.
The duration of treatment should cover the entire duration of the surgery until skin closure.

Method of administration

Cloxacillin-Medo injection is intended for intramuscular or intravenous administration.

4.3 Contraindications

Cloxacillin-Medo is contraindicated to patients hypersensitive to the active substance or other penicillins, cephalosporins, or penicillamine.
Cloxacillin- Medo should not be administered by sub-conjunctival injection.

4.4. Special warnings and precautions for use

Cloxacillin should be given with caution to patients who have had previous hypersensitivity reactions (anaphylactic reactions) to the cephalosporin's, penicillin's or other drugs. If serious acute hypersensitivity or allergic reactions take place, patients should be treated with pressor amines, antihistamines corticosteroids and/or other emergency measures. Hypersensitivity reactions can sometimes be quite severe or even fatal. Even though anaphylaxis is more likely to happen after parenteral administration they have also been induced by oral administration as well.

Extensive use of antibiotics may encourage the overgrowth of non-susceptible organisms, including fungi. In such a case, appropriate measures should be taken. It is also advised to evaluate, periodically, the renal, hepatic and hematopoietic systems.

In streptococcal infections, treatment must be adequate to eliminate the organism (10 days minimum); otherwise the sequelae of streptococcal disease may occur. The cultures should be taken when the treatment has finished so to determine whether streptococci have been eradicated.

Use caution in administration in newborns due to the risk of hyperbilirubinemia due to binding competition on serum proteins (nuclear jaundice).

Penicillins are excreted largely unchanged by the kidney. Because renal function is incompletely developed in infants, the rate of elimination of the drug tends to be slow. Penicillin-type drugs should therefore be administered with caution, particularly in neonates, and organ system function should be evaluated frequently.

4.5. Interaction with other medicinal products and other forms of interaction

Bacteriostatic antibiotics given concurrently with cloxacillin might decrease the bacteriocidal effect of penicillins as it has been shown *in vitro*. Nevertheless, the clinical significance of this interaction is not well documented.

Beta-adrenergic blockers given with cloxacillin can induce anaphylactic reactions that would make it even more difficult to treat anaphylaxis due to allergic reaction.

Chloramphenicol and cloxacillin co-administration would result to weaken the penicillin's effect and to increase the half-life of chloramphenicol.

Oral anticoagulants or heparin administrated in conjunction with high dosage of IV penicillins turn the anticoagulants agents less effective and possibly increase the risk of bleeding.

Probenecid tends to block the renal tubular secretion of penicillins and in consequence penicillins stays longer in the blood circulation.

Oral contraceptives and concomitant use of penicillins has been related with unintended pregnancies and menstrual changes. The reason being that penicillins interfere with the absorption of oral contraceptives.

4.6. Fertility, pregnancy and lactation

Pregnancy

In clinical practice, analysis of a large number of exposed pregnancies did not appear to reveal any malformative or foetotoxic effect of penicillins.

Therefore, cloxacillin may be prescribed during pregnancy if necessary.

Breast-feeding

Because cloxacillin passes into breast milk, possible suspension of breast feeding should be envisaged.

4.7. Effects on the ability to drive and use machinery

Cloxacillin does not influence the patient's ability to drive or operate machinery.

4.8. Undesirable effects

Cloxacillin, as other penicillins produces rarely adverse reactions and they are usually mild and ephemeral.

Adverse reactions listed below are classified according to frequency and System Organ Class (SOC). Frequency categories are defined according to the following convention: Very common (≥ 1/10), Common (≥ 1/100 to <

1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000), Not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Not known: Hematological reactions which are reversible including anemia, thrombopenia and leucopenia.

Immune system disorders

Very rare: anaphylactic shock.

Not known: Allergic reactions have been reported whose symptoms are fever, urticarial rash, eosinophilia, Quincke's edema,

Nervous system disorders:

Not known: High dosage of cloxacillin given to patients especially to those with renal insufficiency, may induce encephalopathie*s* which includes conscience troubles, non-physiological movement and sudden attacks of convulsion.

Gastrointestinal disorders

Rare: pseudo membranous colitis; in such case the uptake of cloxacillin should be discontinued.

Not known: nausea, vomiting, diarrhea.

Hepatobiliary disorders

Very rare: Augmentation of the transaminase enzymes ASAT and ALAT and hepatic icterus.

Not known: Cholestatic jaundice.

Skin and subcutaneous tissue disorders

Very rare: Stevens-Johnson syndrome and polymorph erythema

Not known: Skin rashes maculopapular which may be of allergic origin or not

Renal and urinary disorders

Not known: Possibility of acute immuno-allergic interstitial nephritis.

<u>Reporting of suspected adverse reactions</u>

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events

should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9. Overdosage

There has not been reported any incident of overdose of cloxacillin but should it occur discontinue medication, treat symptomatically and institute supportive measures as required.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Beta-lactamase resistant penicillin's, Antibacterials for systemic use.

ATC code: J01CF02

Cloxacillin is an antibacterial antibiotics of the beta-lactam family of the penicillin M group.

Spectrum of antibacterial activity

Critical concentrations separate the sensitive strains from the strains with intermediate sensitivity and the latter from the resistant ones:

Oxacillin (staphylococcus): S ≤ 2 mg/l and R > 2 mg/l

The prevalence of acquired resistance may vary according to geography and the weather for certain species. It is therefore useful to have information on local resistance prevalence, especially for the treatment of severe infections. These data can only give an indication about the probability of a bacterial starin's sensitivity to this antibiotic.

5.2. Pharmacokinetic properties

Absorption

Cloxacillin is stable in gastric environment. It is well absorbed by the digestive mucous (70%).

Distribution

- After oral administration, maximum blood concentrations are obtained after 1 hour and are proportional to the administered dose. They are in order of 9 mg/l for one dose of 500 mg.

- After intramuscular injection, maximum blood concentrations are obtained after about 45 minutes. In adults, they are 26 mg/l for one dose of 1g, 15 mg/l for one dose of 500 mg and 8 mg/l for one dose of 250 mg.

- After intravenous injection of 2g perfused for 20 minutes, the value of serum peak obtained at the end of the perfusion is 280 mg/l.
- Half-life is in the order of 45 minutes in patients with normal renal functions.
- Plasma protein bounding is in the order of 90%.
- The product diffuses the foetal blood, synovial liquid and bone tissue into the amniotic fluid.

Biotransformation

Cloxacillin is metabolized to a limited extent.

Elimination

After oral administration, the non-absorbed fraction is eliminated by the intestinal route in an inactive form. The absorbed fraction is eliminated in an active form essentially through urine and for 10% through the bile duct.

After administration by injection, the elimination is:

-Urinary, in an active form, in 6 hours, approximately 70 to 80% of the injected dose

- Biliary, in an active form, 20 to 30% of the injected dose.

5.3. Preclinical safety data

Animal studies showed no teratogenesis, carcinogenesis or mutagenesis. There have been no relevant studies with humans.

6. PHARMACEUTICAL DATA

6.1. List of excipients

None

6.2. Incompatibilities:

Cloxacillin is incompatible with solutions of aminoacids, lipid emulsions and blood for transfusion

6.3. Shelf-life

As packaged for sale:

The expiry date of the product is indicated on the packaging materials.

Reconstituted solution:

The product should be used immediately.

Diluted solution:

Reconstituted solution of Cloxacillin- Medo powder for solution for injection/infusion can be further diluted with Glucose 5% or Sodium Chloride 0.9%. The solutions are physically stable at 25°C for 24 hours when diluted with Sodium Chloride 0.9% and for 12 hours when diluted with Dextrose 5%.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. Reconstitution/Dilution should take place in controlled and validated aseptic conditions.

6.4. Special precautions for storage

Store below 25°C.

6.5. Nature and contents of container

Clear type III glass vials, nominal capacity 8 ml sealed with 20mm rubber stopper, and aluminium caps, labelled, and packed in a card carton.

Boxes of 1, 10, 25, 50 and 100 vials are available.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

No special precautions for disposal.

Preparation of the solution for i.m administration: Add 5 ml of water for injections into each vial of Cloxacillin-Medo 1g, respectively and shake well until complete dissolution. The solution should not be mixed with another product. Any solution left pending must be discarded.

The content of each vial of Cloxacillin-Medo 500 mg should be dissolved in 1.6 ml of water for injections to provide a concentration of 250 mg/ml and shake well until complete dissolution. The solution should not be mixed with another product. Any solution left pending must be discarded.

DO NOT USE INTRAMUSCULAR SOLVENT BY INTRAVENOUS ROUTE.

Preparation for i.v. administration: Add 20 ml of water for injections into each vial of Cloxacillin Medo 1g, respectively and shake well. For intravenous injection each vial of Cloxacillin-Medo 500 mg, respectively, should be dissolved in 10-ml water for injection and shake well.

Further dilution:

500 mg: For slow intravenous infusion reconstituted solution of Cloxacillin-Medo 500 mg can be further diluted with Glucose 5% or Sodium chloride 0.9% to concentrations between 1-20 mg/ml.

1 gr: For slow intravenous infusion Cloxacillin -Medo 1 gr can be further diluted in 100 ml of an infusion fluid. Infuse the solution slowly over a period of 60 minutes.

Reconstitution should be carried out under suitable aseptic precautions. Following reconstitution the solution should be visually examined for any foreign particulate matter and discarded if any is observed. It is recommended that reconstituted solution is used immediately following preparation.

7. MANUFACTURER:

Medochemie Ltd.- Factory B, 48 Iapetou Street, Agios Athanassios Industrial area,
4101 Agios Athanassios Limassol, Cyprus

8. MARKETING AUTHORIZATION HOLDER

A.L.MEDI-MARKET LTD, 3 Hakatif St., Emek Hefer Industrial Park, 3877701, Israel

9. MARKETING AUTHORIZATION NUMBER

Cloxacillin-Medo 500 mg: 163-32-35479-00
Cloxacillin-Medo 1 gr: 170-15-36456-99

Approved in July 2022