SUMMARY OF PRODUCT CHARACTERISTICS

1. NAMEOFTHEMEDICINALPRODUCT

Cloxacillin Sodium Capsules USP 500 mg (M-CLOX 500)

2. QUALITATIVEANDQUANTITATIVECOMPOSITION

Each hard gelatin contains:
Cloxacillin sodiumUSP Equivalent to Cloxacillin500 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICALFORM

Size 0, Blue cap and yellow body capsules filled with white granular powder.

4. CLINICALPARTICULARS

4.1 Therapeuticindications

Itisuseinthetreatmentofinfectionscausedbystreptococciwhenassociatedwithsensitivepenicillinase-producing staphylococci; also in the treatment of all staphylococcalinfections, whether penicillin G-sensitive orresistant.

In infections suspected of being caused by penicillinase-producing staphylococci, cloxacillinmay be used for initial treatment after appropriate specimens have been taken for cultureand beforeresultsofmicrobialsusceptibilitytestsareknown.Iftheresultsofidentificationand susceptibility tests indicate that the infecting organism is not apenicillinase-producing staphylococcus susceptible to cloxacillin, cloxacillin should be discontinued and treatmentwithan appropriate alternative agentinstituted.

To reduce the development of drug-resistant bacteria and maintain the effectiveness andotherantibacterial drugs, Cloxacillin sodium should be used only to treat infections that are provenor strongly suspected to be caused by susceptible bacteria. When culture andsusceptibility

informationareavailable,theyshouldbeconsideredinselectingormodifyingantibacterialtherapy. In the absence of such data, local epidemiology and susceptibility patternsmay contribute to the empiric selection oftherapy.

4.2 Posology and method of administration

Adults:

Mild to moderate infections: 250 to 500 mg every 6 hours. It should be given l to 2 hoursbeforemealsasthepresenceoffoodinthestomachandsmallintestinereducesabsorption.Maintain therapy for a minimum of 5days.

Larger doses may be required for very severeinfections. A daily dose of 6 g should not beexceeded.

Children:

Up to 5 kg (11 lb) body weight: 250mg/day.

Over5kg(11lb)uptoapproximately40kg(85lb)bodyweight:50mg/kg/day.Totaldaily dosage must be divided into 4 doses, 1 dose given every 6hours.

In infections associated with streptococcus pyogenes, treatment should be continued for atleast10 days to reduce the risk of glomerulonephritis or rheumaticfever.

4.3 Contraindications

Cloxacillin should not be given to patients with a history of penicillin allergy or administered to neonates born of mothers hypersensitive to penicillin.

Patients allergic to cephalosporins may also be allergic to penicillins.

Cloxacillin is incompatible with aminoglycosides, tetracyclines, erythromycin and polymyxin B.

4.4 Specialwarningsandprecautionsforuse

Warnings:

Seriousandoccasionallyfatalhypersensitivity(anaphylactoid)reactionshavebeenreportedin patients receiving penicillin therapy. These reactions are more apt to occur in individuals withahistory of sensitivity to multiple allergens. Careful inquiry should be made concerningprevious hypersensitivity reactions to penicillins, cephalosporins or other allergens. If an allergicor anaphylactic reaction occurs, discontinue treatment and administer the usual agents,e.g. antihistamines, pressor amines,corticosteroids.

Safety for use in pregnancy has not beenestablished.

Development of Drug ResistantBacteria

PrescribingCloxacillinintheabsenceofaprovenorstronglysuspectedbacterialinfectionis unlikely to provide benefit to the patient and risks the development of drug-resistantbacteria.

Precautions:

Candidiasis and other superinfections may occur, especially in debilitated andmalnourished patients,orthosewithlowresistancetoinfectionduetocorticosteroids,immunosuppressiveagents or irradiation. If superinfection occurs, institute appropriatemeasures.

During long-term therapy, renal, hepatic and hematopoietic functions should bechecked periodically.

Experienceinprematureandnewborninfantsislimited.Cautiousadministrationofthedrugto such patients and frequent evaluation of organ system function isrecommended.

The passage of any penicillin from blood into brain is facilitated by inflamed meningesand duringcardiopulmonarybypass.Inthepresenceofsuchfactors,particularlyinrenalfailurewhen high serum concentrations can be attained, central nervous system adverse effects including myoclonia, convulsive seizures and depressed consciousness can beexpected. Although this complication has not been reported with cloxacillin, it should beanticipated.

4.5 Interaction with other medicinal products and other forms of interaction

BCG (Intravesical): Antibiotics may diminish the therapeutic effect of BCG (Intravesical). Avoid combination

BCG Vaccine (Immunization): Antibiotics may diminish the therapeutic effect of BCG Vaccine (Immunization). Monitor therapy

Methotrexate:Penicillins may increase the serum concentration of Methotrexate. Monitor therapy

Mycophenolate:Penicillins may decrease serum concentrations of the active metabolite(s) of Mycophenolate. This effect appears to be the result of impaired enterohepatic recirculation. Monitor therapy

Probenecid: May increase the serum concentration of Penicillins. Management: Avoid the routine use of penicillins and probenecid, but this combination may be used advantageously in select cases with careful monitoring. Monitor for toxic effects of penicillins if probenecid is initiated or the dose is increased. Consider therapy modification

Sodium Picosulfate: Antibiotics may diminish the therapeutic effect of Sodium Picosulfate. Management: Consider using an alternative product for bowel cleansing prior to a colonoscopy in patients who have recently used or are concurrently using an antibiotic. Consider therapy modification

Tetracycline Derivatives: May diminish the therapeutic effect of Penicillins. Consider therapy modification

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. Management: Vaccination with live attenuated typhoid vaccine (Ty21a) should be avoided in patients being treated with systemic antibacterial agents. Use of this vaccine should be postponed until at least 3 days after cessation of antibacterial agents. Consider therapy modification

Vitamin K Antagonists (eg, warfarin): Cloxacillin may diminish the anticoagulant effect of Vitamin K Antagonists. Cloxacillin may enhance the anticoagulant effect of Vitamin K Antagonists. Monitor therapy

Acute haemolytic anaemia

Care should be taken when administering high doses of cloxacillin especially to patients with impaired renal function as there is a risk of neuro-toxicity and congestive heart failure.

Disturbance of electrolyte balance may occur following administration of large doses. Increases in liver enzyme values have been reported.

Renal and haematological systems should be monitored during prolonged and high dose therapy, patients with syphilis may exhibit the Jarish-Herxheimer reaction and should also therefore be monitored

4.6 Fertility, pregnancy and lactation

Pregnancy

Cloxacillin has been assigned to pregnancy category B. There are no controlled data in human pregnancies; however, there are no literature reports of congenital abnormalities associated

with it. Cloxacillin should only be given during pregnancy when need has been clearly established.

Breastfeeding

There are no data on the excretion of cloxacillin into human milk. Other penicillins are excreted into human milk in small amounts. Adverse effects in the nursing infant are unlikely.

4.7 Effectsonabilitytodriveandusemachines

Nostudiesontheeffectsontheability todriveandusemachineshavebeenperformed.However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), whichmayinfluencetheabilityto driveand usemachines.

4.8 Undesirableeffects

Gastrointestinaldisturbances,suchasnausea,vomiting,epigastricdiscomfort,flatulenceand loosestools,havebeennotedinsomepatients.Rarely,mildleukopeniahasoccurred.Mildly elevatedSGOTlevels(lessthan100units)havebeenreportedinafewpatientsforwhompre- therapeutic determinations were not made. Fever, anaphylaxis and allergicreactions(rash, urticaria) including wheezing and sneezing, have occasionally beenencountered.

Eosoinophilia,withorwithoutovertallergicmanifestations,hasbeennotedinsomepatients during therapy. Thrombophlebitis has occurred occasionally I.V.therapy.

Reportingofsuspectedadversereactions

Reportingsuspectedadversereactionsafterauthorisationofthemedicinalproductisimportant.It allows continued monitoring of the benefit/risk balance of the medicinal product.Healthcareprofessionalsare askedto reportany suspectedadverse reactions via theYellow CardSchemeat:www.mhra.gov.uk/yellowcard.

4.9 Overdose

When penicillin reaches a certain (as yet undetermined) concentration in the cerebrospinalfluid, neurotoxic symptoms may occur consisting of myoclonia, convulsive seizures, anddepressed consciousness. Unless administration of the drug is stopped or its dosage reduced, thesyndromemayprogresstocomaanddeath.Penicillindoesnotnormallycrosstheblood-brainbarrierto any substantial extent, but when massive doses are used (several grams a day) in the presenceof inflamed meninges and/or impaired renal function, or in elderly patients, the drug may causetheabove- mentioned toxic reactions. No antidote isrequired.

Discontinue medication, induce prompt elimination of unabsorbed drug. Employ supportive measures to control allergic reactions with conventional therapy (i.e., administration of empinephrive corticosteroids, antihistamines) as indicated. In patients with renal function impairment cloxacillin class antibiotics and be removed by hemodiallysis but not by peritonialdialysis.

Treatment ofoverdose:

Stop administration temporarily - promote excretion (dialysis,etc.). Toxic serum levels and the lethal serum level of cloxacillin in man are notknown

5. PHARMACOLOGICALPROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Semisynthetic penicillin antibiotics

ATC code:J01CF02.

Mechanism of action:

Inhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibit the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Sodiumcloxacillinmonohydrateisrapidlybutincompletelyabsorbedfromthegastrointestinaltra ct after oraladministration.

Whenadoseof500mgcloxacillinsodium(2x250mgcloxacillinsodiumcapsules)was administeredtofastingadultvolunteersameanpeakplasmalevelof8.5mcg/mLwasobtained with a Tmax of 0.88hr.

A dose of 500 mg cloxacillin sodium reconstituted granules for oral solution yielded peakplasmalevels of 13.3 mcg/mL with a Tmax of 0.58 hr. in fasting adultvolunteers.

Oral doses of 250 mg sodium cloxacillin to adult fasting volunteers resulted in 4.8 mcg/mLpeak serum levels with a Tmax of 1hr.

Mean urinary excretion of cloxacillin after an oral dose of 500 mg was found to be 37%.8Totalurinary excretion in healthy volunteers was 62% of an intravenously injected dose of 750mg (250 mg/hr for threehours).

Fooddelaystheabsorptionofcloxacillinsodium.cloxacillin.9,10Sodiumcloxacillinisbound to serum proteins to the extent of94%.

Theplasmahalf-lifeofcloxacillinisreportedtobe25minutesinhealthyvolunteersfollowing infusion of 750 mg over a 3 hour period.12 The plasma half-life in uremic patients wasincreasedto 49minutes.

Cloxacillin passage across the CNS barrier is insufficient for practical purposes unlessthemeninges are inflamed. Cloxacillin passes the placental barrier as do the penicillins to theextentof about 50% of the mothers plasmalevel.
Serum concentrations are enhanced if probenecid is givenconcomitantly

5.2 Pharmacokinetic properties

Absorption:

Cloxacillin sodium is incompletely absorbed from the gastro intestinal tract after oral administration, and absorption is further reduced by the presence of food in the stomach. After an oral dose of 500 mg, a peak plasma concentration of 7 to 14 µg/ml is obtained in faring subjects in 1 to 2 hours. Absorption is more complete when given by intramuscular injection and peak plasma concentrations of about 15 µg/ml have been observed 30 minutes after a dose of 500 mg. Doubling the dose can double the plasma concentrations. Oral: ~50%; reduced by food

Distribution:

Widely to most body fluids and bone; penetration into cells, into eye, and across normal meninges is poor; inflammation increases amount that crosses blood-brain barrier.

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 to 1 hour. 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 bone.

Biotransformation:

Metabolised by liver to active and inactive metabolites

Elimination:

Cloxacillin is metabolised to a limited extent, and the unchanged drug and metabolites are excreted in the urine by glomerular filtration and renal tubular secretion. About 35% of an oral dose is excreted in the urine and upto 10% in the bile.

5.3 Preclinical safety data:

Not applicable

6. PHARMACEUTICALPARTICULARS

6.1 Listof excipients

- Ethyl cellulose
- Colloidal silicon dioxide
- Acetone
- Talc
- Maize starch
- Magnesium stearate

6.2 Incompatibilities

Notapplicable

6.3 Shelf life

36months.

6.4 Specialprecautionsforstorage

Store in a dry place below 30°C. Protect from light.

6.5 Natureandcontents ofcontainer

PrimaryContainer(s): Cloxacillin sodium Capsules(M-CLOX 500) isavailable in 10x10's, 50x10's & 100x 10's Strip pack

SecondaryContainer:

Each Strip packed in a Printed Carton with relevant batch details along withleaflet.

- Carton: ITCCyber XLwithaquavarnishsideopenwith300GSMmulti-colours.
- Leaflet:60GSMMaplithopaper.

OuterContainer:

Such cartons are packed in Export Worthy 5/7 Ply Shippers. These shippers are labeled with product name and relevant batch details and sealed with BOPP tape. Shippersare then strapped with Polypropylenetapes.

6.6Specialprecautionsfordisposalandotherhandling

Not applicable

7. Marketing authorizationholder

NameandPermanentaddressoftheMarketingauthorizationholder:

Medopharm, Private limited

"MEDOHOUSE"

25, Puliyur II Mainroad,Trustpuram, Chennai-600024,

Tamil Nadu,India.

PH: +9144-30149992/30149955

Fax: 260211286283

Manufacturing Siteaddress:

Medopharm Private Limited,

No. 50, KayarambeduVillage,

Guduvanchery-603 202, Tamil Nadu,India.

8. Number (s) in the National register of finished pharmaceuticalproducts

First registration – MED/IND/006 Certificate No.: 280/04

Second registration - MED/IND/006 Certificate No.: R/044/10

Renewal registration - 06296/08041/REN/2021

9. Date of first authorization/renewal of theauthorization

First authorization – 18/06/2012

Second authorization - 18/08/2017

Renewal authorization - 25.07.2021

10. Date of revision of thetext

13.07.2023