PRODUCT MONOGRAPH

PrTEVA-CLOXACILLIN

(cloxacillin sodium)
250 and 500 mg Capsules
125 mg/5 mL Granules for Oral Solution

USP

Antibiotic

Teva Canada Limited
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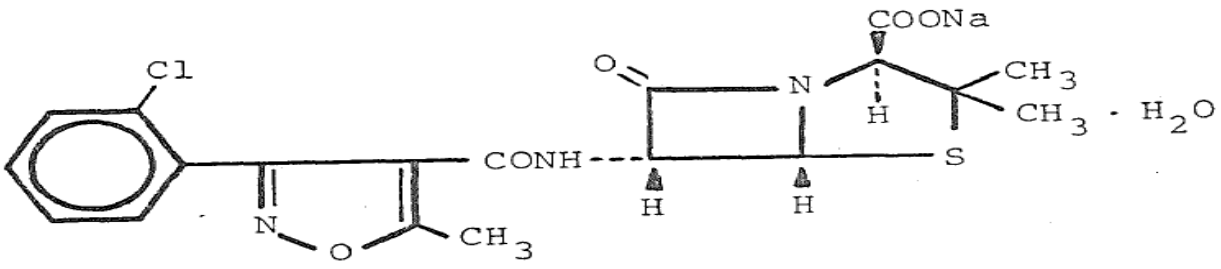
Date of Revision:
September 28, 2016

Control: 190001

STRUCTURAL FORMULA AND CHEMISTRY

Cloxacillin Sodium:



Molecular Formula: $C_{19}H_{17}ClN_3NaO_5S\bullet H_2O$

Molecular Weight: 475.88 g/mol

Chemical Name: Monosodium 6-[3-(o-chlorophenyl)-5-methyl-4- isoxazolecarboxamido]-3,3-dimethyl-7-oxo-4- thia-l-azabicyclo[3.2.0]heptane-2-carboxy- late monohydrate.

Description: Cloxacillin sodium is a white, odorless, crystalline powder, with an intensely bitter taste. Each g represents 2.1 mEq of sodium. One part is soluble in 2.5 parts of water, and a 10% aqueous solution has a pH of 5 to 7.

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THERAPEUTIC CLASSIFICATION

Cloxacillin sodium is an antibiotic belonging to the semi-synthetic penicillin family.

ACTION

TEVA-CLOXACILLIN exhibits a bacterial action against sensitive organisms during the active multiplication stage. It acts through the inhibition of biosynthesis of cell wall mucopeptides.

INDICATIONS AND CLINICAL USE

TEVA-CLOXACILLIN (cloxacillin sodium) finds use in the treatment of infections caused by streptococci when associated with sensitive penicillinase-producing staphylococci; also in the treatment of all staphylococcal infections, whether penicillin G-sensitive or resistant.

In infections suspected of being caused by penicillinase-producing staphylococci, cloxacillin may be used for initial treatment after appropriate specimens have been taken for culture and before results of microbial susceptibility tests are known. If the results of identification and susceptibility tests indicate that the infecting organism is not a penicillinase-producing staphylococcus susceptible to cloxacillin, cloxacillin should be discontinued and treatment with an appropriate alternative agent instituted.

CONTRAINDICATIONS

A history of allergic reactions to penicillin or cephalosporins.

WARNINGS

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.

Safety for use in pregnancy has not been established.

PRECAUTIONS

Candidiasis and other superinfections 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.

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

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.

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, central nervous system 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.

ADVERSE REACTIONS

Gastrointestinal disturbances, such as nausea, vomiting, epigastric discomfort, flatulence and loose stools, have been noted in some patients. Rarely, mild leukopenia has occurred.Mildly elevated SGOT levels (less than 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.

Eosoinophilia, with or without overt allergic manifestations, has been noted in some patients during therapy. Thrombophlebitis has occurred occasionally I.V. therapy.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

When penicillin reaches a certain (as yet undetermined) concentration in the cerebrospinal fluid, 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. No antidote is required.

Treatment of overdose:
Stop administration temporarily - promote excretion (dialysis, etc.).

Toxic serum levels and the lethal serum level of cloxacillin in man are not known.

MICROBIOLOGY

TEVA-CLOXACILLIN (cloxacillin sodium) is bactericidal and has an anti- bacterial spectrum similar to that of benzylpenicillin but is less active. It is also effective in the dosage recommended for treatment of infections caused by streptococci and penicillin-G sensitive staphylococci.

The average minimal inhibitory concentrations (M.I.C.) of sodium cloxacillin monohydrate for these organisms are as follows: [1, 2, 3, 4, 5]

MICROORGANISMS	USUAL M.I.C. µg/mL	M.I.C. RANGE µg/mL
Streptococcus pneumoniae	0.20	0.10-0.80
Staphylococcus aureus non-penicillinase producing	0.20	0.10-1.60
Staphylococcus aureus penicillinase producing	0.40	0.10-1.60
Streptococcus pyogenes	0.05	0.02-0.10

PHARMACOLOGY

Sodium cloxacillin monohydrate is rapidly but incompletely absorbed from the gastrointestinal tract after oral administration.

When a dose of 500 mg TEVA-CLOXACILLIN (2x 250 mg TEVA-CLOXACILLIN Capsules) was administered to fasting adult volunteers a mean peak plasma level of 8.5 µg/mL was obtained with a T_{max} of 0.88 hr.[6]

A dose of 500 mg TEVA-CLOXACILLIN reconstituted granules for oral solution yielded peak plasma levels of 13.3 µg/mL with a T_{max} of 0.58 hr. in fasting adult volunteers.[7]

Oral doses of 250 mg sodium cloxacillin to adult fasting volunteers resulted in 4.8 µg/mL peak serum levels with a T_{max} of 1 hr.[8]

Mean urinary excretion of cloxacillin after an oral dose of 500 mg was found to be 37%.[8] Total urinary excretion in healthy volunteers was 62% of an intravenously injected dose of 750 mg (250 mg/hr for three hours). [12]

Food delays the absorption of cloxacillin sodium.cloxacillin. [9, 10] Sodium cloxacillin is bound to serum proteins to the extent of 94%. [11]

The plasma half-life of cloxacillin is reported to be 25 minutes in healthy volunteers following infusion of 750 mg over a 3 hour period. [12] The plasma half-life in uremic patients was increased to 49 minutes.

Cloxacillin passage across the CNS barrier is insufficient for practical purposes unless the meninges are inflamed. Cloxacillin passes the placental barrier as do the penicillins to the extent of about 50% of the mothers plasma level.

Serum concentrations are enhanced if probenecid is given concomitantly. [10]

TOXICOLOGY

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 LD_{50} in mice was more than 5,000 mg/kg and 1,200 mg/kg by intravenous injection. [3]

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. [3]

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.[3]

Teratogenicity

No evidence of teratogenicity was reported in a study of sodium cloxacillin given intramuscularly to female rabbits.[13] Six pregnant rabbits were administered 250 mg/kg cloxacillin from the 8th day to the 16th of pregnancy. The animals given cloxacillin had no abortions and delivered normal sized litters with no fetal abnormalities.

DOSAGE AND ADMINISTRATION

Adults: Mild to moderate infections: 250 to 500 mg every 6 hours.
It should be given 1 to 2 hours before meals as the presence of food in the stomach and small intestine reduces absorption. Maintain therapy for a minimum of 5 days.
Larger doses may be required for very severe infections.
A daily dose of 6 g should not be exceeded.

Children: Up to 5 kg (11 lb) body weight: 250 mg/day.
Over 5 kg (11 lb) up to approximately 40 kg (85 lb) body weight: 50 mg/kg/day. Total daily dosage must be divided into 4 doses, 1 dose given every 6 hours.

In infections associated with streptococcus pyogenes, treatment should be continued for at least 10 days to reduce the risk of glomerulonephritis or rheumatic fever.

AVAILABILITY OF DOSAGE FORMS

TEVA-CLOXACILLIN (cloxacillin sodium) is available as:
250 mg: orange and black capsule (size #1) imprinted 'novo 250' containing 250 mg of cloxacillin.
500 mg: orange and black capsule (size #0) imprinted 'novo 500' containing 500 mg of cloxacillin.
125 mg/5 mL: cherry flavoured solution.

Supplied: Both 250 mg and 500 mg capsules are supplied in bottles of 100. The granules for oral solution are supplied in bottles of 100 mL.

STORAGE AND STABILITY

Capsules: Store 15 – 25°C
Granules for Oral Solution: Reconstituted Solution: - 14 days under refrigeration (6°C).

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