

PRESCRIBING INFORMATION

PrAPO-CLOXI

Cloxacillin Sodium Capsules

250 and 500 mg cloxacillin

USP

ANTIBIOTIC

**APOTEX INC.
150 Signet Drive
Toronto, Ontario
M9L 1T9**

**DATE OF REVISION:
July 7, 2020**

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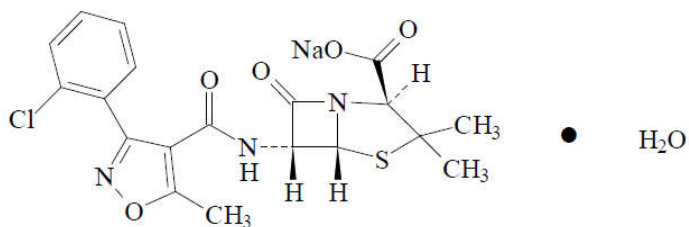
PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common Name: Cloxacillin Sodium

Chemical Names: 1) 4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[[3-(2-chlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo-, monosodium salt, monohydrate, [2*S*-(2 α ,5 α ,6 β)]-
2) Monosodium (2*S*, 5*R*, 6*R*)-6-[3-(*o*-chlorophenyl)-5-methyl-4-isoxazolecarboxamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0]heptane-2-carboxylate monohydrate

Structural Formula:



Molecular Formula: C₁₉H₁₇ClN₃NaO₅S · H₂O

Molecular Weight: 475.88 g/mol

Description: Cloxacillin sodium is a white, odorless, crystalline powder. It is freely soluble in water, soluble in alcohol and slightly soluble in chloroform.

Composition

In addition to cloxacillin sodium, APO-CLOXI capsules also contain the non-medicinal ingredients colloidal silicon dioxide, stearic acid, and talc (as an antistatic agent). The capsule shells, imprinted with edible white ink, contain the non-medicinal ingredients D&C yellow #10, FD&C blue #1, FD&C red #40, FD&C yellow #6, gelatin, silicon dioxide, sodium lauryl sulfate and titanium dioxide.

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THERAPEUTIC CLASSIFICATION

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

ACTION

APO-CLOXI 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

APO-CLOXI (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.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of APO-CLOXI and other antibacterial drugs, APO-CLOXI should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

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.

Susceptibility/Resistance

Development of Drug Resistant Bacteria

Prescribing APO-CLOXI 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.

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCAR) such as acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) have been reported in association with beta-lactam treatment. When SCAR is suspected, APO-CLOXI should be discontinued and appropriate therapy and/or measures should be taken.

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 superinfection 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 myoclonia, 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.

Eosinophilia, 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

APO-CLOXI (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. mcg/mL	M.I.C. RANGE mcg/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 cloxacillin sodium (2 x 250 mg cloxacillin sodium capsules) was administered to fasting adult volunteers a mean peak plasma level of 8.5 mcg/mL was obtained with a T_{max} of 0.88 hr.⁶

A dose of 500 mg cloxacillin sodium reconstituted granules for oral solution yielded peak plasma levels of 13.3 mcg/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 mcg/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 LD₅₀ 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.

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

Capsules

250 mg: Each orange and black no. 2 capsule, identified APO 250, contains cloxacillin sodium equivalent to cloxacillin 250 mg. Available in bottles of 100 and 1000 capsules.

500 mg: Each orange and black no. 0 capsule, identified APO 500, contains cloxacillin sodium equivalent to cloxacillin 500 mg. Available in bottles of 100 and 500.

STORAGE AND STABILITY

Stability and Storage Recommendations

Store at room temperature not exceeding 25°C.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

**Pr APO-CLOXI
Cloxacillin Sodium Capsules**

**250 and 500 mg cloxacillin
USP**

Read this carefully before you start taking APO-CLOXI and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about APO-CLOXI.

What is APO-CLOXI used for?

APO-CLOXI is used to treat infections that are caused by certain bacteria.

Antibacterial drugs like APO-CLOXI treat only bacterial infections. They do not treat viral infections.

How does APO-CLOXI work?

APO-CLOXI is an antibiotic that works by:

- Stopping the growth of bacteria.
- Killing bacteria.

What are the ingredients in APO-CLOXI?

Medicinal ingredients:

Cloxacillin Sodium

Non-medicinal ingredients:

Capsule: Colloidal silicon dioxide, stearic acid, and talc (as an antistatic agent). The capsule shell, imprinted with edible white ink, contain D&C yellow #10, FD&C blue #1, FD&C red #40, FD&C yellow #6, gelatin, silicon dioxide, sodium lauryl sulfate and titanium dioxide.

APO-CLOXI comes in the following dosage forms:

Capsules: 250 mg and 500 mg

Do not use APO-CLOXI if:

- You have had an allergic reaction to APO-CLOXI or other medicines such as cephalosporins or penicillins.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-CLOXI. Talk about any health conditions or problems you may have, including if you:

- Have severe kidney disease with or without significant liver disease
- Are pregnant or could become pregnant during treatment
- Are breast feeding

How to take APO-CLOXI:

- Take APO-CLOXI 1-2 hours before eating.
- Although you may feel better early in treatment, APO-CLOXI should be used exactly as directed.
- Misuse or overuse of APO-CLOXI could lead to the growth of bacteria that will not be killed by APO-CLOXI (resistance). This means that APO-CLOXI may not work for you in the future.
Do not share your medicine.

Usual Dose:

Adults: 250 mg to 500 mg every 6 hours. Do not take more than 6000 mg daily.

Overdose:

If you think you have taken too much APO-CLOXI, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using APO-CLOXI?

These are not all the possible side effects you may feel when taking APO-CLOXI. If you experience any side effects not listed here, contact your healthcare professional.

- Upper stomach pain
- Flatulence

Other side effects may occur that usually do not need medical attention. These side effects may go away during treatment as your body adjusts to the medicine. However, check with your doctor for any side effect that seems unusual or that is especially bothersome.

Serious side effects and what to do about them:

Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Rare	an allergic reaction (difficulty in breathing, closing of the throat, swelling of the lips, face or tongue; hives or a rash)			√
	redness, or itching			√
	severe nausea, vomiting, or diarrhea			√
	Severe Cutaneous Adverse Reactions (SCAR) (severe skin reactions that may also affect other organs): • Skin peeling, scaling, or blistering (with or			√

Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
without pus) which may also affect your eyes, mouth, nose or genitals, itching, severe rash, bumps under the skin, skin pain, skin color changes (redness, yellowing, purplish) <ul style="list-style-type: none"> • Swelling and redness of eyes or face • Flu-like feeling, fever, chills, body aches, swollen glands, cough • Shortness of breath, chest pain or discomfort 			

This is not a complete list of side effects. For any unexpected effects while taking APO-CLOXI, contact your doctor or pharmacist.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

How to store APO-CLOXI:

Capsules: Store at room temperature not exceeding 25°C.

Keep out of reach and sight of children.

If you want more information about APO-CLOXI:

- Talk to your healthcare professional
- Find the full Prescribing Information that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>). Find the Patient Medication Information on the manufacturer's website <http://www.apotex.ca/products>, or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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