

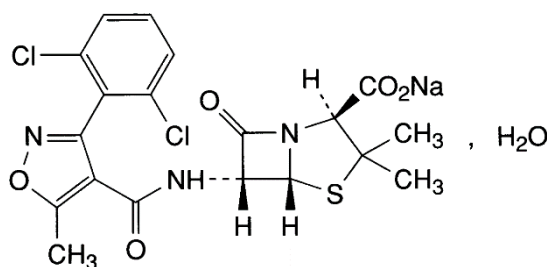
PRODUCT INFORMATION

Name of the Medicine

Active ingredient: dicloxacillin (as dicloxacillin sodium).

Chemical name: (6R)-6-[3-(2, 6-dichlorophenyl)-5-methylisoxazole-4-carboxamido]-penicillanate.

Structural formula:



Molecular Formula: $C_{19}H_{16}Cl_2N_3NaO_5S \cdot H_2O$

Molecular Weight: 510.3

CAS Registry No: 13412-64-1

Description

Dicloxacillin sodium is an antibiotic and a member of the isoxazolyl penicillins. Dicloxacillin sodium is a white or almost white, crystalline powder. It is hygroscopic, freely soluble in water, soluble in alcohol and in methanol.

Each capsule contains dicloxacillin sodium equivalent to 250 mg or 500 mg dicloxacillin. The inactive ingredients present are colloidal anhydrous silica, magnesium stearate, gelatin, titanium dioxide, purified water and TekPrint SW-9008 (ARTG No: 2328).

Pharmacology

Pharmacokinetics

Absorption. Dicloxacillin is resistant to destruction by acid. Absorption from the gastrointestinal tract is rapid, in fasting adults, 50% to 94% of an oral dose was absorbed with peak levels occurring 0.5 to 2 hours. The bioavailability of dicloxacillin is decreased in the presence of food.

Serum levels after oral administration are directly proportional to dosage at unit doses of 125 mg, 250 mg, and 500 mg as measured at the 2-hour level. Single oral doses of dicloxacillin 500 mg produced peak serum concentrations of 10 to 18 microgram/mL.

Distribution. Dicloxacillin is 95 - 99% bound to serum proteins, mainly albumin. Dicloxacillin is distributed into bone, bile, pleural fluid, and synovial fluid. Only minimal concentrations are attained in the cerebrospinal fluid.

Metabolism and Excretion. The elimination half-life of dicloxacillin is approximately 0.7 hours. Dicloxacillin is partially metabolised to microbiologically active (5-hydroxymethyl derivative of dicloxacillin) and inactive metabolites. Dicloxacillin and its metabolites are rapidly excreted in the urine by glomerular filtration and tubular secretion, approximately 50% of the absorbed dose is excreted unchanged in the urine. The drug is also

partially excreted in the faeces via biliary elimination.

Reduced plasma concentrations have been reported in patients with cystic fibrosis. This is attributed to enhanced elimination of the drug in these patients.

In patients with severe renal impairment, the half life of dicloxacillin has been reported to increase two to three fold, however, extra renal elimination prevents significant drug accumulation in these patients (see Dosage and Administration).

Dicloxacillin is not dialysable. Only minimal amounts are removed by haemodialysis or peritoneal dialysis.

Pharmacological Actions

Dicloxacillin sodium is a semisynthetic penicillin that resists inactivation by staphylococcal β -lactamase (penicillinase). Penicillinase resistant penicillins exert a bactericidal action against penicillin-susceptible microorganisms during active multiplication. All penicillins inhibit the biosynthesis of the bacterial cell wall.

Dicloxacillin is a narrow spectrum antibiotic with activity against the following Gram-positive organisms: susceptible staphylococci, *Streptococcus pyogenes*, "Viridans" group streptococci, *Streptococcus pneumoniae*. Because of its resistance to the enzyme penicillinase, it is active against penicillinase producing staphylococci.

Dicloxacillin is not active against methicillin-resistant *Staphylococcus aureus*.

Disc Susceptibility Tests

The most precise estimates of antibiotic susceptibility are given by quantitative methods that require measurement of zone diameters. The results of agar diffusion sensitivity tests for methicillin determined in accordance with NCCLS[^] M100-S6, M2-A5, can be applied to other β -lactamase-resistant penicillins including dicloxacillin. The NCCLS "Zone Interpretative Standards and Equivalent Minimum Inhibitory Concentrations (MIC) Breakpoints for organisms other than *Haemophilus spp*, *Neisseria gonorrhoea*, and *Streptococcus*," gives sensitivity results for methicillin against various staphylococcal bacteria, which are as follows:-

Bacteria	Methicillin discs 5 microgram				
	Zone diameter, Nearest Whole mm			Equivalent MIC breakpoints (microgram/ mL)	
	Susceptible	Intermediate	Resistant	Susceptible	Resistant
staphylococci	≥ 14	10-13	≤ 9	≤ 8	≥ 16

[^] Available from NCCLS, Lancaster avenue, Villanova, Pennsylvania 19085, USA

A report of 'susceptible' indicates the infecting organism is likely to response to therapy. A report of 'intermediate' suggests the organism would be susceptible if high dosage is used or if the infection is confined to tissues in which high concentrations of dicloxacillin are obtained, for example in urine. A report of 'resistant' indicates that the infection is unlikely to response to therapy with the antibiotic.

Indications

Treatment of confirmed or suspected staphylococcal and other Gram positive coccal infections, including skin and skin structure and wound infections, infected burns, cellulitis, osteomyelitis and pneumonia (note: benzylpenicillin is the drug of choice for the treatment of streptococcal pneumonia).

Bacteriological studies should be performed to determine the causative organisms and their susceptibility to dicloxacillin. Dicloxacillin has less intrinsic antibacterial activity and a narrower spectrum than benzylpenicillin.

Dicloxacillin should therefore not be used in infections due to organisms susceptible to benzylpenicillin.

Important Note: When it is judged necessary that treatment is initiated before definitive culture and sensitivity results are known, if the microbiology report later indicates that the infection is due to an organism other than a benzylpenicillin resistant staphylococcus sensitive to dicloxacillin, the physician is advised to continue therapy with a drug other than dicloxacillin or any other penicillinase-resistant penicillin.

Contraindications

A history of a previous hypersensitivity reaction to any penicillins, or to any component of the formulation.

Precautions

Anaphylaxis. Serious, and occasionally fatal, hypersensitivity (anaphylactoid) reactions have occurred in patients receiving penicillin. Serious anaphylactic reactions require immediate emergency treatment with adrenaline. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins.

Before commencing therapy with any penicillin, a careful enquiry about sensitivity or allergic reactions to penicillins, cephalosporins or other allergens should be made before dicloxacillin is prescribed. There is clinical and laboratory evidence of cross-allergenicity among among bicyclic β -lactam antibiotics including penicillins, cephalosporins, cephamycins, 1-oxa- β -lactams and carbapenems. Should an allergic reaction occur during therapy, the drug should be discontinued and appropriate measures taken.

Pseudomembranous colitis. Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including dicloxacillin. A toxin produced with *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy).

Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (e.g. Lomotil), may prolong and/or worsen the condition and should not be used.

Cholestatic hepatitis. Dicloxacillin has been associated with cholestatic hepatotoxicity and jaundice. The patterns of liver function test results and biopsy histology are similar to those with flucloxacillin.

In the period 1981 to 1994, the Swedish Adverse Drug Reactions Advisory Committee (SADRAC) received 20 reports of adverse hepatic reactions which were possibly or probably related to dicloxacillin. During this period, 10.7 million defined daily doses (DDD) of dicloxacillin were prescribed in Sweden, giving a frequency of 1.8 reactions per million DDD. Over the same period, SADRAC received 127 adverse hepatic reaction reports (77 possible, 47 probable, 3 unclassified) related to flucloxacillin, giving a frequency of 4.3 reactions per million DDD. Although the limitations of retrospective data reliant on spontaneous physician reporting are obvious, the SADRAC figures suggest that adverse hepatic events occur, or at least are reported, less frequently with

dicloxacillin than with flucloxacillin.

Despite the reduced frequency of hepatic reactions to dicloxacillin, dicloxacillin should only be used in older patients (55 years or more) when such use is clearly justifiable on clinical grounds.

Bacteriological studies to determine the causative organisms and their susceptibility to the penicillinase resistant penicillins should be performed. In the treatment of suspected staphylococcal infections, therapy should be changed to another active agent if culture tests fail to demonstrate the presence of staphylococci.

As with any potent drug, periodic assessment of organ-system function, including hepatic, renal and haematopoietic, should be made during prolonged therapy. White blood cell counts and differential cell counts should be obtained prior to initiation of therapy with dicloxacillin.

Periodic urinalysis should be performed, and serum urea, creatinine, AST and ALT concentrations should be determined during therapy with dicloxacillin. Dosage alterations should be considered if these values become elevated. Dicloxacillin should be discontinued if abnormal liver function tests develop whilst on therapy.

The use of antibiotics may result in the overgrowth of nonsusceptible organisms. Should superinfection occur, appropriate treatment should be initiated and discontinuation of dicloxacillin therapy should be considered. This oral preparation should not be relied upon in patients with severe illness or with nausea, vomiting, gastric dilatation, cardiospasm, intestinal hypermotility.

Rare reports have been received during postmarketing surveillance of oesophageal burning, oesophagitis and oesophageal ulceration, particularly after ingestion of dicloxacillin capsules with an insufficient quantity of water and/or before going to bed. To minimise the risk of developing such events, dicloxacillin should be taken with at least 120 mL of water and should NOT be taken in the supine position or immediately before going to bed.

High doses (2 to 4g/day) of dicloxacillin administered prophylactically to geriatric patients undergoing arthroplasties have been reported to be associated with elevations of serum creatinine and nephrotoxicity. Renal function should be assessed prior to starting dicloxacillin and doses appropriately reduced in the presence of kidney dysfunction when high doses are considered (see DOSAGE and ADMINISTRATION, Impaired Renal Impairment).

Use in Pregnancy (Category B2)

Safety for use in pregnancy has not been established.

Use in Lactation

Dicloxacillin is distributed into milk. Therefore, caution should be exercised when dicloxacillin is administered to a nursing woman.

Use in Children

Penicillinase resistant penicillins (especially methicillin) may not be completely excreted in newborn infants because of incompletely developed renal function. This may result in abnormally high blood levels. Frequent blood level determinations and dosage adjustments when necessary are advisable in these patients. All newborn infants treated with penicillins should be monitored closely for clinical and laboratory evidence of toxic or adverse effects. Experience in the neonatal period is limited. Therefore, a dose for newborn is not recommended at this time.

Interactions With Other Medicines

Probenecid increase and prolongs serum penicillin concentrations. Probenecid administered concomitantly with penicillins slows the rate of excretion by competitively inhibiting renal tubular secretion of penicillin.

Dicloxacillin may reduce the anticoagulant effects of warfarin. Careful monitoring of prothrombin time is suggested during concomitant therapy, and adjustment of the anticoagulant dose may be necessary.

Concurrent administration of oxacillin with phenytoin resulted in decreased phenytoin serum concentrations due possibly to impaired phenytoin absorption.

Adverse Reactions

The following adverse reactions to dicloxacillin have, where possible, been grouped by frequency according to the following criteria.

very common	≥1/10
common	≥1/100 and <1/10
uncommon	≥1/1 000 and <1/100
rare	≥1/10 000 and <1/1 000
very rare	<1/10 000

- **Gastrointestinal**

<i>Common:</i>	gastrointestinal disturbances such as nausea, vomiting, epigastric discomfort, flatulence, and loose stools
<i>Rare:</i>	pseudomembranous colitis, oesophageal ulcer, oesophageal pain, oesphagitis (see Precautions)

- **Hypersensitivity and Skin**

<i>Common:</i>	skin rashes, urticaria and pruritus
<i>Very rare:</i>	laryngospasm, bronchospasm, angiodema
<i>Frequency unknown:</i>	anaphylactic reactions, laryngeal edema, serum sickness, wheezing, sneezing

- **Hepatobiliary**

<i>Very rare:</i>	cholestatic hepatitis (see Precautions)
<i>Frequency unknown:</i>	Aspartate aminotransferase increased, alanine aminotransferase increased, blood alkaline phosphatase increased, liver-function test abnormal

- **Renal**

<i>Uncommon:</i>	renal failure, renal impairment, renal tubular disorder, nephritis interstitial, nephropathy, haematuria, proteinuria
<i>Frequency unknown:</i>	transient, generally minor deterioration in the renal function of elderly patients given high doses of dicloxacillin intravenously.

- **Haematological**

<i>Uncommon:</i>	eosinophilia
<i>Frequency unknown:</i>	agranulocytosis or neutropenia. Haematolytic anaemia, leukopenia, granulocytopenia, thrombocytopenia and bone marrow depression have been associated with the use of penicillinase resistant

penicillins

- **Neurological**

Frequency unknown: Generalised epileptic convulsion, myoclonus confusional state, neurotoxicity, lethargy.

Neurotoxicity similar to that observed with benzylpenicillin (e.g. seizures) may occur with large intravenous doses of the penicillinase resistant penicillins, especially in patients with impaired renal function.

- **Vascular Disorders**

Uncommon: phlebitis, thrombophlebitis

Very rare: Circulatory collapse, hypotension

- **Musculoskeletal, connective tissue and bone disorders**

Frequency unknown: myalgia, arthralgia, muscle twitching[±]

- **General Disorders**

Very rare: death in the context of hypersensitivity

Uncommon: pain

Frequency unknown: malaise, pyrexia

[±] These events may occur with large intravenous doses of penicillinase-resistant penicillins, especially in patients with renal insufficiency.

Dosage and Administration

Microbiological studies to determine the causative organism and their susceptibility to the penicillinase resistant penicillins should be performed. The duration of treatment varies with the type and severity of infection as well as the overall condition of the patient. Therefore, treatment duration should be determined by the clinical and bacteriological response of the patient. Treatment should be continued for at least 48 to 72 hours after the patient has become asymptomatic and cultures are negative. In severe staphylococcal infections, treatment with penicillinase resistant penicillins should be continued for at least 14 days. The treatment of endocarditis and osteomyelitis requires a longer term of therapy.

Infections caused by group A beta-haemolytic Streptococci should be treated for at least 10 days to help prevent the occurrence of acute rheumatic fever or acute glomerulonephritis.

The capsules should be administered on an empty stomach, one to two hours before food.

For mild to moderate infections:

Adults and children more than 12 years of age: 250 mg, 6 hourly

In more severe infections the dosage may be doubled.

Impaired renal function: As dicloxacillin is excreted primarily by the kidneys, the half life in patients with renal failure is increased (see Pharmacology). Limited clinical data suggest that in severe renal impairment the dosing interval may be increased to 8 hourly but no change in the individual dose is needed.

Impaired hepatic function: Adequate data are not available on the use of dicloxacillin in such patients. It may be prudent, however, to reduce the dicloxacillin dose in patients with significant liver disease.

Overdosage

Treatment of dicloxacillin overdosage should be symptomatic and supportive. There is no specific antidote. Dicloxacillin is not removed by haemodialysis or peritoneal dialysis.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

Presentation and Storage Conditions

Distaph 250, Dicloxacillin 250 mg capsule: white body and cap, marked 'DX' and '250'; HDPE bottles and PVC/PE/PVDC/Al blister packs* of 24 and 30*.

Distaph 500, Dicloxacillin 500 mg capsule: white body and cap, marked 'DX' and '500'; HDPE bottles and PVC/PE/PVDC/Al blister packs* of 24 and 30*.

* Not marketed in Australia

Distaph capsules should be kept in a well closed container and stored in a dry place below 25°C.

Poison Schedule

S4

Name and Address of the Sponsor

Alphapharm Pty Limited

Level 1, 30 The Bond
30-34 Hickson Road
Millers Point NSW 2000

ABN 93 002 359 739

www.alphapharm.com.au

Date of First Inclusion in the Australian Register of Therapeutic Goods (the ARTG)

14/05/1997

Date of Most Recent Amendment

28/10/2014

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