PRODUCT INFORMATION

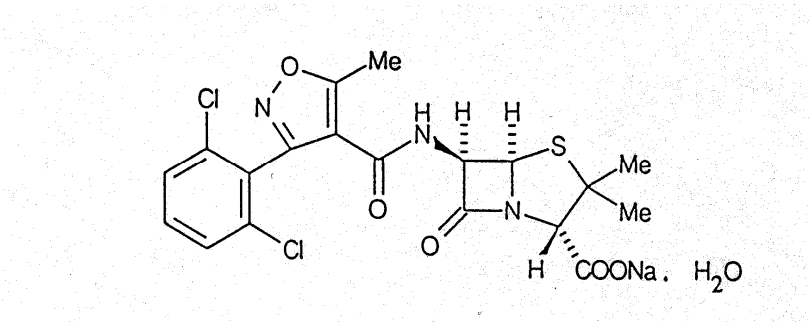
DICLOCIL®

(dicloxacillin sodium)

CAPSULES

NAME OF THE DRUG

Dicloxacillin sodium is sodium (6R)-6-[3-(2,6-dichlorophenyl)-5-methylisoxazole-4-carboxamido]-penicillanate monohydrate; it is a penicillinase-resistant, acid-resistant, semisynthetic penicillin with the following structure.



DESCRIPTION

Dicloxacillin sodium is a white or off-white crystalline powder.

Diclocil capsules contain dicloxacillin sodium equivalent to 250mg or 500mg dicloxacillin. Inactive ingredients are magnesium stearate, silica colloidal anhydrous, gelatin and titanium dioxide.

PHARMACOLOGY

Pharmacokinetics:
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 serum levels reached within 0.5 to 2 hours. Food in the gastrointestinal tract decreases the absorption of dicloxacillin. Serum levels after oral administration are directly proportional to dosage at unit doses of 125mg, 250mg, and 500mg as measured at the 2-hour level. Single oral doses of dicloxacillin 500 mg produced peak serum concentrations of 10 to 18 μg/mL.

Dicloxacillin is 95% to 99% bound to serum proteins, mainly albumin. Dicloxacillin is distributed into bone, bile, pleural fluid, and synovial fluid. Only minimal concentrations are attained in cerebrospinal fluid.
The elimination half-life of dicloxacillin is approximately 0.7 hours. Dicloxacillin is partially

metabolized 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.

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

Pharmacological Actions:
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 Concentration (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, Pensylvannia 19085, USA
A report of "susceptible" indicates the infecting organism is likely to respond 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 respond to therapy with the antibiotic.

INDICATIONS

DICLOCIL® is indicated in the 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.

Bacteriological studies should be performed to determine the causative organisms and their susceptibility to dicloxacillin.

DICLOCIL® should not be used in infections due to organisms susceptible to penicillin G.

> **Important Note:** When it is judged necessary that the treatment be initiated before definitive culture and sensitivity results are known, if the microbiology report later indicates the infection is due to an organism other than a penicillin-G-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 previous hypersensitivity reactions to any of the penicillins, or to any component of the formulation.

WARNINGS

Serious and occasionally fatal anaphylactic reactions have occurred in patients receiving penicillins. Serious anaphylactic reactions require immediate emergency treatment with adrenaline, intravenous fluids and steroids, oxygen, and airway management, including intubation, as indicated. Although anaphylaxis is more frequent following a parenteral administration, it has occurred in patients receiving oral penicillins.

PRECAUTIONS

As with any penicillin, a careful inquiry 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 the penicillins and partial cross-allergenicity 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.

The use of antibiotics may result in the overgrowth of nonsusceptible organisms. Should superinfection occur, appropriate treatment should be initiated and discontinuation of Diclocil therapy should be considered.

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics, including dicloxacillin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity may range from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who develop diarrhea 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 such as oral antibacterial agents effective against *Clostridium difficile* (eg oral vancomycin) should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis eg opiates and diphenoxylate with atropine (Lomotil) may prolong 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. Information collected by the Swedish Adverse Drug Reaction Advisory Committee over the period 1981 to 1994 provides 20 reports of liver damage possibly or probably caused by dicloxacillin. Over this period a total of 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 period there were 127 reports of liver damage possibly or probably caused by flucloxacillin, at a frequency of 4.3 reactions per million DDD. Although there are obvious limitations of retrospective data reliant upon spontaneous physician reporting, the SADRAC figures suggest that adverse hepatic events occur, or at least are reported, less frequently with dicloxacillin than 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.

Periodic assessment of organ system function, including renal, hepatic, and haematopoietic systems should be made during prolonged therapy with dicloxacillin.

White blood cell counts and differential cell counts should be obtained prior to initiation of therapy and at least weekly during therapy with dicloxacillin.

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

These oral presentations should not be relied upon in patients with severe illness or with nausea, vomiting, gastric dilatation, cardiospasm or intestinal hypermotility.

Rare reports have been received during postmarketing surveillance of oesophageal burning, oesophagitis and oesophageal ulceration, particularly after ingestion of DICLOCIL® capsules with an insufficient quantity of water and/or before going to bed. To minimise the risk of developing such events, DICLOCIL® 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 arthoplasties 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, Renal Impairment).**

Drug Interactions

Probenecid increases 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 response to warfarin. Careful monitoring of prothrombin times is suggested during concomitant therapy, and dosage of the anticoagulant adjusted as required.

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

Use in Pregnancy Category B2

The safe use of dicloxacillin 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.

Paediatric Use

Because of incompletely developed renal function in newborns, penicillinase-resistant penicillins (especially methicillin) may not be completely excreted, resulting in abnormally high blood levels. Frequent blood level determinations and dosage adjustments when necessary are advisable in these patients. All newborns 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 the newborn is not recommended at this time.

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	≥1/1000 and <1/100
rare	≥1/10000 and <1/1000
very rare	<1/10000

Gastrointestinal

Common: gastrointestinal disturbances such as nausea, vomiting, epigastric discomfort, flatulence, and loose stools

Rare: Pseudomembranous colitis (see PRECAUTIONS).

Rare: Oesphageal ulcer, oesphageal pain, oesphagitis (**see PRECAUTIONS)**

Hypersensitivity and Skin

Common: skin rashes, urticaria and pruritis.
Very rare: laryngospasm, bronchospasm, angiodema
Frequency unknown: anaphylactic reactions, laryngeal edema, serum sickness, wheezing, sneezing

Hepatobiliary

Rare: cholestatic hepatitis (see PRECAUTIONS)
Frequency unknown: Aspartate aminotransferase increased, alanine aminotransferase increased, blood alkaline phosphatase increased, liver function test abnormal.

Renal

Uncommon:	Renal failure, renal impairment, renal tubular disorder, nephritis interstitial, nephropathy, haematuria, proteinuria.
Frequency Unknown	Transient, generally minor deterioration in the renal function of elderly patients given high doses of dicloxacillin intravenously.

Haematological

Uncommon:	eosinophilia
Frequency unknown:	agranulocytosis or neutropenia. Haematolytic anemia, 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 penicillin G (eg 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 pencillinase-resistant penicillins, especially in patients with renal insufficiency.

DOSAGE AND ADMINISTRATION

Diclocil capsules should be administered on an empty stomach, one or two hours before food.

Bacteriological studies to determine the causative organisms and their susceptibility to dicloxacillin should be performed. Duration of therapy varies with the type and severity of infection as well as the overall condition of the patient. Therefore, it should be determined by the clinical and bacteriologic response of the patient. Therapy should be continued for at least 48 to 72 hours after the patient has become asymptomatic and cultures are negative. In severe staphylococcal infections, therapy should be continued for at least 14 days. The treatment of endocarditis and osteomyelitis requires a longer term of therapy.

Adults: 250 mg every 6 hours, the dose may be doubled to 500mg every six hours in severe infections.

Experience in the neonatal period is limited. Therefore, a dose for the newborn is not recommended at this time.

Renal Impairment: Adjustment of dosage is generally not necessary in patients with mild to moderate impairment of renal function. In patients with severe impairment of renal function, consideration should be given to reduction of dose or an increase in dosage interval **(see PRECAUTIONS).**

OVERDOSAGE

Nothing is known regarding overdosage. Treatment of dicloxacillin overdose should be symptomatic and supportive.

In case of overdose, immediately contact the Poisons Information Centre on 13 11 26 for advice.

PRESENTATION

DICLOCIL® (dicloxacillin sodium) capsules contain dicloxacillin sodium equivalent to 250mg or 500mg of dicloxacillin.

250mg capsules, in blister packs of 24
500mg capsules, in blister packs of 24

SPONSOR

Bristol-Myers Squibb Australia Pty Ltd
556 Princes Highway
NOBLE PARK, VIC 3174

ARTG NUMBERS:

DICLOCIL® Capsules 250mg	AUST R 75593
DICLOCIL® Capsules 500mg	AUST R 75592

TGA Approval Date: November 21, 1996
Safety Update 14 November 2008