PRODUCT INFORMATION

DICLOCIL®

(dicloxacillin sodium)

POWDER FOR INJECTION

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

Diclocil® powder for injection is a fine white crystalline powder, containing only dicloxacillin 500mg or 1g as sodium dicloxacillin.

CLINICAL PHARMACOLOGY

Pharmacokinetics:

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. 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:-

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Methicillin discs 5 microgram</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zone diameter, Nearest Whole mm</td>
</tr>
<tr>
<td></td>
<td>Susceptible</td>
</tr>
<tr>
<td>staphylococci</td>
<td>≥14</td>
</tr>
</tbody>
</table>

†Available from NCCLS, Lancaster avenue, Villanova, Pennsylvania 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® powder for injection is intended as initial treatment for serious infections when high and immediate blood concentrations are desired. As soon as appropriate, the patient should be transferred to oral therapy.

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 initially to determine the causative organisms and their susceptibility to dicloxacillin however DICLOCIL® may be used prior to the availability of laboratory test results to initiate therapy in patients in whom an infection due to penicillinase-producing staphylococci is suspected.

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

DICLOCIL® is contraindicated in persons who have shown hypersensitivity to any of the penicillins or 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.

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, cephemycins, 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 dicloxacillin 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 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 such as oral antibacterial agents effective against *Clostridium difficile* (e.g., oral vancomycin) should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis e.g., 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.

Bacteriologic 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. 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.

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

High doses (2 to 4 g/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 being considered.

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 (SGOT), and ALT (SGPT) 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.

Dicloxacillin must not be administered intraarterially. Like other drugs, endothelial damage is caused by intraarterial administration.

The IV administration of dicloxacillin has been associated with moderate to severe phlebitis, which on occasions has required discontinuation of treatment. This has been reported both when dicloxacillin has been administered by slow intravenous injection and when administered by intravenous infusion. Intravenous infusion is the preferred method of administration where the volume status of the patient permits.

**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.

Aminoglycosides and penicillins are physically and/or chemically incompatible and can mutually inactivate each other *in vitro* (see Dosage and Administration).

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

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.

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.

ADVERSE EVENTS

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

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>very common</td>
<td>≥1/10</td>
</tr>
<tr>
<td>common</td>
<td>≥1/100 and &lt;1/10</td>
</tr>
<tr>
<td>uncommon</td>
<td>≥1/1000 and &lt;1/100</td>
</tr>
<tr>
<td>rare</td>
<td>≥1/10000 and &lt;1/1000</td>
</tr>
<tr>
<td>very rare</td>
<td>&lt;1/10000</td>
</tr>
</tbody>
</table>

Gastrointestinal

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

Rare: Pseudomembranous colitis (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 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 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
Muculoskeletal, connective tissue and bone disorders

Frequency unknown: Myalgia, arthralgia, muscle twitching‡

General Disorders and administration site conditions:

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 real insufficiency.

Local

Local pain and thrombophlebitis have been reported following intravenous administration (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

If the patient complains of pain during infusion, the infusion should be stopped and the patient evaluated. Based on experience with other penicillinase-resistant penicillins, the risk of phlebitis and thrombophlebitis may be reduced by prolonging infusion time or using a less concentrated solution (see also DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION

Microbiological studies to determine the causative organisms and their susceptibility to the penicillinase-resistant penicillins 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 with penicillinase-resistant penicillins should be continued for at least 14 days. The treatment of endocarditis and osteomyelitis requires a longer term of therapy.

Diclocil should preferably be administered by intravenous infusion to reduce the potential for thrombophlebitis, but may also be given by slow intravenous injection (see PRECAUTIONS).

For more severe infections such as those of the lower respiratory tract or disseminated infections:

Adults and children weighing 40 kg or more: 250 mg to 500 mg every 6 hours.

Children weighing less than 40 kg: 25 to 50 mg/kg/day or higher in equally divided doses every 6 hours. (6.25 to 12.5 mg/kg every 6 hours).
Larger doses, 100 mg/kg/day or more, may be given in very severe infections.

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

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

**Renal Impairment**

Renal function should be assessed prior to starting dicloxacillin and doses appropriately reduced in the presence of kidney dysfunction when high doses are being considered.

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.

**OVERDOSAGE**

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

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

**RECONSTITUTION**

Dissolve Diclocil in sterile water for injection. Add 10mL to the 500mg vial and 15-20mL to the 1g vial.

Because this product does not contain a preservative, use as soon as possible after reconstitution and preparation. If storage is necessary, hold at 2\(^{°}\text{C}-8\(^{°}\text{C}\) for not more than 24 hours or not more than 4 hours at room temperature.

**For Intravenous Infusion:**

Constitute as above prior to adding to the intravenous solution. Stability studies at concentrations of 0.5 and 2 mg/mL in various intravenous solutions (0.9% sodium chloride, 5% glucose, and 0.18% saline/4% glucose) showed no evidence of degradation when stored for 24 hours at 25\(^{°}\text{C}\) or in the refrigerator.
**Solution for intermittent intravenous infusion** - Dicloxacillin dissolved in water (as above) added to at least 100mL (100-250mL) of intravenous solution and infused over at least 60 minutes.

The risk of vascular irritation/phlebitis may be reduced by prolonged infusion time or less concentrated solution (dilution with at least 500mL intravenous solution).

**Solution for continuous intravenous infusion** - Dicloxacillin dissolved in water (as above) added to intravenous solution (maximum concentration 2mg/mL).

**For Direct Intravenous Use:**

Use Direct IV injection for fluid restricted patients only; direct IV administration increases the risk of thrombophlebitis (see PRECAUTIONS)

500mg or 1g dicloxacillin dissolved in water for injection (as above), withdraw the entire contents and administer over a period of 3-5 minutes for the 500mg dose and at least 5 minutes for the 1g dose.

**CAUTION:** More rapid administration may result in convulsive seizures.

**Incompatibilities** –

DICLOCIL® should not be mixed with Hartman’s solution (Compound sodium lactate IV infusion BP) for infusion or direct injection. Mixing dicloxacillin dissolved in water with Hartman’s solution may result in the formation of a precipitate which has been associated with pain on infusion.

DICLOCIL® should not be mixed with an amino glycoside in the syringe because amino glycosides and penicillins are physically and/or chemically incompatible and can mutually inactivate each other in vitro. Because of physical and chemical incompatibilities, it is recommended that intravenous solutions of penicillins and amino glycosides should not be mixed during concomitant therapy and the drugs should be administered in separate syringes (See PRECAUTIONS, Drug Interactions). In general, it is advisable to administer these antibiotics separately.

**PRESENTATION**

500mg vials, packs of 5
1g vials, packs of 5
SPONSOR

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

AUSTRALIAN REGISTRATION NUMBERS

500mg powder for injection  AUST R 56803
1g  powder for injection  AUST R 56804

TGA approval date:  August 5, 1997
Amendment:  January 19, 1998
Safety Update  14 November 2008