AUSTRALIAN PRODUCT INFORMATION

DISTAPH®

Dicloxacillin sodium capsules

1 NAME OF THE MEDICINE

Dicloxacillin (as dicloxacillin sodium)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains dicloxacillin sodium equivalent to 250 mg or 500 mg dicloxacillin as the active ingredient.

Excipients with known effect in DISTAPH 250 capsules: sulfites and 21.2 mg of sodium per dose

Excipients with known effect in DISTAPH 500 capsules: sulfites and 42.5 mg of sodium per dose

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

DISTAPH 250 : Dicloxacillin 250 mg capsule: Size 2 capsule with white opaque body and cap, printed 'DX' on the cap and '250' on the body in black

DISTAPH 500 : Dicloxacillin 500 mg capsule: Size 0 capsule with white opaque body and cap, printed 'DX' on the cap and '500' on the body in black

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC 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.

4.2 DOSE AND METHOD OF 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.

Dosage adjustment in Hepatic Impairment

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.

Dosage adjustment in Renal Impairment

As dicloxacillin is excreted primarily by the kidneys, the half life in patients with renal failure is increased (see Section 5.2 PHARMACOKINETIC PROPERTIES, Excretion). 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.

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Anaphylaxis

Serious, and occasionally fatal, hypersensitivity (anaphylactoid) reactions have occurred in patients receiving penicillin. Serious anaphylactic reactions require immediate emergency treatment with adrenaline (epinephrine), 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 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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Dosage adjustment in Renal Impairment).

Use in the Elderly

No data available.

Paediatric Use

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.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No data available.

Use in Pregnancy

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

Common:	gastrointestinal disturbances such as nausea, vomiting, epigastric discomfort, flatulence, and loose stools
Rare:	pseudomembranous colitis, oesophageal ulcer, oesophageal pain, oesophagitis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

Hypersensitivity and Skin

Common:	skin rashes, urticaria and pruritus
Very rare:	laryngospasm, bronchospasm, angioedema
Frequency unknown:	anaphylactic reactions, laryngeal oedema, serum sickness, wheezing, sneezing

Hepatobiliary

Very rare:	cholestatic hepatitis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

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 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.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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 Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

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 pneumonia*. 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.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

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

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.

Excretion

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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The inactive ingredients present are colloidal anhydrous silica, magnesium stearate, gelatin, titanium dioxide, purified water and TekPrint SW-9008 Black Ink (ARTG PI No: 2328).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: HDPE bottles with HDPE screw caps
Pack sizes: 24 and 30 capsules

Some pack sizes may not marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 226506 – DISTAPH 250 dicloxacillin 250mg (as sodium) capsule bottle

AUST R 226508 – DISTAPH 500 dicloxacillin 500mg (as sodium) capsule bottle

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

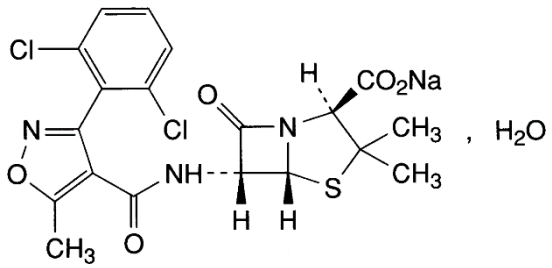
6.7 PHYSICOCHEMICAL PROPERTIES

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.

Chemical Structure

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

Structural formula:



Molecular Formula: $C_{19}H_{16}Cl_2N_3NaO_5S,H_2O$ Molecular Weight: 510.3

CAS Number

13412-64-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

14/05/1997

10 DATE OF REVISION

09/11/2022

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
2	Add Schedule 1 declaration
6.4	Update to storage conditions

6.5	Add closure material Insert AUST R numbers
8	Update sponsor details

DISTAPH® is a Viatris company trade mark

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