**Distaph**

**Dicloxacillin (sodium)**

**PRODUCT INFORMATION**

**Name of the Medicine**

The active ingredient of Distaph capsules is dicloxacillin (as dicloxacillin sodium).

Dicloxacillin sodium is the monohydrate sodium salt of dicloxacillin. The chemical name for dicloxacillin sodium is (6R)-6-[3-(2, 6-dichlorophenyl)-5-methylisoxazole-4-carboxamido]-penicillanate. The structural formula for dicloxacillin sodium is:

![Structural formula of dicloxacillin sodium](image)

Molecular Formula: $\text{C}_{19}\text{H}_{16}\text{Cl}_{2}\text{N}_{3}\text{NaO}_{5}\text{S,H}_{2}\text{O}$

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 silica – colloidal anhydrous, magnesium stearate, gelatin, titanium dioxide, sodium lauryl sulfate, water – potable, TekPrint SW-9008 (ARTG No: 2328) and TekPrint SW-9009 (ARTG No: 2343).

**Pharmacology**

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.

**Pharmacokinetics**

**Absorption**. Dicloxacillin is resistant to inactivation by gastric acid and is rapidly absorbed from the gastrointestinal tract. Bioavailability after oral dosing to fasting adults has been reported to range from 50 to 94% with peak levels occurring 1 to 2 hours post administration. 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.** Approximately 50% of the absorbed dose of dicloxacillin is excreted unchanged in the urine. The remainder is excreted in the urine as metabolites of dicloxacillin, primarily the microbiologically active 5-hydroxymethyl analogue. Renal excretion occurs through both passive glomerular filtration and active tubular secretion. The elimination half life of dicloxacillin is reported to be 30 to 40 minutes in healthy adults.

Patients with cystic fibrosis eliminate dicloxacillin more rapidly than do healthy individuals. Limited clinical studies suggest a need for an increased dose.

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 removed by haemodialysis or peritoneal dialysis.

**Microbiology**

Dicloxacillin is a narrow spectrum antibiotic with activity against the following Gram-positive organisms: *Staphylococcus aureus* (penicillinase and non penicillinase producing), coagulase negative staphylococcal species (penicillinase and non penicillinase producing), *Streptococcus pyogenes*, "Viridans" group streptococci, *Streptococcus pneumoniae*.

Dicloxacillin has no clinically useful activity against methicillin resistant Staphylococci nor Enterococcal species. It is not active against Gram-negative bacilli.

**Disc Susceptibility Tests**

Dilution or diffusion techniques - either quantitative (MIC) or breakpoint - should be used following a regularly updated, recognised and standardised method (eg. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated, or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small, uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Note: The prevalence of resistance may vary geographically for selected species, and local information on resistance is desirable, particularly when treating severe infections.

**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 \( \beta \)-lactam antibiotics (e.g. penicillins, cephalosporins), or to any component of the formulation, is a contraindication to the use of dicloxacillin.

**Precautions**

**Anaphylaxis.** Serious, and occasionally fatal, hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. Before commencing therapy with any penicillin, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. There is clinical and laboratory evidence of cross-allergenicity among the penicillins and partial cross allergenicity among bicyclic \( \beta \)-lactam antibiotics including penicillins, cephalosporins, cephamycins, 1-oxa-\( \beta \)-lactams and carbapenems. If an allergic reaction occurs, appropriate therapy should be instituted and Distaph therapy discontinued.

Serious anaphylactoid reactions require emergency treatment with adrenaline. Oxygen, intravenous steroids and airway management including intubation should also be administered as indicated.

**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 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 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.** On rare occasions the use of isoxazolyl penicillins has been associated with the development of a potentially severe and prolonged cholestatic hepatitis and jaundice. This reaction has been reported to occur most often in elderly patients or those treated for prolonged periods (more than 14 days).

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 for the last 14 years suggest that adverse hepatic events occur, or at least are reported, less frequently with dicloxacillin than with flucloxacillin.
Comparison of the case details and laboratory reports from the literature and the SADRAC reports concerning hepatic reactions with dicloxacillin and flucloxacillin, indicates that although both drugs cause a similar pattern of liver damage, it is less marked with dicloxacillin. To date, no case reports of the sort associated with flucloxacillin (severe cholestatic jaundice lasting for several months, often with severe pruritus) have been identified for dicloxacillin.

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. If abnormal liver function tests develop whilst on therapy, dicloxacillin should be discontinued.

The possibility of bacterial and fungal superinfection should be kept in mind during long-term therapy. If overgrowth of resistant organisms occurs, appropriate measures should be taken.

This oral preparation should not be relied upon in patients with severe illness or with nausea, vomiting, gastric dilatation, cardiospasm, intestinal hypermotility, or known gastrointestinal absorptive disorders.

Use in Pregnancy (Category B2)

Safety for use in pregnancy has not been established. Dicloxacillin should not be used in pregnancy unless considered essential by the physician.

Use in Lactation

Dicloxacillin is excreted in breast milk and should be used with caution in breastfeeding mothers.

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, and a dose for newborn infants is not recommended at this time.

Interactions

Probenecid decreases renal tubular excretion of dicloxacillin with a resulting elevation of serum levels.
Dicloxacillin may antagonise the anticoagulant effects of warfarin as a result of induction of hepatic microsomal enzymes by dicloxacillin. Close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary.

Dicloxacillin may lead to a reduction in plasma phenytoin levels. Phenytoin levels should be monitored in patients treated with dicloxacillin.

**Adverse Reactions**

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

- **very common**: $\geq 1/10$
- **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)

- **Hypersensitivity and Skin**
  - **Common**: skin rashes, urticaria and pruritus
  - **Frequency unknown**: anaphylactic reactions

- **Hepatobiliary**
  - **Very rare**: cholestatic hepatitis (see Precautions)
  - **Frequency unknown**: minor and transient changes in the results of liver-function tests

- **Renal**
  - **Frequency unknown**: renal tubular damage and interstitial nephritis, 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, leucopenia, granulocytopenia, thrombocytopenia and bone marrow depression have been associated with the use of penicillinase resistant penicillins

- **Neurological**
  - **Frequency unknown**: 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.
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.

Presentation

**Distaph 250**, Dicloxacillin 250 mg capsule: white body and cap, marked ‘DX’ and ‘250’; bottles of 24.

**Distaph 500**, Dicloxacillin 500 mg capsule: white body and cap, marked ‘DX’ and ‘500’; bottles of 24.

Storage

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

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Name and Address of the Sponsor

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*Approved by the Therapeutic Goods Administration on 16 December 2005.*