TEXT OF OFFICIAL PACKAGE CIRCULAR-DI-7891-2-1 March, 1968

Description: DYNAPEN (sodium dicloxacillin monohydrate) is a new antibacterial agent of the isoxazolyl penicillin series. It is the monohydrate sodium salt of 3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl penicillin. The drug resists destruction by the enzyme penicillinase (beta-lactamase). It has been demonstrated to be especially efficacious in the treatment of penicillinase-producing staphylococcal infections and effective in the treatment of other commonly encountered Gram-positive coccal infections.

Pharmacology: DYNAPEN (sodium dicloxacillin monohydrate) is resistant to destruction by acid and is exceptionally well absorbed from the gastrointestinal tract. Oral administration of dicloxacillin gives blood levels considerably in excess of those attained with equivalent doses of any other presently available oral penicillin. The levels are comparable to those achieved with intramuscular administration of similar doses of penicillin G. Studies[1] with an oral dose of 125 mg. gave average serum levels at 60 minutes of 4.74 mcg./ml. At four hours, average levels were 0.62 mcg./ml. The 125 mg. dose gave peak blood levels 5 times higher than those of 250 mg. of penicillin G and 2 to 4 times higher than those of 250 mg. of potassium phenoxymethyl penicillin. Serum levels after oral administration are directly proportional to dosage at unit doses of 125, 250, 500, and 1000 mg.[1,2,3] as measured at the two-hour level.

Actions (Microbiology): DYNAPEN (sodium dicloxacillin monohydrate) is active against most Gram-positive cocci including beta-hemolytic streptococci, pneumococci, and sensitive staphylococci. Because of its resistance to the enzyme penicillinase, it is active against penicillinase-producing staphylococci.

The average Minimal Inhibitory Concentrations (M.I.C.'s) of DYNAPEN (sodium dicloxacillin monohydrate) for these organisms are as follows:

	Average M.I.C. (mcg./ml.)
Group A beta-hemolytic streptococcus	0.05
Diplococcus pneumoniae	0.10
Staphylococcus (nonpenicillinase-producing)	0.20
Staphylococcus (penicillinase-producing)	0.30

Indications: The principal indications for DYNAPEN (sodium dicloxacillin monohydrate) are in the treatment of infections known to be due to penicillinase-producing staphylococci and in initiating treatment of those infections where a penicillinase-producing staphylococcus is suspected.

Bacteriologic studies to determine [illegible] ucative organisms and their sensitivity to dicloxacillin [illegible] d be performed. When the infecting organism is sus[illegible] to penicillin G, the physician is advised to use pen[illegible] phenoxymethyl penicillin (penicillin V), phenethicil[illegible] ter appropriate antibiotic therapy because of the [illegible] appearance in the environment of organisms resist[illegible] the penicillinase-resistant semisynthetic penicillins.

Clinical studies demonstrate the drug is also effective in the dosages recommended in the treatment of respiratory and skin and soft tissue infections due to streptococci, pneumococci, and nonpenicillinase-producing staphylococci. Infections of other sites due to sensitive organisms may also be expected to respond.

Indicated surgical procedures should be performed.

Contraindications: A history of allergic reactions to penicillins should be considered a contraindication.

Precautions: As with any penicillin, a careful inquiry about sensitivity or allergic reactions to penicillin or other antigens should be made before the drug is prescribed. Allergic reactions are more likely to occur in hypersensitive individuals. Should an allergic reaction occur during therapy, the drug should be discontinued and the patient treated with the usual agents (epinephrine, corticosteroids, antihistamines).

As with other agents capable of altering flora, the possibility of superinfection with mycotic organisms or other pathogens exists during the periods of use of this drug. Should superinfection occur, appropriate treatment should be initiated and discontinuation of dicloxacillin therapy should be considered.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic systems, is strongly recommended.

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

Safety for use in pregnancy has not been established.

Adverse Reactions: Gastrointestinal disturbances such as nausea, vomiting, epigastric discomfort, flatulence, and loose stools have been noted in some patients receiving DYNAPEN (sodium dicloxacillin monohydrate). Pruritus, urticaria, skin rashes, and allergic symptoms have been occasionally encountered, as with all penicillins. Mildly elevated SGOT levels (less than 100 units) have been reported in a few patients for whom pretherapeutic determinations were not made. Minor changes in the results of cephalin flocculation tests have been noted without other evidence of hepatic dysfunction. Eosinophilia, with or without overt allergic manifestations, has been noted in some patients during therapy.

Dosage: For mild-to-moderate upper respiratory and localized skin and soft tissue infections due to sensitive organisms:

Adults and children weighing 40 Kg. (88 lbs.) or more: 125 mg. q. 6h.

Children weighing less than 40 Kg. (88 lbs.): 12.5 mg./Kg./day in divided doses q. 6h.

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

Adults and children weighing 40 Kg. (88 lbs.) or more: 250 mg. q. 6h. or higher.

Children weighing less than 40 Kg. (88 lbs.): 25 mg./Kg./day, or higher, in divided doses q. 6h.

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

Studies indicate that this material is best absorbed when taken on an empty stomach, preferably one to two hours before meals.

N.B.: Infections caused by Group A beta-hemolytic streptococci should be treated for at least 10 days to help prevent the occurrence of acute rheumatic fever or acute glomerulonephritis.

Supply:
List 78923—DYNAPEN (sodium dicloxacillin monohydrate) Capsules, 125 mg., bottles of 24.
Also available:
List 78566—Oral Suspension, 62.5 mg./5 ml., 80 ml. bottle.

References: 1. Data on file at Bristol Laboratories. **2.** Bennett, J. V., Gravenkemper, C. F., Brodie, J. L., and Kirby, W. M. M., "Dicloxacillin, a New Antibiotic: Clinical Studies and Laboratory Comparisons with Oxacillin and Cloxacillin." Antimicrobial Agents and Chemotherapy, 1964, pp. 257-262. **3.** Naumann, P. and Kempf, E., "Dicloxacillin, a New Acid and Penicillinase Stable Oral Penicillin." Arzneimittel-Forschung, 15, pp. 139-145, 1965.

Bristol Telephone Service: (315) 437-6060. If you have any question relating to the use of DYNAPEN (sodium dicloxacillin monohydrate) or any other Bristol product, please call this number *collect*. A physician in the Medical Department of Bristol Laboratories will be available to answer your question.

BRISTOL
Bristol Laboratories
Division of Bristol-Myers Co.
Syracuse, New York 13201