EXHIBIT B

Copy of the Package Insert
for the Listed Drug:
Apothecon Nafcillin Sodium for Injection, USP

APOTHECON
A BRISTOL-MYERS SQUIBB COMPANY

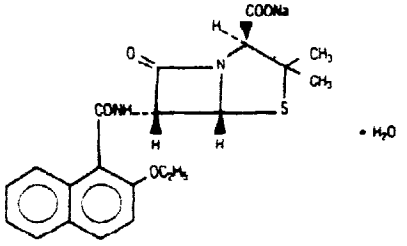
NAFCILLIN SODIUM FOR INJECTION, USP

For Intramuscular or Intravenous Injection

DESCRIPTION

Nafcillin Sodium For Injection USP is a semisynthetic antibiotic substance derived from 6-amino-penicillanic acid It is the sodium salt in a parenteral dosage form

NAFCILLIN SODIUM



$C_{21}H_{21}N_2NaO_5S\ H_2O$ 454 47 [CAS 7177-50-6]

4-Thia-1-azabicyclo [3 2 0]heptane-2-carboxylic acid, 6[[(2-ethoxy-1-naphthalenyl) carbonyl] amino]-3,3-dimethyl-7-oxo-monosodium salt, monohydrate [2S (2α, 5α, 6β)]

CLINICAL PHARMACOLOGY

MICROBIOLOGY. Penicillinase-resistant penicillins exert a bactericidal action against penicillin-susceptible microorganisms during the state of active multiplication All penicillins inhibit the biosynthesis of the bacterial cell wall

The drugs in this class are highly resistant to inactivation by staphylococcal penicillinase and are active against penicillinase-producing and nonpenicillinase-producing strains of **Staphylococcus aureus**.

The penicillinase-resistant penicillins are active in vitro against a variety of other bacteria.

Susceptibility Plate Testing: Quantitative methods of susceptibility testing that require measurement of zone diameters or minimal inhibitory concentrations (MIC's) give the most precise estimates of antibiotic susceptibility One such procedure has been recommended for use with discs to test susceptibility to this class of drugs Interpretations correlate diameters on the disc test with MIC values. A penicillinase-resistant class disc may be used to determine microbial susceptibility to cloxacillin, dicloxacillin, methicillin, nafcillin, and oxacillin With this procedure, employing a 5 microgram methicillin sodium disc, a report from the laboratory of "susceptible" (zone of at least 14 mm) indicates that the infecting organism is likely to respond to therapy A report of "resistant" (zone of less than 10 mm) indicates that the infecting organism is not likely to respond to therapy A report of "intermediate susceptibility" (zone of 10 to 13 mm) suggests that the organism might be susceptible if high doses of the antibiotic are used, or if the infection is confined to tissues and fluids (eg, urine) in which high antibiotic levels are attained

In general, all staphylococci should be tested against the penicillin G disc and against the methicillin disc. Routine methods of antibiotic susceptibility testing may fail to detect strains of organisms resistant to the penicillinase-resistant penicillins For this reason, the use of large inocula and 48-hour incubation periods may be necessary to obtain accurate susceptibility studies with these antibiotics Bacterial strains which are resistant to one of the penicillinase-resistant penicillins should be considered resistant to all of the drugs in the class

PHARMACOKINETICS

Intramuscular injections of Nafcillin Sodium, USP 1 gram produced peak serum levels in 0 5 to 1 hour of 7 61 μg/mL The degree of protein binding reported has been 89 9 + / − 1 5% With normal doses Nafcillin is found in therapeutic concentrations in the pleural bile and amniotic fluids Insignificant concentrations are found in the cerebrospinal fluid and aqueous humor Blood concentrations may be tripled by the concurrent use of probenecid Clinical studies with nafcillin sodium in infants under three days of age and prematures have revealed higher blood levels and slower rates of urinary excretion than in older children and adults A high concentration of nafcillin sodium is excreted via the bile About 30% of an intramuscular dose is excreted in the urine

INDICATIONS AND USAGE

The penicillinase-resistant penicillins are indicated in the treatment of infections caused by penicillinase-producing staphylococci which have demonstrated susceptibility to the drugs Cultures and susceptibility tests should be performed initially to determine the causative organism and their sensitivity to the drug (See **CLINICAL PHARMACOLOGY—Susceptibility Plate Testing**)

The penicillinase-resistant penicillins may be used to initiate therapy in suspected cases of resistant staphylococcal infections prior to the availability of laboratory test results The penicillinase-resistant penicillins should not be used in infections caused by organisms susceptible to penicillin G If the susceptibility tests indicate that the infection is due to an organism other than a resistant staphylococcus, therapy should not be continued with a penicillinase-resistant penicillin

CONTRAINDICATIONS

A history of a hypersensitivity (anaphylactic) reaction to any penicillin is a contraindication

WARNINGS

Serious and occasionally fatal hypersensitivity (anaphylactic shock with collapse) reactions have occurred in patients receiving penicillin The incidence of anaphylactic shock in all penicillin-treated patients is between 0 015 and 0 04 percent Anaphylactic shock resulting in death has occurred in approximately 0 002 percent of the patients treated Although anaphylaxis is more frequent following a parenteral administration, it has occurred in patients receiving oral penicillins

When penicillin therapy is indicated, it should be initiated only after a comprehensive patient drug and allergy history has been obtained If an allergic reaction occurs, the drug should be discontinued and the patient should receive supportive treatment eg, artificial maintenance of ventilations, pressor amines, antihistamines and corticosteroids Individuals with a history of penicillin hypersensitivity may also experience allergic reactions when treated with a cephalosporin

PRECAUTIONS

GENERAL. Penicillinase-resistant penicillins should generally not be administered to patients with a history of sensitivity to any penicillin

Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma Whenever allergic reactions occur penicillin should be withdrawn unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to penicillin therapy

The oral route of administration should not be relied upon in patients with severe illness, or with nausea vomiting, gastric dilation, cardiospasm or intestinal hypermotility Occasionally patients will not absorb therapeutic amounts of orally administered penicillin

The use of antibiotics may result in overgrowth of nonsusceptible organisms If new infections due to bacteria or fungi occur the drug should be discontinued and appropriate measures taken

Laboratory Tests. Bacteriologic studies to determine the causative organisms and their susceptibility to the penicillinase-resistant penicillins should be performed (See **CLINICAL PHARMACOLOGY—Microbiology**). 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 hematopoietic should be made during prolonged therapy with the penicillinase-resistant penicillins.

Blood cultures, white blood cell, and differential cell counts should be obtained prior to initiation of therapy and at least weekly during therapy with penicillinase-resistant penicillins.

Periodic urinalysis, blood urea nitrogen, and creatinine determinations should be performed during therapy with the penicillinase-resistant penicillins and dosage alterations should be considered if these values become elevated. If any impairment of renal function is suspected or known to exist, a reduction in the total dosage should be considered and blood levels monitored to avoid possible neurotoxic reactions (See **DOSAGE AND ADMINISTRATION**).

SGOT and SGPT values should be obtained periodically during therapy to monitor for possible liver function abnormalities.

Drug Interactions: Tetracycline, a bacteriostatic antibiotic, may antagonize the bactericidal effect of penicillin and concurrent use of these drugs should be avoided.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term animal studies have been conducted with these drugs.

Studies on reproduction (nafcillin) in rats and rabbits reveal no fetal or maternal abnormalities before conception and continuously through weaning (one generation).

Pregnancy Category B: Reproduction studies performed in the mouse, rat, and rabbit have revealed no evidence of impaired fertility or harm to the fetus due to the penicillinase-resistant penicillins. Human experience with the penicillins during pregnancy has not shown any positive evidence of adverse effects on the fetus. There are, however, no adequate or well-controlled studies in pregnant women showing conclusively that harmful effects of these drugs on the fetus can be excluded. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Penicillins are excreted in breast milk. Caution should be exercised when penicillins are administered to a nursing woman.

Pediatric Use: Because of incompletely developed renal function in newborns, penicillinase-resistant penicillins (especially methicillin) may not be completely excreted, with abnormally high blood levels resulting. Frequent blood levels are advisable in this group with dosage adjustments when necessary. All newborns treated with penicillins should be monitored closely for clinical and laboratory evidence of toxic or adverse effects (See **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

Body as a Whole. The reported incidence of allergic reactions to penicillins ranges from 0.7 to 10 percent (See **WARNINGS**). Sensitization is usually the result of treatment but some individuals have had immediate reactions to penicillin when first treated. In such cases, it is thought that the patients may have had prior exposure to the drug via trace amounts present in milk and vaccines.

Two types of allergic reactions to penicillin are noted clinically, immediate and delayed.

Immediate reactions usually occur within 20 minutes of administration and range in severity from urticaria and pruritus to angioneurotic edema, laryngospasm, bronchospasm, hypotension, vascular collapse, and death. Such immediate anaphylactic reactions are very rare (See **WARNINGS**) and usually occur after parenteral therapy but have occurred in patients receiving oral therapy. Another type of immediate reaction, an accelerated reaction, may occur between 20 minutes and 48 hours after administration and may include urticaria, pruritus, and fever. Although laryngeal edema, laryngospasm, and hypotension occasionally occur, fatality is uncommon.

Delayed allergic reactions to penicillin therapy usually occur after 48 hours and sometimes as late as 2 to 4 weeks after initiation of therapy. Manifestations of this type of reaction include serum sickness-like symptoms (ie, fever, malaise, urticaria, myalgia, arthralgia, abdominal pain) and various skin rashes. Nausea, vomiting, diarrhea, stomatitis, black or hairy tongue, and other symptoms of gastrointestinal irritation may occur, especially during oral penicillin therapy.

Nervous System Reactions: Neurotoxic reactions similar to those observed with penicillin G may occur with large intravenous doses of the penicillinase-resistant penicillins especially in patients with renal insufficiency.

Urogenital Reactions: Renal tubular damage and interstitial nephritis have been associated with the administration of methicillin sodium and infrequently with the administration of nafcillin and oxacillin. Manifestations of this reaction may include rash, fever, eosinophilia, hematuria, proteinuria, and renal insufficiency. Methicillin-induced nephropathy does not appear to be dose-related and is generally reversible upon prompt discontinuation of therapy.

Metabolic Reactions: Agranulocytosis, neutropenia, and bone marrow depression have been associated with the use of methicillin sodium, nafcillin, oxacillin, and cloxacillin. Hepatotoxicity, characterized by fever, nausea, and vomiting associated with abnormal liver function tests, mainly elevated SGOT levels, has been associated with the use of oxacillin and cloxacillin.

DOSAGE AND ADMINISTRATION

The penicillinase-resistant penicillins are available for oral administration and for intramuscular and intravenous injection. The sodium salts of methicillin, oxacillin, and nafcillin may be administered parenterally and the sodium salts of cloxacillin, dicloxacillin, oxacillin, and nafcillin are available for oral use.

Bacteriologic studies to determine the causative organisms and their sensitivity to the penicillinase-resistant penicillins should always 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 bacteriological response of the patient. In severe staphylococcal infections, therapy with penicillinase-resistant penicillins should be continued for at least 14 days. Therapy should be continued for at least 48 hours after the patient has become afebrile, asymptomatic, and cultures are negative. The treatment of endocarditis and osteomyelitis may require a longer term of therapy.

Concurrent administration of the penicillinase-resistant penicillins and probenecid increases and prolongs serum penicillin levels. Probenecid decreases the apparent volume of distribution and slows the rate of excretion by competitively inhibiting renal tubular secretion of penicillin. Penicillin-probenecid therapy is generally limited to those infections where very high serum levels of penicillin are necessary.

Oral preparations of the penicillinase-resistant penicillins should not be used as initial therapy in serious, life-threatening infections (See **PRECAUTIONS—General**). Oral therapy with the penicillinase-resistant penicillins may be used to follow-up the previous use of a parenteral agent as soon as the clinical condition warrants. For intramuscular gluteal injections, care should be taken to avoid sciatic nerve injury. With intravenous administration, particularly in elderly patients, care should be taken because of the possibility of thrombophlebitis.

RECOMMENDED DOSAGES FOR NAFCILLIN SODIUM FOR INJECTION, USP

Drug	Adults	Infants and Children < 40 kg (88 lbs)	Other Recommendations
Nafcillin	500 mg IM every 4 to 6 hrs IV every 4 hrs	25 mg/kg IM twice daily	Neonates 10 mg/kg IM twice daily
	1 gram IM or IV every 4 hrs (severe infections)		

DIRECTIONS FOR USE

For Intramuscular Use: Reconstitute with Sterile Water for Injection, USP 0.9% Sodium Chloride Injection, USP or Bacteriostatic Water for Injection, USP (with benzyl alcohol or parabens): add 1.8 mL to the 500 mg vial for 2 mL resulting solution; 3.4 mL to the 1 g vial for 4 mL resulting solution; 6.6 mL to the 2 g vial for 8 mL resulting solution. *All reconstituted vials have a concentration of 250 mg per mL.*

The clear solution should be administered by deep intragluteal injection immediately after reconstitution.

Reconstituted Stability: Reconstitute with the required amount of Sterile Water for Injection, USP 0.9% Sodium Chloride Injection, USP or Bacteriostatic Water for Injection, USP (with benzyl alcohol or parabens). The resulting solutions are stable for 3 days at room temperature or 7 days under refrigeration and 90 days frozen.

For Direct Intravenous Use: The required amount of drug should be diluted in 15 to 30 mL of Sterile Water for Injection, USP or Sodium Chloride Injection, USP and injected over a 5- to 10-minute period. This may be accomplished through the tubing of an intravenous infusion if desirable.

For Administration by Intravenous Drip: Reconstitute as directed above (For Intramuscular Use) prior to diluting with Intravenous Solution.

STABILITY PERIODS FOR NAFCILLIN SODIUM FOR INJECTION, USP

Concentration mg/mL	Sterile H_2O for Injection	Isotonic Sodium Chloride	M/6 Molar Sodium Lactate Solution	5% Dextrose in H_2O	5% Dextrose in 0.45% NaCl	10% Invert Sugar	Lactated Ringers Solution
ROOM TEMPERATURE (25° C)							
10-200	24 Hrs	24 Hrs					
30			24 Hrs				
2-30				24 Hrs	24 Hrs		
10-30						24 Hrs	24 Hrs
REFRIGERATION (4° C)							
10-200	7 Days	7 Days					
10-30			7 Days	7 Days	7 Days	7 Days	7 Days
FROZEN (-15° C)							
250	90 Days	90 Days					
10-250			90 Days	90 Days	90 Days	90 Days	90 Days

Only those solutions listed above should be used for the intravenous infusion of Nafcillin Sodium, USP. The concentration of the antibiotic should fall within the range specified. The drug concentration and the rate and volume of the infusion should be adjusted so that the total dose of nafcillin is administered before the drug loses its stability in the solution in use.

There is no clinical experience available on the use of this agent in neonates or infants for this route of administration.

This route of administration should be used for relatively short-term therapy (24 to 48 hours) because of the occasional occurrence of thrombophlebitis particularly in elderly patients.

If another agent is used in conjunction with nafcillin therapy, **it should not be physically mixed** with nafcillin but should be administered separately.

Pharmacy Bulk Package: This glass vial contains 10 grams Nafcillin Sodium For Injection, USP and is designed for use in the pharmacy in preparing I.V. additives. Add 93 mL Sterile Water for Injection, USP or 0.9% Sodium Chloride Injection, USP. The resulting solution will contain 100 mg nafcillin activity per mL. Solutions in a concentration of 10 mg to 200 mg per mL are stable for 24 hours at room temperature or 7 days under refrigeration. Solutions in a concentration of 250 mg per mL are stable for 3 days at room temperature or 7 days under refrigeration and 90 days frozen.

CAUTION: NOT TO BE DISPENSED AS A UNIT.

FOR INFORMATION ONLY

"Piggyback" I.V. Package. This glass vial contains the labeled quantity of Nafcillin and is intended for intravenous administration. The diluent and volume are specified on the label of each package.

When the "piggyback" vial is reconstituted with either Sterile Water for Injection, USP or 0.9% Sodium Chloride Injection, USP and the resulting solutions are in a concentration of 10 to 200 mg/mL, the solutions are stable for 24 hours at room temperature or 7 days under refrigeration and 90 days frozen.

HOW SUPPLIED

Nafcillin Sodium For Injection, USP Nafcillin sodium equivalent to 500 mg, 1 gram, 2 grams, or 10 grams nafcillin per vial.

NDC 0015-7224-20—500 mg vial packaged in 10s
NDC 0015-7225-20—1 gram vial packaged in 10s
NDC 0015-7226-20—2 gram vial packaged in 10s
NDC 0015-7101-28—10 gram Pharmacy Bulk Package packaged in 10s

Also Available

NDC 0015-7195-28—1 gram "Piggyback" packaged in 10s
NDC 0015-7196-28—2 gram "Piggyback" packaged in 10s

For information on package sizes available, refer to current price schedule.

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