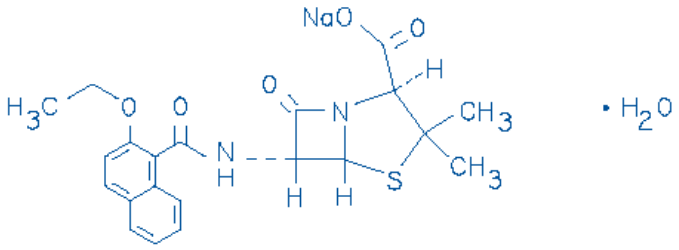
Nafcillin Injection, USP
in PL 2040 Plastic Container
For Intravenous Use Only
GALAXY Container (PL 2040 Plastic)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Nafcillin Injection, USP and other antibacterial drugs, Nafcillin Injection, USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Nafcillin Injection, USP is a sterile injectable product containing nafcillin which is added as Nafcillin Sodium, USP, a semisynthetic penicillin derived from the penicillin nucleus, 6-aminopenicillanic acid. The chemical name of nafcillin sodium is Monosodium (2*S*,5*R*,6*R*)-6-(2-ethoxy-1-naphthamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate monohydrate. It is resistant to inactivation by the enzyme penicillinase (beta-lactamase). The molecular formula of Nafcillin Sodium, USP is $C_{21}H_{21}N_2NaO_5S \cdot H_2O$. The molecular weight is 454.48. The structural formula of nafcillin sodium is as follows:



Nafcillin Injection, USP is a frozen, iso-osmotic, sterile, nonpyrogenic premixed 50 mL or 100 mL solution containing 1 g or 2 g of nafcillin, respectively, added as Nafcillin Sodium, USP. Dextrose, USP has been added to the above dosages to adjust osmolality (approximately 1.8 g and 3.6 g as dextrose hydrous to the 1 g and 2 g dosages, respectively). Sodium Citrate Hydrous, USP has been added as a buffer (approximately 90 mg and 180 mg to the 1 g and 2 g dosages, respectively). The pH has been adjusted with hydrochloric acid and may have been adjusted with sodium hydroxide. The pH is 6.5 (6.0 to 8.5). The solution is intended for intravenous use after thawing to room temperature.

This GALAXY container is fabricated from a specially designed multilayer plastic (PL 2040). Solutions are in contact with the polyethylene layer of this container and can leach out certain chemical components of the plastic in very small amounts within the expiration period. The suitability of the plastic has been confirmed in tests in animals according to the USP biological tests for plastic containers, as well as by tissue culture toxicity studies.

CLINICAL PHARMACOLOGY

In a study of five healthy adults administered a single 500 mg dose of nafcillin by intravenous injection over seven minutes, the mean plasma concentration of the drug was approximately 30 mcg/mL at 5 minutes after injection. The mean area under the plasma concentration-versus-time curve (AUC) for nafcillin in this study was 18.06 mcg·h/mL.

The serum half-life of nafcillin administered by the intravenous route ranged from 33 to 61 minutes as measured in three separate studies.

In contrast to the other penicillinase-resistant penicillins, only about 30% of nafcillin is excreted as unchanged drug in the urine of normal volunteers, and most within the first six hours. Nafcillin is primarily eliminated by nonrenal routes, namely hepatic inactivation and excretion in the bile.

Nafcillin binds to serum proteins, mainly albumin. The degree of protein binding reported for nafcillin is 89.9 ± 1.5%. Reported values vary with the method of study and the investigator.

The concurrent administration of probenecid with nafcillin increases and prolongs plasma concentrations of nafcillin. Probenecid significantly reduces the total body clearance of nafcillin with renal clearance being decreased to a greater extent than nonrenal clearance.

The penicillinase-resistant penicillins are widely distributed in various body fluids, including bile, pleural, amniotic and synovial fluids. With normal doses insignificant concentrations are found in the aqueous humor of the eye. High nafcillin CSF levels have been obtained in the presence of inflamed meninges.

Renal failure does not appreciably affect the serum half-life of nafcillin; therefore, no modification of the usual nafcillin dosage is necessary in renal failure with or without hemodialysis. Hemodialysis does not accelerate the rate of clearance of nafcillin from the blood.

A study which assessed the effects of cirrhosis and extrahepatic biliary obstruction in man demonstrated that the plasma clearance of nafcillin was significantly decreased in patients with hepatic dysfunction. In these patients with cirrhosis and extrahepatic obstruction, nafcillin excretion in the urine was significantly increased from about 30 to 50% of the administered dose, suggesting that renal disease superimposed on hepatic disease could further decrease nafcillin clearance.

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. Nafcillin sodium has been shown to be active against most isolates of the following microorganism, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section.

Gram-Positive Bacteria

Staphylococcus aureus

Susceptibility Test Methods

Susceptibility of staphylococcal isolates to nafcillin may be inferred by testing penicillin and either oxacillin or cefoxitin[1]. For staphylococcal isolates, penicillin susceptibility implies susceptibility to other beta-lactam agents, and penicillin resistance implies resistance to penicillinase-labile penicillins. Resistance to oxacillin (or cefoxitin) implies resistance to all other beta-lactam agents, except newer agents with activity against methicillin-resistant *S. aureus*. Routine testing of nafcillin is not advised.

INDICATIONS AND USAGE

Nafcillin is indicated in the treatment of infections caused by penicillinase-producing staphylococci which have demonstrated susceptibility to the drug. Culture and susceptibility tests should be performed initially to determine the causative organism and its susceptibility to the drug (see **CLINICAL PHARMACOLOGY - Susceptibility Test Methods**).

Nafcillin may be used to initiate therapy in suspected cases of resistant staphylococcal infections prior to the availability of susceptibility test results. Nafcillin 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 Nafcillin Injection, USP.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Nafcillin Injection, USP and other antibacterial drugs, Nafcillin Injection, USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATION

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

Solutions containing dextrose may be contraindicated in patients with known allergy to corn or corn products.

WARNINGS

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam antibacterial drugs. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. Before initiating therapy with Nafcillin, inquire about previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, discontinue Nafcillin and institute appropriate therapy.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Nafcillin Injection, USP, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS

General

Nafcillin 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 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.

The liver/biliary tract is the primary route of nafcillin clearance. Caution should be exercised when patients with concomitant hepatic insufficiency and renal dysfunction are treated with nafcillin. Serum levels should be measured and the dosage adjusted appropriately to avoid possible neurotoxic reactions associated with very high concentrations (see **DOSAGE AND ADMINISTRATION**).

Prescribing Nafcillin Injection, USP in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Laboratory Tests

Bacteriologic studies to determine the causative organisms and their susceptibility to nafcillin 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 nafcillin. White blood cell and differential cell counts should be obtained prior to initiation of therapy and periodically during therapy with nafcillin. Periodic urinalysis, blood urea nitrogen, and creatinine determinations should be performed during therapy with nafcillin. 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.

Nafcillin in high dosage regimens, i.e., 2 grams every 4 hours, has been reported to decrease the effects of warfarin. When nafcillin and warfarin are used concomitantly, the prothrombin time should be closely monitored and the dose of warfarin adjusted as necessary. This effect may persist for up to 30 days after nafcillin has been discontinued.

Nafcillin when administered concomitantly with cyclosporine has been reported to result in subtherapeutic cyclosporine levels. The nafcillin-cyclosporine interaction was documented in a patient during two separate courses of therapy. When cyclosporine and nafcillin are used concomitantly in organ transplant patients, the cyclosporine levels should be monitored.

Drug/Laboratory Test Interactions

Nafcillin in the urine can cause a false-positive urine reaction for protein when the sulfosalicyclic acid test is used, but not with the dipstick.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long term animal studies have been conducted with these drugs. Studies on reproduction (nafcillin) in rats and mice reveal no fetal or maternal abnormalities before conception and continuously through weaning (one generation).

Pregnancy

Pregnancy Category B

Reproduction studies have been performed in the mouse with oral doses up to 20 times the human dose and orally in the rat at doses up to 40 times the human dose and have revealed no evidence of impaired fertility or harm to the rodent fetus due to nafcillin. There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, nafcillin should be used during pregnancy only if clearly needed.

Nursing Mothers

Penicillins are excreted in human milk. Caution should be exercised when penicillins are administered to a nursing woman.

Pediatric Use

The liver/biliary tract is the principal route of nafcillin elimination. Because of immature hepatic and renal function in pediatric patients, nafcillin excretion may be impaired, with abnormally high serum levels resulting. Serum levels should be monitored and the dosage adjusted appropriately. There are no approved pediatric patient dosage regimens for intravenous nafcillin. Safety and effectiveness in pediatric patients have not been established.

The potential for toxic effects in pediatric patients from chemicals that may leach from the single dose premixed intravenous preparation in plastic containers has not been determined.

Geriatric Use

Clinical studies of Nafcillin Injection, USP did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Nafcillin Injection, USP contains 76.6 mg (3.33 mEq) of sodium per gram. At the usual recommended doses, patients would receive between 230 and 460 mg/day (10.0 and 20.0 mEq) of sodium. The geriatric population may respond with a blunted natriuresis to salt loading. This may be clinically important with regard to such diseases as congestive heart failure.

Information for Patients

Patients should be counseled that antibacterial drugs including Nafcillin Injection, USP should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Nafcillin Injection, USP is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or

not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Nafcillin Injection, USP or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

ADVERSE REACTIONS

Body as a Whole

The reported incidence of allergic reactions to penicillin 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 or vaccines. Two types of allergic reactions to penicillins 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 (i.e., 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.

Local Reactions

Pain, swelling, inflammation, phlebitis, thrombophlebitis, and occasional skin sloughing at the injection site have occurred with intravenous administration of nafcillin (see **DOSAGE AND ADMINISTRATION**). Severe tissue necrosis with sloughing secondary to subcutaneous extravasation of nafcillin has been reported.

Nervous System Reactions

Neurotoxic reactions similar to those observed with penicillin G could occur with large intravenous or intraventricular doses of nafcillin especially in patients with concomitant hepatic insufficiency and renal dysfunction (see **PRECAUTIONS**).

Urogenital Reactions

Renal tubular damage and interstitial nephritis have been associated infrequently with the administration of nafcillin. Manifestations of this reaction may include rash, fever, eosinophilia, hematuria, proteinuria, and renal insufficiency.

Gastrointestinal Reactions

Pseudomembranous colitis has been reported with the use of nafcillin. The onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see **WARNINGS**).

Metabolic Reactions

Agranulocytosis, neutropenia, and bone marrow depression have been associated with the use of nafcillin.

OVERDOSAGE

Neurotoxic reactions similar to those observed with penicillin G may arise with intravenous doses of nafcillin especially in patients with concomitant hepatic insufficiency and renal dysfunction (see **PRECAUTIONS**).

In the case of overdosage, discontinue nafcillin, treat symptomatically and institute supportive measures as required. Hemodialysis does not increase the rate of clearance of nafcillin from the blood.

DOSAGE AND ADMINISTRATION

Nafcillin Injection, USP supplied as a premixed frozen solution is to be administered as an intravenous infusion. The usual I.V. dosage for adults is 500 mg every 4 hours. For severe infections, 1 g every 4 hours is recommended. Administer slowly over at least 30 to 60 minutes to minimize the risk of vein irritation and extravasation. Bacteriologic studies to determine the causative organisms and their susceptibility to nafcillin 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 nafcillin 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 duration of therapy.

Nafcillin-probenecid therapy is generally limited to those infections where very high serum levels of nafcillin are necessary.

No dosage alterations are necessary for patients with renal dysfunction, including those on hemodialysis. Hemodialysis does not accelerate nafcillin clearance from the blood.

For patients with hepatic insufficiency and renal failure, measurement of nafcillin serum levels should be performed and dosage adjusted accordingly.

With intravenous administration, particularly in elderly patients, care should be taken because of the possibility of thrombophlebitis.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Do not add supplementary medication to Nafcillin Injection, USP.

Store in a freezer capable of maintaining a temperature of -20°C (-4°F) or less.

DIRECTIONS FOR USE OF GALAXY CONTAINER (PL 2040 PLASTIC)

Nafcillin Injection, USP in GALAXY container (PL 2040 Plastic) is for intravenous administration using sterile equipment.

Storage

Store in a freezer capable of maintaining a temperature of -20°C/-4°F.

Thawing of Plastic Containers

Thaw frozen container at room temperature (25°C/77°F) or under refrigeration (5°C/41°F). [DO NOT FORCE THAW BY IMMERSION IN WATER BATHS OR BY MICROWAVE IRRADIATION.] Check for minute leaks by squeezing bag firmly. If leaks are detected, discard solution as sterility may be impaired.

Do not add supplementary medication.

Visually inspect the container. If the outlet port protector is damaged, detached, or not present, discard container as solution path sterility may be impaired. Components of the solution may precipitate in the frozen state and will dissolve upon reaching room temperature with little or no agitation. Potency is not affected. Agitate after solution has reached room temperature. If after visual inspection the solution remains cloudy or if an insoluble precipitate is noted or if any seals are not intact, the container should be discarded.

The thawed 1 g and 2 g solutions are stable for 21 days under refrigeration (5°C/41°F) or 72 hours at room temperature (25°C/77°F). **Do not refreeze**.

Caution: Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

Preparation for intravenous administration

1. Suspend container from eyelet support.
2. Remove protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

HOW SUPPLIED/STORAGE AND HANDLING

Nafcillin Injection, USP is supplied as a premixed frozen iso-osmotic solution in 50 mL and 100 mL single dose GALAXY containers (PL 2040 Plastic) as follows:

2G3540	NDC 0338-1017-41	1 gram nafcillin in 50 mL
2G3556	NDC 0338-1019-48	2 grams nafcillin in 100 mL

Store at or below -20°C/-4°F. See **Directions for Use of GALAXY Container (PL 2040 Plastic).**

Handle frozen product containers with care. Product containers may be fragile in the frozen state.

REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-fifth Informational Supplement*, CLSI document M100-S25 [2015], Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2014.

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