Rev. January 2004

Rx only

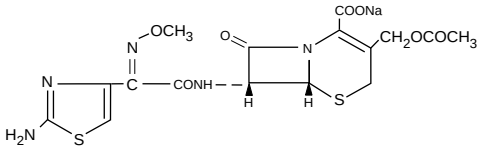
CLAFORAN®

Sterile (cefotaxime for injection, USP)
and
Injection (cefotaxime injection, USP)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of CLAFORAN® (cefotaxime sodium) and other antibacterial drugs, CLAFORAN should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Sterile CLAFORAN® (cefotaxime sodium) is a semisynthetic, broad spectrum cephalosporin antibiotic for parenteral administration. It is the sodium salt of 7-[2-(2-amino-4-thiazolyl) glyoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylate 7^2 (Z)-(o-methyloxime), acetate (ester). CLAFORAN contains approximately 50.5 mg (2.2 mEq) of sodium per gram of cefotaxime activity. Solutions of CLAFORAN range from very pale yellow to light amber depending on the concentration and the diluent used. The pH of the injectable solutions usually ranges from 5.0 to 7.5. The CAS Registry Number is 64485-93-4.



CLAFORAN is supplied as a dry powder in conventional and ADD-Vantage® System compatible vials, infusion bottles, pharmacy bulk package bottles, and as a frozen, premixed, iso-osmotic injection in a buffered diluent solution in plastic containers. CLAFORAN, equivalent to 1 gram and 2 grams cefotaxime, is supplied as frozen, premixed, iso-osmotic injections in plastic containers. Solutions range from very pale yellow to light amber. Dextrose Hydrous, USP has been added to adjust osmolality (approximately 1.7 g and 700 mg to the 1 g and 2 g cefotaxime dosages, respectively). The injections are buffered with sodium citrate hydrous, USP. The pH is adjusted with hydrochloric acid and may be adjusted with sodium hydroxide.

The plastic 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

Following IM administration of a single 500 mg or 1 g dose of CLAFORAN to normal volunteers, mean peak serum concentrations of 11.7 and 20.5 mcg/mL respectively were attained within 30 minutes and declined with an elimination half-life of approximately 1 hour. There was a dose-dependent increase in serum levels after the IV administration of 500 mg, 1 g, and 2 g of CLAFORAN (38.9, 101.7, and 214.4 mcg/mL respectively) without alteration in the elimination half-life. There is no evidence of accumulation following repetitive IV infusion of 1 g doses every 6 hours for 14 days as there are no alterations of serum or renal clearance. About 60% of the administered dose was recovered from urine during the first 6 hours following the start of the infusion.

Approximately 20-36% of an intravenously administered dose of ^{14}C-cefotaxime is excreted by the kidney as unchanged cefotaxime and 15-25% as the desacetyl derivative, the major metabolite. The desacetyl metabolite has been shown to contribute to the bactericidal activity. Two other urinary metabolites (M_2 and M_3) account for about 20-25%. They lack bactericidal activity.

A single 50 mg/kg dose of CLAFORAN was administered as an intravenous infusion over a 10- to 15-minute period to 29 newborn infants grouped according to birth weight and age. The mean half-life of cefotaxime in infants with lower birth weights ($\leq$1500 grams), regardless of age, was longer (4.6 hours)

than the mean half-life (3.4 hours) in infants whose birth weight was greater than 1500 grams. Mean serum clearance was also smaller in the lower birth weight infants. Although the differences in mean half-life values are statistically significant for weight, they are not clinically important. Therefore, dosage should be based solely on age. (See DOSAGE AND ADMINISTRATION section.)
Additionally, no disulfiram-like reactions were reported in a study conducted in 22 healthy volunteers administered CLAFORAN and ethanol.

Microbiology

The bactericidal activity of cefotaxime sodium results from inhibition of cell wall synthesis. Cefotaxime sodium has *in vitro* activity against a wide range of gram-positive and gram-negative organisms. Cefotaxime sodium has a high degree of stability in the presence of ß-lactamases, both penicillinases and cephalosporinases, of gram-negative and gram-positive bacteria. Cefotaxime sodium has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section.

Aerobes, Gram-positive:
Enterococcus spp.
*Staphylococcus aureus**, including ß-lactamase-positive and negative strains
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus pyogenes (Group A beta-hemolytic streptococci)
Streptococcus spp.
*Staphylococci which are resistant to methicillin/oxacillin must be considered resistant to cefotaxime sodium.

Aerobes, Gram-negative:
Acinetobacter spp.
Citrobacter spp.
Enterobacter spp.
Escherichia coli
Haemophilus influenzae (including ampicillin-resistant strains)
Haemophilus parainfluenzae
Klebsiella spp. (including *Klebsiella pneumoniae*)
Morganella morganii
Neisseria gonorrhoeae (including ß-lactamase-positive and negative strains)
Neisseria meningitidis
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Serratia marcescens

NOTE: Many strains of the above organisms that are multiply resistant to other antibiotics, e.g. penicillins, cephalosporins, and aminoglycosides, are susceptible to cefotaxime sodium. Cefotaxime sodium is active against some strains of *Pseudomonas aeruginosa.*

Anaerobes:
Bacteroides spp., including some strains of *Bacteroides fragilis*
Clostridium spp. (**Note:** Most strains of *Clostridium difficile* are resistant.)
Fusobacterium spp. (Including *Fusobacterium nucleatum*).
Peptococcus spp.
Peptostreptococcus spp.

Cefotaxime sodium also demonstrates *in vitro* activity against the following microorganisms **but the clinical significance is unknown**. Cefotaxime sodium exhibits *in vitro* minimal inhibitory concentrations (MICs) of 8 mcg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of cefotaxime sodium in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials:

Aerobes, Gram-negative:
Providencia spp.
Salmonella spp. (including *Salmonella typhi*)
Shigella spp.

Cefotaxime sodium is highly stable *in vitro* to four of the five major classes of 5-lactamases described by Richmond et al.[1], including type IIIa (TEM) which is produced by many gram-negative bacteria. The drug

is also stable to ß-lactamase (penicillinase) produced by staphylococci. In addition, cefotaxime sodium shows high affinity for penicillin-binding proteins in the cell wall, including PBP: Ib and III.
Cefotaxime sodium and aminoglycosides have been shown to be synergistic *in vitro* against some strains of *Pseudomonas aeruginosa* but the clinical significance is unknown.

Susceptibility Tests

Dilution techniques:

Quantitative methods that are used to determine minimum inhibitory concentrations (MICs) provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure uses a standardized dilution method[1] (broth or agar) or equivalent with cefotaxime sodium powder. The MIC values obtained should be interpreted according to the following criteria:

When testing organisms[a] other than *Haemophilus* spp., *Neisseria gonorrhoeae*, and *Streptococcus* spp.

MIC (mcg/mL)	Interpretation
≤8	Susceptible (S)
16-32	Intermediate (I)
≥64	Resistant (R)

When testing *Haemophilus* spp.[b]

MIC (mcg/mL)	Interpretation[c]
≤2	Susceptible (S)

When testing *Streptococcus*[d]

MIC (mcg/mL)	Interpretation
≤0.5	Susceptible (S)
1	Intermediate (I)
≥2	Resistant (R)

When testing *Neisseria gonorrhoeae*[e]

MIC (mcg/mL)	Interpretation[c]
≤0.5	Susceptible (S)

a. Staphylococci exhibiting resistance to methicillin/oxacillin, should be reported as also resistant to cefotaxime despite apparent *in vitro* susceptibility.
b. Interpretive criteria is applicable only to tests performed by broth microdilution method using Haemophilus Test Media.[2]
c. The absence of resistant strains precludes defining any interpretations other than susceptible.
d. *Streptococcus pneumoniae* must be tested using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.
e. Interpretive criteria applicable only to tests performed by agar dilution method using GC agar base with 1% defined growth supplement.[2]

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 that 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.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedure. Standard cefotaxime sodium powder should provide the following MIC values:

Microorganism	MIC (mcg/mL)
Escherichia coli ATCC 25922	0.06-0.25
Staphylococcus aureus ATCC 29213	1-4
Pseudomonas aeruginosa ATCC 27853	4-16
Haemophilus influenzae[a] ATCC 49247	0.12-0.5
Streptococcus pneumoniae[b] ATCC 49619	0.06-0.25
Neisseria gonorrhoeae[c] ATCC 49226	0.015-0.06

a. Ranges applicable only to tests performed by broth microdilution method using Haemophilus Test Media.[2]
b. Ranges applicable only to tests performed by broth microdilution method using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.[2]
c. Ranges applicable only to tests performed by agar dilution method using GC agar base with 1% defined growth supplement.[2]

Diffusion Techniques:

Quantitative methods that require measurements of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 mcg cefotaxime sodium to test the susceptibility of microorganisms to cefotaxime sodium. Reports from the laboratory providing results of the standard single-disk susceptibility test using a 30 mcg cefotaxime sodium disk should be interpreted according to the following criteria:

When testing organisms[a] other than *Haemophilus* spp., *Neisseria gonorrhoeae*, and *Streptococcus* spp.

MIC (mcg/mL)	Interpretation
≥23	Susceptible (S)
15-22	Intermediate (I)
≤14	Resistant (R)

When testing *Haemophilus* spp.[b]

Zone Diameter (mm)	Interpretation[c]
≥26	Susceptible (S)

When testing *Streptococcus* other than *Streptococcus pneumoniae*

Zone Diameter (mm)	Interpretation
≥28	Susceptible (S)
26-27	Intermediate (I)
≤25	Resistant (R)

When testing *Neisseria gonorrhoeae*[d]

Zone Diameter (mm)	Interpretation[c]
≥31	Susceptible (S)

a. Staphylococci exhibiting resistance to methicillin/oxacillin, should be reported as also resistant to cefotaxime despite apparent *in vitro* susceptibility.
b. Interpretive criteria is applicable only to tests performed by disk diffusion method using Haemophilus Test Media.[3]
c. The absence of resistant strains precludes defining any interpretations other than susceptible.
d. Interpretive criteria applicable only to tests performed by disk diffusion method using GC agar base with 1% defined growth supplement.[3]

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for cefotaxime sodium.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30 mcg cefotaxime sodium disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism	Zone Diameter (mm)
Escherichia coli ATCC 25922	29-35
Staphylococcus aureus ATCC 25923	25-31
Pseudomonas aeruginosa ATCC 27853	18-22
Haemophilus influenzae [a] ATCC 49247	31-39
Neisseria gonorrhoeae [b] ATCC 49226	38-48

a. Ranges applicable only to tests performed by disk diffusion method using Haemophilus Test Media.[3]
b. Ranges applicable only to tests performed by disk diffusion method using GC agar base with 1% defined growth supplement.[3]

Anaerobic Techniques:

For anaerobic bacteria, the susceptibility to cefotaxime sodium as MICs can be determined by standardized test methods.[4] The MIC values obtained should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
≤16	Susceptible (S)
32	Intermediate (I)
≥64	Resistant (R)

Interpretation is identical to that stated above for results using dilution techniques.

As with other susceptibility techniques, the use of laboratory control microorganisms is required to control the technical aspects of the laboratory standardized procedures. Standardized cefotaxime sodium powder should provide the following MIC values:

Microorganism	MIC (mcg/mL)
Bacteroides fragilis [a] ATCC 25285	8-32
Bacteroides thetaiotaomicron ATCC 29741	16-64
Eubacterium lantem ATCC 43055	64-256

a. Ranges applicable only to tests performed by agar dilution method.

INDICATIONS AND USAGE

Treatment

CLAFORAN is indicated for the treatment of patients with serious infections caused by susceptible strains of the designated microorganisms in the diseases listed below.

(1) Lower respiratory tract infections, including pneumonia, caused by *Streptococcus pneumoniae* (formerly *Diplococcus pneumoniae*), *Streptococcus pyogenes** (Group A streptococci) and other streptococci (excluding enterococci, e.g., *Enterococcus faecalis*), *Staphylococcus aureus* (penicillinase and non-penicillinase producing), *Escherichia coli, Klebsiella* species*, Haemophilus influenzae* (including ampicillin resistant strains), *Haemophilus parainfluenzae, Proteus mirabilis, Serratia marcescens**, *Enterobacter* species, indole positive *Proteus* and *Pseudomonas* species (including *P. aeruginosa*).

(2) Genitourinary infections. Urinary tract infections caused by *Enterococcus* species, *Staphylococcus epidermidis*, *Staphylococcus aureus**, (penicillinase and non-penicillinase producing), *Citrobacter* species, *Enterobacter* species, *Escherichia coli*, *Klebsiella* species*, Proteus mirabilis, Proteus vulgaris**, *Providencia stuartii, Morganella morganii*, Providencia rettgeri*, Serratia marcescens* and *Pseudomonas* species (including *P. aeruginosa*). Also, uncomplicated gonorrhea (cervical/urethral and rectal) caused by *Neisseria gonorrhoeae*, including penicillinase producing strains.

(3) Gynecologic infections, including pelvic inflammatory disease, endometritis and pelvic cellulitis caused by *Staphylococcus epidermidis*, *Streptococcus* species, *Enterococcus* species, *Enterobacter* species*, *Klebsiella* species*, *Escherichia coli, Proteus mirabilis, Bacteroides* species (including *Bacteroides fragilis**), *Clostridium* species, and anaerobic cocci (including *Peptostreptococcus* species and *Peptococcus* species) and *Fusobacterium* species (including *F. nucleatum**).

CLAFORAN, like other cephalosporins, has no activity against *Chlamydia trachomatis*. Therefore, when cephalosporins are used in the treatment of patients with pelvic inflammatory disease and *C. trachomatis* is one of the suspected pathogens, appropriate anti-chlamydial coverage should be added.

(4) Bacteremia/Septicemia caused by *Escherichia coli, Klebsiella* species, and *Serratia marcescens*, *Staphylococcus aureus* and *Streptococcus* species (including *S. pneumonia*).
(5) Skin and skin structure infections caused by *Staphylococcus aureus* (penicillinase and non-penicillinase producing), *Staphylococcus epidermidis, Streptococcus pyogenes* (Group A streptococci) and other streptococci, *Enterococcus* species, *Acinetobacter* species*, *Escherichia coli, Citrobacter* species (including *C. freundii**), *Enterobacter* species, *Klebsiella* species, *Proteus mirabilis, Proteus vulgaris**, *Morganella morganii, Providencia rettgeri**, *Pseudomonas* species, *Serratia marcescens, Bacteroides* species, and anaerobic cocci (including *Peptostreptococcus** species and *Peptococcus* species).
(6) Intra-abdominal infections including peritonitis caused by *Streptococcus* species*, *Escherichia coli, Klebsiella* species, *Bacteroides* species, and anaerobic cocci (including *Peptostreptococcus** species and *Peptococcus** species) *Proteus mirabilis**, and *Clostridium* species*.
(7) Bone and/or joint infections caused by *Staphylococcus aureus* (penicillinase and non-penicillinase producing strains), *Streptococcus* species (including *S. pyogenes**), *Pseudomonas* species (including *P. aeruginosa**), and *Proteus mirabilis**.
(8) Central nervous system infections, e.g., meningitis and ventriculitis, caused by *Neisseria meningitidis, Haemophilus influenzae, Streptococcus pneumoniae, Klebsiella pneumoniae** and *Escherichia coli**.
(*) Efficacy for this organism, in this organ system, has been studied in fewer than 10 infections.
Although many strains of enterococci (e.g., *S. faecalis*) and *Pseudomonas* species are resistant to cefotaxime sodium *in vitro*, CLAFORAN has been used successfully in treating patients with infections caused by susceptible organisms.
Specimens for bacteriologic culture should be obtained prior to therapy in order to isolate and identify causative organisms and to determine their susceptibilities to CLAFORAN. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.
In certain cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, CLAFORAN may be used concomitantly with an aminoglycoside. The dosage recommended in the labeling of both antibiotics may be given and depends on the severity of the infection and the patient's condition. Renal function should be carefully monitored, especially if higher dosages of the aminoglycosides are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. It is possible that nephrotoxicity may be potentiated if CLAFORAN is used concomitantly with an aminoglycoside.

Prevention
The administration of CLAFORAN preoperatively reduces the incidence of certain infections in patients undergoing surgical procedures (e.g., abdominal or vaginal hysterectomy, gastrointestinal and genitourinary tract surgery) that may be classified as contaminated or potentially contaminated.
In patients undergoing cesarean section, intraoperative (after clamping the umbilical cord) and postoperative use of CLAFORAN may also reduce the incidence of certain postoperative infections. See **DOSAGE AND ADMINISTRATION** section.
Effective use for elective surgery depends on the time of administration. To achieve effective tissue levels, CLAFORAN should be given 1/2 or 1 1/2 hours before surgery. See **DOSAGE AND ADMINISTRATION** section.
For patients undergoing gastrointestinal surgery, preoperative bowel preparation by mechanical cleansing as well as with a non-absorbable antibiotic (e.g., neomycin) is recommended.
If there are signs of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapy may be instituted.
To reduce the development of drug-resistant bacteria and maintain the effectiveness of CLAFORAN and other antibacterial drugs, CLAFORAN 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.

CONTRAINDICATIONS

CLAFORAN is contraindicated in patients who have shown hypersensitivity to cefotaxime sodium or the cephalosporin group of antibiotics.

WARNINGS

BEFORE THERAPY WITH CLAFORAN IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFOTAXIME SODIUM, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN WITH CAUTION TO PATIENTS WITH TYPE I HYPERSENSITIVITY REACTIONS TO PENICILLIN. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO CLAFORAN OCCURS, DISCONTINUE TREATMENT WITH THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

During post-marketing surveillance, a potentially life-threatening arrhythmia was reported in each of six patients who received a rapid (less than 60 seconds) bolus injection of cefotaxime through a central venous catheter. Therefore, cefotaxime should only be administered as instructed in the DOSAGE AND ADMINISTRATION section.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefotaxime, and may range from mild to life threatening. Therefore, it is important to consider its diagnosis in patients with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of Clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of colitis may respond to drug discontinuance alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

When the colitis is not relieved by drug discontinuance or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should also be considered.

PRECAUTIONS

General

Prescribing CLAFORAN 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.

CLAFORAN should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Because high and prolonged serum antibiotic concentrations can occur from usual doses in patients with transient or persistent reduction of urinary output because of renal insufficiency, the total daily dosage should be reduced when CLAFORAN is administered to such patients. Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organism.

Although there is no clinical evidence supporting the necessity of changing the dosage of cefotaxime sodium in patients with even profound renal dysfunction, it is suggested that, until further data are obtained, the dose of cefotaxime sodium be halved in patients with estimated creatinine clearances of less than 20 mL/min/1.73 m^2.

When only serum creatinine is available, the following formula[5] (based on sex, weight, and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

$$\frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine}}$$

Males:

$$\frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine}} \times 0.85$$

Females:

As with other antibiotics, prolonged use of CLAFORAN may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

As with other beta-lactam antibiotics, granulocytopenia and, more rarely, agranulocytosis may develop during treatment with CLAFORAN, particularly if given over long periods. For courses of treatment lasting longer than 10 days, blood counts should therefore be monitored.
CLAFORAN, like other parenteral anti-infective drugs, may be locally irritating to tissues. In most cases, perivascular extravasation of CLAFORAN responds to changing of the infusion site. In rare instances, extensive perivascular extravasation of CLAFORAN may result in tissue damage and require surgical treatment. To minimize the potential for tissue inflammation, infusion sites should be monitored regularly and changed when appropriate.

Information for patients

Patients should be counseled that antibacterial drugs including CLAFORAN should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When CLAFORAN 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 CLAFORAN or other antibacterial drugs in the future.

Drug Interactions

Increased nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside antibiotics.

Drug/Laboratory Test Interactions

Cephalosporins, including cefotaxime sodium, are known to occasionally induce a positive direct Coombs' test.

Carcinogenesis, Mutagenesis

Lifetime studies in animals to evaluate carcinogenic potential have not been conducted. CLAFORAN was not mutagenic in the mouse micronucleus test or in the Ames' test. CLAFORAN did not impair fertility to rats when administered subcutaneously at doses up to 250 mg/kg/day (0.2 times the maximum recommended human dose based on mg/m^2) or in mice when administered intravenously at doses up to 2000 mg/kg/day (0.7 times the recommended human dose based on mg/m^2).

Pregnancy: Teratogenic Effects: Pregnancy Category B:

Reproduction studies have been performed in pregnant mice given CLAFORAN intravenously at doses up to 1200 mg/kg/day (0.4 times the recommended human dose based on mg/m^2) or in pregnant rats when administered intravenously at doses up to 1200 mg/kg/day (0.8 times the recommended human dose based on mg/m^2). No evidence of embryotoxicity or teratogenicity was seen in these studies. There are no well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects

Use of the drug in women of child-bearing potential requires that the anticipated benefit be weighed against the possible risks.
In perinatal and postnatal studies with rats, the pups in the group given 1200 mg/kg/day of CLAFORAN were significantly lighter in weight at birth and remained smaller than pups in the control group during the 21 days of nursing.

Nursing Mothers

CLAFORAN is excreted in human milk in low concentrations. Caution should be exercised when CLAFORAN is administered to a nursing woman.

Pediatric Use

See Precautions above regarding perivascular extravasation. The potential for toxic effects in pediatric patients from chemicals that may leach from the plastic in single dose Galaxy® containers (premixed CLAFORAN Injection) has not been determined.

ADVERSE REACTIONS

CLAFORAN is generally well tolerated. The most common adverse reactions have been local reactions following IM or IV injection. Other adverse reactions have been encountered infrequently.

The most frequent adverse reactions (greater than 1%) are:

Local (4.3%)—Injection site inflammation with IV administration. Pain, induration, and tenderness after IM injection.

Hypersensitivity (2.4%)—Rash, pruritus, fever, eosinophilia and less frequently urticaria and anaphylaxis.

Gastrointestinal (1.4%)—Colitis, diarrhea, nausea, and vomiting.

Symptoms of pseudomembranous colitis can appear during or after antibiotic treatment.

Nausea and vomiting have been reported rarely.

Less frequent adverse reactions (less than 1%) are:

Cardiovascular System—Potentially life-threatening arrhythmias following rapid (less than 60 seconds) bolus administration via central venous catheter have been observed.

Hematologic System—Neutropenia, transient leukopenia, eosinophilia, thrombocytopenia and agranulocytosis have been reported. Some individuals have developed positive direct Coombs Tests during treatment with CLAFORAN and other cephalosporin antibiotics. Rare cases of hemolytic anemia have been reported.

Genitourinary System—Moniliasis, vaginitis.

Central Nervous System—Headache.

Liver—Transient elevations in SGOT, SGPT, serum LDH, and serum alkaline phosphatase levels have been reported.

Kidney—As with some other cephalosporins, interstitial nephritis and transient elevations of BUN and creatinine have been occasionally observed with CLAFORAN.

Cutaneous-As with other cephalosporins, isolated cases of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported.

Cephalosporin Class Labeling

In addition to the adverse reactions listed above which have been observed in patients treated with cefotaxime sodium, the following adverse reactions and altered laboratory tests have been reported for cephalosporin class antibiotics: allergic reactions, hepatic dysfunction including cholestasis, aplastic anemia, hemorrhage, and false-positive test for urinary glucose.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced. See **DOSAGE AND ADMINISTRATION** and **OVERDOSAGE**. If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

OVERDOSAGE

The acute toxicity of CLAFORAN was evaluated in neonatal and adult mice and rats. Significant mortality was seen at parenteral doses in excess of 6000 mg/kg/day in all groups. Common toxic signs in animals that died were a decrease in spontaneous activity, tonic and clonic convulsions, dyspnea, hypothermia, and cyanosis.

Cefotaxime sodium overdosage has occurred in patients. Most cases have shown no overt toxicity. The most frequent reactions were elevations of BUN and creatinine. Patients who receive an acute overdosage should be carefully observed and given supportive treatment.

DOSAGE AND ADMINISTRATION

Adults

Dosage and route of administration should be determined by susceptibility of the causative organisms, severity of the infection, and the condition of the patient (see table for dosage guideline). CLAFORAN may be administered IM or IV after reconstitution. Premixed CLAFORAN Injection is intended for IV administration after thawing. The maximum daily dosage should not exceed 12 grams.

GUIDELINES FOR DOSAGE OF CLAFORAN

Type of Infection	Daily Dose (grams)	Frequency and Route
Gonococcal urethritis/ cervicitis in males and females	0.5	0.5 gram IM (single dose)
Rectal gonorrhea in females	0.5	0.5 gram IM (single dose)
Rectal gonorrhea in males	1	1 gram IM (single dose)
Uncomplicated infections	2	1 gram every 12 hours IM or IV
Moderate to severe infections	3-6	1-2 grams every 8 hours IM or IV
Infections commonly needing antibiotics in higher dosage (e.g., septicemia)	6-8	2 grams every 6-8 hours IV
Life-threatening infections	up to 12	2 grams every 4 hours IV

If *C. trachomatis* is a suspected pathogen, appropriate anti-chlamydial coverage should be added, because cefotaxime sodium has no activity against this organism.
To prevent postoperative infection in contaminated or potentially contaminated surgery, the recommended dose is a single 1 gram IM or IV administered 30 to 90 minutes prior to start of surgery.

Cesarean Section Patients

The first dose of 1 gram is administered intravenously as soon as the umbilical cord is clamped. The second and third doses should be given as 1 gram intravenously or intramuscularly at 6 and 12 hours after the first dose.

Neonates, Infants, and Children

The following dosage schedule is recommended:

Neonates (birth to 1 month):

0-1 week of age	50 mg/kg per dose every 12 hours IV
1-4 weeks of age	50 mg/kg per dose every 8 hours IV

It is not necessary to differentiate between premature and normal-gestational age infants.

Infants and Children (1 month to 12 years):

For body weights less than 50 kg, the recommended daily dose is 50 to 180 mg/kg IM or IV body weight divided into four to six equal doses. The higher dosages should be used for more severe or serious infections, including meningitis. For body weights 50 kg or more, the usual adult dosage should be used; the maximum daily dosage should not exceed 12 grams.

Impaired Renal Function—see **PRECAUTIONS** section.

NOTE: As with antibiotic therapy in general, administration of CLAFORAN should be continued for a minimum of 48 to 72 hours after the patient defervesces or after evidence of bacterial eradication has been obtained; a minimum of 10 days of treatment is recommended for infections caused by Group A beta-hemolytic streptococci in order to guard against the risk of rheumatic fever or glomerulonephritis; frequent bacteriologic and clinical appraisal is necessary during therapy of chronic urinary tract infection and may be required for several months after therapy has been completed; persistent infections may require treatment of several weeks and doses smaller than those indicated above should not be used.

Preparation of CLAFORAN Sterile

CLAFORAN for IM or IV administration should be reconstituted as follows:

Strength	Diluent (mL)	Withdrawable Volume (mL)	Approximate Concentration (mg/mL)
500 mg vial* (IM)	2	2.2	230
1g vial* (IM)	3	3.4	300
2g vial* (IM)	5	6.0	330
500 mg vial* (IV)	10	10.2	50
1g vial* (IV)	10	10.4	95
2g vial* (IV)	10	11.0	180
1g infusion	50-100	50-100	20-10
2g infusion	50-100	50-100	40-20

(*) in conventional vials

Shake to dissolve; inspect for particulate matter and discoloration prior to use. Solutions of CLAFORAN range from very pale yellow to light amber, depending on concentration, diluent used, and length and condition of storage.

For intramuscular use: Reconstitute VIALS with Sterile Water for Injection or Bacteriostatic Water for Injection as described above.

For intravenous use: Reconstitute VIALS with at least 10 mL of Sterile Water for Injection. Reconstitute INFUSION BOTTLES with 50 or 100 mL of 0.9% Sodium Chloride Injection or 5% Dextrose Injection. For other diluents, see **COMPATIBILITY AND STABILITY** section.

NOTE: Solutions of CLAFORAN must not be admixed with aminoglycoside solutions. If CLAFORAN and aminoglycosides are to be administered to the same patient, they must be administered separately and not as mixed injection.

A SOLUTION OF 1 G CLAFORAN IN 14 ML OF STERILE WATER FOR INJECTION IS ISOTONIC.

IM Administration: As with all IM preparations, CLAFORAN should be injected well within the body of a relatively large muscle such as the upper outer quadrant of the buttock (i.e., gluteus maximus); aspiration is necessary to avoid inadvertent injection into a blood vessel. Individual IM doses of 2 grams may be given if the dose is divided and is administered in different intramuscular sites.

IV Administration: The IV route is preferable for patients with bacteremia, bacterial septicemia, peritonitis, meningitis, or other severe or life-threatening infections, or for patients who may be poor risks because of lowered resistance resulting from such debilitating conditions as malnutrition, trauma, surgery, diabetes, heart failure, or malignancy, particularly if shock is present or impending.

For intermittent IV administration, a solution containing 1 gram or 2 grams in 10 mL of Sterile Water for Injection can be injected over a period of three to five minutes. Cefotaxime should not be administered over a period of less than three minutes. (See WARNINGS). With an infusion system, it may also be given over a longer period of time through the tubing system by which the patient may be receiving other IV solutions. However, during infusion of the solution containing CLAFORAN, it is advisable to discontinue temporarily the administration of other solutions at the same site.

For the administration of higher doses by continuous IV infusion, a solution of CLAFORAN may be added to IV bottles containing the solutions discussed below.

Directions for use of CLAFORAN Injection in Galaxy Container (PL 2040 Plastic)

CLAFORAN Injection in Galaxy containers (PL 2040 plastic) is for continuous or intermittent infusion using sterile equipment.

Storage

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

Thawing of Plastic Container

Thaw frozen container at room temperature or under refrigeration (at or below 5°C). [DO NOT FORCE THAW BY IMMERSION IN WATER BATHS OR BY MICROWAVE IRRADIATION.]

Check for minute leaks by squeezing container firmly. If leaks are detected, discard solution as sterility may be impaired.

DO NOT ADD SUPPLEMENTARY MEDICATION.

The container should be visually inspected. 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 or outlet ports are not intact, the container should be discarded.

The thawed solution is stable for 10 days under refrigeration (at or below 5°C) or 24 hours at or below 22°C. Do not refreeze thawed antibiotics.

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.

Preparation of CLAFORAN Sterile in ADD-Vantage® System

CLAFORAN Sterile 1 g or 2 g may be reconstituted in 50 mL or 100 mL of 5% Dextrose or 0.9% Sodium Chloride in the ADD-Vantage® diluent container. Refer to enclosed, separate INSTRUCTIONS FOR ADD-VANTAGE® SYSTEM.

Compatibility and Stability

Solutions of CLAFORAN Sterile reconstituted as described above **(Preparation of CLAFORAN Sterile)** remain chemically stable (potency remains above 90%) as follows when stored in original containers and disposable plastic syringes:

Strength	Reconstituted Concentration mg/mL	Stability at or below 22°C	Stability under Refrigeration (at or below 5°C)	
			Original Containers	Plastic Syringes
500 mg vial IM	230	12 hours	7 days	5 days
1g vial IM	300	12 hours	7 days	5 days
2g vial IM	330	12 hours	7 days	5 days
500 mg vial IV	50	24 hours	7 days	5 days
1g vial IV	95	24 hours	7 days	5 days
2g vial IV	180	12 hours	7 days	5 days
1g infusion bottle	10-20	24 hours	10 days	
2g infusion bottle	20-40	24 hours	10 days	

Reconstituted solutions stored in original containers and plastic syringes remain stable for 13 weeks frozen.

Reconstituted solutions may be further diluted up to 1000 mL with the following solutions and maintain satisfactory potency for 24 hours at or below 22°C, and at least 5 days under refrigeration (at or below 5°C): 0.9% Sodium Chloride Injection; 5 or 10% Dextrose Injection; 5% Dextrose and 0.9% Sodium Chloride Injection, 5% Dextrose and 0.45% Sodium Chloride Injection; 5% Dextrose and 0.2% Sodium Chloride Injection; Lactated Ringer's Solution; Sodium Lactate Injection (M/6); 10% Invert Sugar Injection, 8.5% TRAVASOL® (Amino Acid) Injection without Electrolytes.

Solutions of CLAFORAN Sterile reconstituted in 0.9% Sodium Chloride Injection or 5% Dextrose Injection in Viaflex® plastic containers maintain satisfactory potency for 24 hours at or below 22°C, 5 days under refrigeration (at or below 5°C) and 13 weeks frozen. Solutions of CLAFORAN Sterile reconstituted in 0.9% Sodium Chloride Injection or 5% Dextrose Injection in the ADD-Vantage® flexible containers maintain satisfactory potency for 24 hours at or below 22°C. DO NOT FREEZE.

NOTE: CLAFORAN solutions exhibit maximum stability in the pH 5-7 range. Solutions of CLAFORAN should not be prepared with diluents having a pH above 7.5, such as Sodium Bicarbonate Injection.

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

HOW SUPPLIED

Sterile CLAFORAN is a dry off-white to pale yellow crystalline powder supplied in vials and bottles containing cefotaxime sodium as follows:

500 mg cefotaxime (free acid equivalent) in vials in packages of 10 (NDC 0039-0017-10).

1 g cefotaxime (free acid equivalent) in vials in packages of 10 (NDC 0039-0018-10), packages of 25 (NDC 0039-0018-25), packages of 50 (NDC 0039-0018-50); infusion bottles in packages of 10 (NDC 0039-0018-11).

2 g cefotaxime (free acid equivalent) in vials in packages of 10 (NDC 0039-0019-10), packages of 25 (NDC 0039-0019-25), packages of 50 (NDC 0039-0019-50); infusion bottles in packages of 10 (NDC 0039-0019-11).

1 g cefotaxime (free acid equivalent) in ADD-Vantage® System vials in packages of 25 (NDC 0039-0023-25) and 50 (NDC 0039-0023-50).

2 g cefotaxime (free acid equivalent) in ADD-Vantage® System vials in packages of 25 (NDC 0039-0024-25) and 50 (NDC 0039-0024-50).

ADD-Vantage® System diluents (5% Dextrose or 0.9% Sodium Chloride) are available from Abbott Laboratories.

Also available:

Pharmacy Bulk Package:

10g cefotaxime (free acid equivalent) in bottles (NDC 0039-0020-01)

NOTE: CLAFORAN in the dry state should be stored below 30°C. The dry material as well as solutions tend to darken depending on storage conditions and should be protected from elevated temperatures and excessive light.

Premixed CLAFORAN Injection is supplied as a frozen, iso-osmotic, sterile, nonpyrogenic solution in 50 mL single dose Galaxy® containers (PL 2040 plastic) as follows:

1 g cefotaxime (free acid equivalent) in packages of 12 (NDC 0039-0037-05) 2G3518.
2 g cefotaxime (free acid equivalent) in packages of 12 (NDC 0039-0038-05) 2G3519.

NOTE: Store Premixed CLAFORAN Injection at or below -20°C/-4°F. [See DIRECTIONS FOR USE OF CLAFORAN (cefotaxime injection) IN GALAXY® CONTAINERS (PL 2040 PLASTIC)].

Claforan® Injection supplied as a frozen, iso-osmotic, sterile, nonpyrogenic solution in Galaxy® containers (PL 2040 plastic) is manufactured for Aventis Pharmaceuticals by Baxter Healthcare Corporation.

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2) National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December, 1993.
3) National Committee for Clinical Laboratory Standards. Performance Standard for Antimicrobial Disk Susceptibility Tests - Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December, 1993.
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5) Cockcroft, D.W. and Gault, M.H.: Prediction of Creatinine Clearance from Serum Creatinine, Nephron 16:31-41, 1976.

Sterile cefotaxime sodium US Patents 4,298,606; 5,583,216; 5,159,070; 4,376,203; 5,336,776.
Cefotaxime sodium injection US Patents 4,298,606; 5,583,216; 5,159,070; 4,376,203; 5,336,776.
Galaxy and PL 2040 REG TM Baxter International Inc.
ADD-Vantage REG TM Abbott Laboratories.
US Patents ADD-Vantage System: 4,614,267; 4,614,515; 4,757,911; 4,703,864; 4,784,658; 4,784,259; 4,948,000; 4,936,445; 5,583,216; 5,159,070; 4,376,203; 5,336,776.

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