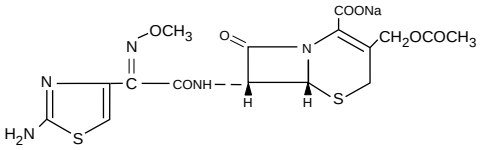
CLAFORAN®
Sterile (cefotaxime for injection, USP)
and Injection (cefotaxime injection, USP)

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 72 (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, 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 (≤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.)

Drug Interactions

A single intravenous dose and oral dose of probenecid (500 mg each) followed by two oral doses of probenecid 500 mg at approximately hourly intervals administered to three healthy male subjects receiving a continuous infusion of cefotaxime increased the steady-state plasma concentration of cefotaxime by approximately 80%. In another study, administration of oral probenecid 500 mg every 6 hours to six healthy male subjects with cefotaxime 1 gram infused over 5 minutes decreased the total clearance of cefotaxime by approximately 50%.

Additionally, no disulfiram-like reactions were reported in a study conducted in 22 healthy volunteers administered CLAFORAN and ethanol.

Microbiology

Mechanism of Action

Cefotaxime sodium is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis. Cefotaxime has activity in the presence of some beta-lactamases, both penicillinases and cephalosporinases, of Gram-negative and Gram-positive bacteria.

Mechanism of Resistance

Resistance to cefotaxime is primarily through hydrolysis by beta-lactamase, alteration of penicillin-binding proteins (PBPs), and decreased permeability.

Susceptibility to cefotaxime will vary geographically and may change over time; local susceptibility data should be consulted, if available. Cefotaxime has been shown to be active against most isolates of the following bacteria both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section:

Gram-positive bacteria

Enterococcus spp.[1]
Staphylococcus aureus (methicillin-susceptible isolates only)
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus pyogenes (Group A beta-hemolytic streptococci)
Streptococcus spp. (Viridans group streptococci)

Gram-negative bacteria

Acinetobacter spp.

Citrobacter spp.[2]
Enterobacter spp.[2]
Escherichia coli[2]
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella spp. (including *Klebsiella pneumoniae*)[2]
Morganella morganii[2]
Neisseria gonorrhoeae (including beta-lactamase-positive and negative strains)
Neisseria meningitidis
Proteus mirabilis[2]
Proteus vulgaris[2]
Providencia rettgeri[2]
Providencia stuartii[2]
Serratia marcescens[2]

[1] *Enterococcus* species may be intrinsically resistant to cefotaxime.
[2] Most extended spectrum beta-lactamase (ESBL)-producing and carbapenemase-producing isolates are resistant to cefotaxime.

Anaerobic bacteria

Bacteroides spp., including some isolates of *Bacteroides fragilis*
Clostridium spp. (most isolates of *Clostridium difficile* are resistant)
Fusobacterium spp. (including *Fusobacterium nucleatum*)
Peptococcus spp.
Peptostreptococcus spp.

The following *in vitro* data are available, **but their clinical significance is unknown**. At least 90 percent of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to 1 mcg/mL. However, the efficacy of cefotaxime in treating clinical infections due to these microorganisms **has not been** established in adequate and well-controlled clinical trials.

Gram-negative bacteria

Providencia spp.
Salmonella spp. (including *Salmonella typhi*)
Shigella spp.

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antimicrobial drug products used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

Dilution techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method (broth or agar) [1,2]. The MIC values should be interpreted according to the criteria provided in Table 1.

Diffusion techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method[2,3]. This procedure uses paper disks impregnated with 30 mcg cefotaxime to test the susceptibility of microorganisms to cefotaxime. The disk diffusion interpretive criteria are provided in Table 1.

Anaerobic techniques

For anaerobic bacteria, the susceptibility to cefotaxime as MICs can be determined by a standardized agar test method[3,4]. The MIC values obtained should be interpreted according to the criteria provided in Table 1.

Table 1: Susceptibility Test Interpretive Criteria for Cefotaxime.

	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion Zone Diameters (mm)		
Pathogen	**(S) Susceptible**	**(I) Intermediate**	**(R) Resistant**	**(S) Susceptible**	**(I) Intermediate**	**(R) Resistant**
Acinetobacter spp.	≤1	2	≥4			
Enterobacteriaceae	≤1	2	≥4	≥26	23–25	≤22
Haemophilus spp.*†	≤1	-	-		-	-
*Neisseria gonorrhoeae**	≤0.5	-	-	≥31	-	-
*Neisseria meningitidis**	≤0.12	-	-	≥34	-	-
Streptococcus pneumoniae‡ meningitis isolates	≤0.5	1	≥2	-	-	-
Streptococcus pneumoniae‡ non-meningitis isolates	≤1	2	≥	-	-	-
Streptococcus spp. beta-hemolytic group*	≤0.5	-	-	≥24	-	-
Viridans group streptococci	≤1	2	≥4	≥28	26–27	≤25
Other *Non-Enterobacteriaceae*§	≤1	2	≥4			
Anaerobic bacteria (agar method)	≤1	2	≥4	-	-	-

Susceptible breakpoints are based on a dose of 1 gram q 8h in patients with normal renal function

Susceptibility of staphylococci to cefotaxime may be deduced from testing only penicillin and either cefoxitin or oxacillin.

*****The current absence of data on resistant isolates precludes defining any category other than "Susceptible". If isolates yield MIC results other than susceptible, they should be submitted to a reference laboratory for additional testing.

† *Haemophilus* spp includes only isolates of *H. influenzae* and *H. parainfluenzae*.

‡Disc diffusion interpretive criteria for cefotaxime discs against *S. pneumoniae* are not available, however, isolates of pneumococci with oxacillin zone diameters of >20 mm are susceptible (MIC ≤0.06 mcg/mL) to penicillin and can be considered susceptible to cefotaxime. *S. pneumoniae* isolates should not be reported as penicillin (cefotaxime)

resistant or intermediate based solely on an oxacillin zone diameter of ≤ 19 mm. The cefotaxime MIC should be determined for those isolates with oxacillin zone diameters ≤ 19 mm.

§Other Non-Enterobacteriaceae include *Pseudomonas* spp. and other nonfastidious, glucose-nonfermenting, gram-negative bacilli, but exclude *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Burkholderia cepacia*, *Burkholderia mallei*, *Burkholderia pseudomallei*, and *Stenotrophomonas maltophilia*.

A report of *Susceptible* indicates that the antimicrobial drug is likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration at the site of infection.. 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 a 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 antimicrobial drug is not likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentrations usually achievable at the site of infection; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individual performing the test[1,2,3,4]. Standard cefotaxime powder should provide the following range of MIC values noted in Table 2. For the diffusion technique using the 30 mcg disk, the criteria in Table 2 should be achieved.

Table 2: Acceptable Quality Control Ranges for Cefotaxime

QC Strain	Minimum Inhibitory Concentrations (mcg/mL)	Disk Diffusion Zone Diameters (mm)
Escherichia coli ATCC 25922	0.03–0.12	29–35
Staphylococcus aureus ATCC 29213	1–4	-
Staphylococcus aureus ATCC 25923	-	25–31
Pseudomonas aeruginosa ATCC 27853	8-32	18–22
Haemophilus influenzae ATCC 49247	0.12–0.5	31–39
Streptococcus pneumoniae ATCC 49619	0.03–0.12	31–39
Neisseria gonorrhoeae ATCC 49226	0.015–0.06	38–48
Bacteroides fragilis ATCC 25285*	8–32	-
Bacteroides thetaiotaomicron ATCC 29741*	16–64	-
Eubacterium lantem ATCC 43055*	64–256	-

*Using the Reference Agar Dilution procedure.

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.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including CLAFORAN, 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

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.

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

$$\text{Females: } 0.85 \times \text{above value}$$

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.

Leukopenia, neutropenia, granulocytopenia and, more rarely, bone marrow failure, pancytopenia, or agranulocytosis may develop during treatment with CLAFORAN. For courses of treatment lasting longer than 10 days, blood counts should therefore be monitored and treatment discontinuation should be considered in case of abnormal results.

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.

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.

Drug Interactions

As with other cephalosporins, CLAFORAN may potentiate the nephrotoxic effects of nephrotoxic drugs such as aminoglycosides, NSAIDs and furosemide.

Probenecid interferes with the renal tubular transfer of cefotaxime, decreasing the total clearance of cefotaxime by approximately 50% and increasing the plasma concentrations of cefotaxime. Administration of cefotaxime in excess of 6 grams/day should be avoided in patients receiving probenecid (see **CLINICAL PHARMACOLOGY, Drug Interactions**).

Drug/Laboratory Test Interactions

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

A false-positive reaction for glucose in the urine may occur with copper reduction tests (Benedict's or Fehling's solution or with CLINITEST tablets), but not with enzyme-based tests for glycosuria. (e.g., CLINISTIX or TesTape). There are no reports in published literature that link elevations of plasma glucose levels to the use of cefotaxime.

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. Although cefotaxime has been reported to cross the placental barrier and appear in cord blood, the effect on the human fetus is not known. 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.

Geriatric Use

Of the 1409 subjects in clinical studies of cefotaxime, 632 (45%) were 65 and over, while 258 (18%) were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see **PRECAUTIONS**, **General**).

ADVERSE REACTIONS

Clinical Trials Experience

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.

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:
Hematologic System - Neutropenia, leukopenia, have been reported. Some individuals have developed positive direct Coombs Tests during treatment with CLAFORAN and other cephalosporin antibiotics.

Genitourinary System - Moniliasis, vaginitis.

Central Nervous System - Headache.

Liver - Transient elevations in AST, ALT, serum LDH, and serum alkaline phosphatase levels have been reported.

Kidney - As with some other cephalosporins, transient elevations of BUN have been occasionally observed with CLAFORAN.

Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of CLAFORAN. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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

Central Nervous System - Administration of high doses of beta-lactam antibiotics, including cefotaxime, particularly in patients with renal insufficiency may result in encephalopathy (e.g. impairment of consciousness, abnormal movements and convulsions). Dizziness has also been reported.

Cutaneous - As with other cephalosporins, isolated cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme have been reported. Acute generalized exanthematous pustulosis (AGEP) has also been reported.

General disorders and administration site conditions - Inflammatory reactions at the injection site, including phlebitis/thrombophlebitis.

Hematologic System - Hemolytic anemia, agranulocytosis, thrombocytopenia, pancytopenia, bone marrow failure.

Hypersensitivity - Anaphylaxis (e.g., angioedema, bronchospasm, malaise possibly culminating in shock), urticaria.

Kidney - Interstitial nephritis, transient elevations of creatinine, acute renal failure.

Liver - Hepatitis, jaundice, cholestasis, elevations of gamma GT and bilirubin.

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. There is a risk of reversible encephalopathy in cases of administration of high doses of beta-lactam antibiotics including cefotaxime. No specific antidote exists. 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.

Geriatric Use

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See **PRECAUTIONS**, **General** and **PRECAUTIONS**, **Geriatric Use**.)

Impaired Renal Function - see **PRECAUTIONS, General**.

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).

2 g cefotaxime (free acid equivalent) in vials in packages of 10 (NDC 0039-0019-10).

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

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

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) and packages of 24 (2 x 12) (NDC 0039-0037-24) 2G3518.

2 g cefotaxime (free acid equivalent) in packages of 12 (NDC 0039-0038-05) and packages of 24 (2 x 12) (NDC 0039-0038-24) 2G3519.

NOTE: Store Premixed CLAFORAN Injection at or below -20°C/-4°F. [See **Directions for use of CLAFORAN 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 sanofi-aventis U.S. LLC by Baxter Healthcare Corporation.

REFERENCES

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3. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard - Twelfth Edition. CLSI document M02-A12, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.

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5. Cockcroft, D.W. and Gault, M.H.: Prediction of Creatinine Clearance from Serum Creatinine, Nephron 16:31-41, 1976.

Rx only

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Bridgewater, NJ 08807
A SANOFI COMPANY

Claforan Injection in Galaxy® Containers:

Manufactured by:
Baxter Healthcare Corporation
Deerfield, IL 60015

Manufactured for:
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Bridgewater, NJ 08807
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