CEFOTAN®

cefotetan disodium for injection
For Intravenous or Intramuscular Use

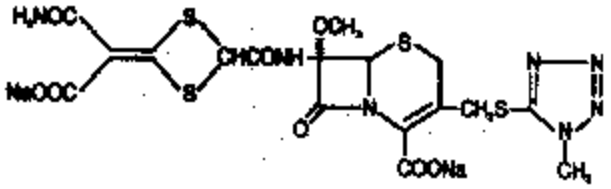
CEFOTAN®

cefotetan injection
In GALAXY® Plastic Container (PL 2040)
For Intravenous Use Only

DESCRIPTION

CEFOTAN (cefotetan disodium for injection) and CEFOTAN (cefotetan injection) in Galaxy®* plastic container (PL 2040) as cefotetan disodium are sterile, semisynthetic, broad-spectrum, beta-lactamase resistant, cephalosporin (cephamycin) antibiotics for parenteral administration. It is the disodium salt of [6R-(6α,7α)]-7-[[[4-(2-amino-1-carboxy-2-oxoethylidene)-1,3-dithietan-2-yl]carbonyl]amino]-7-methoxy-3-[[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. Its molecular formula is $C_{17}H_{15}N_7Na_2O_8S_4$ with a molecular weight of 619.57.

Structural Formula



CEFOTAN (cefotetan disodium for injection) is supplied in vials containing 80 mg (3.5 mEq) of sodium per gram of cefotetan activity. It is a white to pale yellow powder which is very soluble in water. Reconstituted solutions of CEFOTAN (cefotetan disodium for injection) are intended for intravenous and intramuscular administration. The solution varies from colorless to yellow depending on the concentration. The pH of freshly reconstituted solutions is usually between 4.5 to 6.5.

CEFOTAN in the ADD-Vantage Vial† is intended for intravenous use only after dilution with the appropriate volume of ADD-Vantage diluent solution.

CEFOTAN is available in two vial strengths. Each CEFOTAN 1 g vial contains cefotetan disodium equivalent to 1 g cefotetan activity. Each CEFOTAN 2 g vial contains cefotetan disodium equivalent to 2 g cefotetan activity.

CEFOTAN (cefotetan injection) in the Galaxy® plastic container (PL 2040) is a frozen, iso-osmotic, sterile, nonpyrogenic premixed 50 mL solution containing 1 g or 2 g cefotetan as sterile cefotetan disodium. Dextrose, USP has been added to adjust the osmolality to 300 mOsmol/kg (approximately 1.9 g and 1.1 g to the 1 g and 2 g dosages, respectively); sodium bicarbonate has been added to convert cefotetan free acid to the sodium salt. The pH has been adjusted between 4and 6.5 with sodium bicarbonate and may have been adjusted with hydrochloric acid. CEFOTAN (cefotetan injection) in the Galaxy® plastic container (PL 2040) contains 80 mg (3.5 mEq) of sodium per gram of cefotetan activity. After thawing to room temperature, the solution is intended for intravenous use only.

This Galaxy® container is fabricated from a specially designed multilayer plastic (PL 2040). Solutions are in contact with the polyethylene layer of this container and can leach out certain chemical components of the plastic in very small amounts within the expiration dating 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.

CLINICAL PHARMACOLOGY

High plasma levels of cefotetan are attained after intravenous and intramuscular administration of single doses to normal volunteers.

PLASMA CONCENTRATIONS AFTER 1 GRAM IV[a] OR IM DOSE

Mean Plasma Concentration (µg/mL)
Time After Injection

Route	15 min	30 min	1h	2h	4h	8h	12h
IV	92	158	103	72	42	18	9
IM	34	56	71	68	47	20	9

[a]30-minute infusion

PLASMA CONCENTRATIONS AFTER 2 GRAM IV[a] OR IM DOSE
Mean Plasma Concentration (µg/mL)
Time After Injection

Route	5 min	10 min	1h	3h	5h	9h	12h
IV	237	223	135	74	48	22	12[b]
IM	--	20	75	91	69	33	19

[a]Injected over 3 minutes

[b]Concentrations estimated from regression line

The plasma elimination half-life of cefotetan is 3 to 4.6 hours after either intravenous or intramuscular administration.

Repeated administration of CEFOTAN does not result in accumulation of the drug in normal subjects.

Cefotetan is 88% plasma protein bound.

No active metabolites of cefotetan have been detected; however, small amounts (less than 7%) of cefotetan in plasma and urine may be converted to its tautomer, which has antimicrobial activity similar to the parent drug.

In normal patients, from 51% to 81% of an administered dose of CEFOTAN is excreted unchanged by the kidneys over a 24 hour period, which results in high and prolonged urinary concentrations. Following intravenous doses of 1 gram and 2 grams, urinary concentrations are highest during the first hour and reach concentrations of approximately 1700 and 3500 µg/mL respectively.

In volunteers with reduced renal function, the plasma half-life of cefotetan is prolonged. The mean terminal half-life increases with declining renal function, from approximately 4 hours in volunteers with normal renal function to about 10 hours in those with moderate renal impairment. There is a linear correlation between the systemic clearance of cefotetan and creatinine clearance. When renal function is impaired, a reduced dosing schedule based on creatinine clearance must be used. (see DOSAGE AND ADMINISTRATION).

In pharmacokinetics studies of eight elderly patients (greater than 65 years) with normal renal function and six healthy volunteers (aged 25 to 28 years), mean (± 1sd) Total Body Clearance (1.8(0.1) L/h vs. 1.8 (0.3) L/h) and mean Volume of Distribution (10.4(1.2) L vs. 10.3 (1.6)L) were similar following administration of a one gram intravenous bolus dose.

Therapeutic levels of cefotetan are achieved in many body tissues and fluids including:

skin	ureter
muscle	bladder
fat	maxillary sinus mucosa
myometrium	tonsil
endometrium	bile
cervix	peritoneal fluid
ovary	umbilical cord serum
kidney	amniotic fluid

Microbiology

The bactericidal action of cefotetan results from inhibition of cell wall synthesis. Cefotetan has *in vitro* activity against a wide range of aerobic and anaerobic gram-positive and gram-negative organisms. The methoxy group in the 7-alpha position provides cefotetan with a high degree of stability in the presence of beta-lactamases including both penicillinases and cephalosporinases of gram-negative bacteria.

Cefotetan has been shown to be active against most strains of the following organisms **both *in vitro* and in clinical infections (see INDICATIONS AND USAGE)**.

Gram-Negative Aerobes

Escherichia coli
Haemophilus influenzae (including ampicillin-resistant strains)
Klebsiella species (including *K. pneumoniae)*
Morganella morganii
Neisseria gonorrhoeae (nonpenicillinase-producing strains)
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Serratia marcescens

NOTE: Approximately one-half of the usually clinically significant strains of *Enterobacter* species (eg, *E. aerogenes* and *E. cloacae*) are resistant to cefotetan. Most strains of *Pseudomonas aeruginosa* and *Acinetobacter* species are resistant to cefotetan.

Gram-Positive Aerobes

Staphylococcus aureus (including penicillinase- and nonpenicillinase-producing strains)
Staphylococcus epidermidis
Streptococcus agalactiae (group B beta-hemolytic streptococcus)
Streptococcus pneumoniae
Streptococcus pyogenes

NOTE: Methicillin-resistant staphylococci are resistant to cephalosporins. Some strains of *Staphylococcus epidermidis* and most strains of enterococci, eg, *Enterococcus faecalis* (formerly *Streptococcus faecalis)* are resistant to cefotetan.

Anaerobes
Prevotella bivia (formerly *Bacteroides bivius)*
Prevotella disiens (formerly *Bacteroides disiens)*
Bacteroides fragilis
Prevotella melaninogenica (formerly *Bacteroides melaninogenicus)*
Bacteroides vulgatus
Fusobacterium species
Gram-positive bacilli (including *Clostridium* species; see WARNINGS)

NOTE: Most strains of *C. difficile* are resistant (see WARNINGS).

Peptococcus niger
Peptostreptococcus species

NOTE: Many strains of *B. distasonis, B. ovatus* and *B. thetaiotaomicron* are resistant to cefotetan *in vitro*. However, the therapeutic utility of cefotetan against these organisms cannot be accurately predicted on the basis of *in vitro* susceptibility tests alone.

The following *in vitro* data are available but their clinical significance is unknown. Cefotetan has been shown to be active *in vitro* against most strains of the following organisms:

Gram-Negative Aerobes
Citrobacter species (including *C. diversus* and *C. freundii)*
Klebsiella oxytoca
Moraxella (Branhamella) catarrhalis
Neisseria gonorrhoeae (penicillinase-producing strains)
Salmonella species
Serratia species
Shigella species
Yersinia enterocolitica

Anaerobes
Porphyromonas asaccharolytica (formerly *Bacteroides asaccharolyticus)*
Prevotella oralis (formerly *Bacteroides oralis)*
Bacteroides splanchnicus
Clostridium difficile (see WARNINGS)
Propionibacterium species

Veillonella species

Susceptibility Tests

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MIC's). These MIC's provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations or cefotetan powder. The MIC values should be interpreted according to the following criteria:

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

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 which 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 procedures. Standard cefotetan powder should provide the following MIC values:

Microorganism	MIC (µg/mL)
E. coli ATCC 25922	0.06-0.25
S. aureus ATCC 29213	4-16

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of the standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 µg cefotetan to test the susceptibility of microorganisms to cefotetan.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30 µg cefotetan disk should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥ 16	Susceptible (S)
13-15	Intermediate (I)
≤ 12	Resistant (R)

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 cefotetan.

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 µg cefotetan disk should provide the following zone diameters in these laboratory test quality control strains.

Microorganism	Zone Diameter (mm)
E. coli ATCC 25922	28-34
S. aureus ATCC 25923	17-23

Anaerobic Techniques: For anaerobic bacteria, the susceptibility to cefotetan as MIC's can be determined by standardized test methods[3]. The MIC values obtained should be interpreted according to the following criteria:

MIC (µg/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 cefotetan powder should provide the following MIC values:

Microorganism	MIC (µg/mL)
Bacteroides fragilis ATCC 25285	4-16
Bacteroides thetaiotaomicron ATCC 29741	32-128
Eubacterium lentum ATCC 43055	32-128

INDICATIONS AND USAGE

Treatment

CEFOTAN is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:

Urinary Tract Infections caused by *E. coli*, *Klebsiella* spp (including *K. pneumoniae*), *Proteus mirabilis* and *Proteus* spp (which may include the organisms now called *Proteus vulgaris*, *Providencia rettgeri*, and *Morganella morganii*).

Lower Respiratory Tract Infections caused by *Streptococcus pneumoniae*, *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K. pneumoniae*), *E. coli*, *Proteus mirabilis*, and *Serratia marcescens**.

Skin and Skin Structure Infections due to *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*, *Streptococcus pyogenes*, *Streptococcus* species (excluding enterococci), *Escherichia coli*, *Klebsiella pneumoniae*, *Peptococcus niger**, *Peptostreptococcus* species.

Gynecologic Infections caused by *Staphylococcus aureus*, (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*, *Streptococcus* species (excluding enterococci), *Streptococcus agalactiae*, *E. coli*, *Proteus mirabilis*, *Neisseria gonorrhoeae*, Bacteroides species (excluding *B. distasonis*, *B. ovatus*, *B. thetaiotaomicron)*, *Fusobacterium* species*****, and gram-positive anaerobic cocci (including *Peptococcus niger* and *Peptostreptococcus* species).

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

Intra-abdominal Infections caused by *E. coli, Klebsiella* species (including *K. pneumoniae), Streptococcus* species (excluding enterococci), *Bacteroides* species (excluding *B. distasonis, B. ovatus, B. thetaiotaomicron)* and *Clostridium* species*.

Bone and Joint Infections caused by *Staphylococcus aureus.**

*Efficacy for this organism in this organ system was studied in fewer than ten infections.

Specimens for bacteriological examination should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to cefotetan. 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 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, it is possible to use CEFOTAN concomitantly with an aminoglycoside. Cefotetan combinations with aminoglycosides have been shown to be synergistic *in vitro* against many Enterobacteriaceae and also some other gram-negative bacteria. 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.

NOTE: Increases in serum creatinine have occurred when CEFOTAN was given alone. If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, because nephrotoxicity may be potentiated.

Prophylaxis

The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS

CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics and in those individuals who have experienced a cephalosporin associated hemolytic anemia.

WARNINGS

BEFORE THERAPY WITH CEFOTAN IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFOTETAN DISODIUM, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO CEFOTAN OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

AN IMMUNE MEDIATED HEMOLYTIC ANEMIA HAS BEEN OBSERVED IN PATIENTS RECEIVING CEPHALOSPORIN CLASS ANTIBIOTICS. SEVERE CASES OF HEMOLYTIC ANEMIA, INCLUDING FATALITIES, HAVE BEEN REPORTED IN ASSOCIATION WITH THE ADMINISTRATION OF CEFOTETAN. SUCH REPORTS ARE UNCOMMON. IF A PATIENT DEVELOPS ANEMIA ANYTIME WITHIN 2-3 WEEKS SUBSEQUENT TO THE ADMINISTRATION OF CEFOTETAN, THE DIAGNOSIS OF A CEPHALOSPORIN ASSOCIATED ANEMIA SHOULD BE CONSIDERED AND THE DRUG STOPPED UNTIL THE ETIOLOGY IS DETERMINED WITH CERTAINTY. BLOOD TRANSFUSIONS MAY BE CONSIDERED AS NEEDED (See **CONTRAINDICATIONS**).

PATIENTS WHO RECEIVE PROLONGED COURSES OF CEFOTETAN FOR TREATMENT OF INFECTIONS SHOULD HAVE PERIODIC MONITORING FOR SIGNS AND SYMPTOMS OF HEMOLYTIC ANEMIA INCLUDING A MEASUREMENT OF HEMATOLOGICAL PARAMETERS WHERE APPROPRIATE.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefotetan, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present 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 a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation 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. (See ADVERSE REACTIONS.)

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity and, possibly, subsequent bleeding. Those at increased risk include patients with renal or hepatobiliary impairment or poor nutritional state, the elderly, and patients with cancer. Prothrombin time should be monitored and exogenous vitamin K administered as indicated.

PRECAUTIONS

General: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Information for Patients: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc.) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.

Drug Interactions: Increases in serum creatinine have occurred when CEFOTAN was given alone. If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, because nephrotoxicity may be potentiated.

Drug/Laboratory Test Interactions: The administration of CEFOTAN may result in a false positive reaction for glucose in the urine using Clinitest®‡, Benedict's solution, or Fehling's solution. It is recommended that glucose tests based on enzymatic glucose oxidase be used.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels by Jaffe′ reaction and produce false increases in the levels of creatinine reported.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approximately 8-16 times the usual adult human dose) on days 6-35 of life (thought to be developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approximately 2-4 times the usual human dose) only 1 of 10 treated animals was affected, and the degree of degeneration was mild.

Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

Pregnancy: Teratogenic Effects. Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and 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.

Nursing Mothers: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

Geriatric Use: Of the 925 subjects who received cefotetan in clinical studies, 492 (53%) were 60 years and older, while 76 (8%) were 80 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and the other reported clinical experience has not identified differences in responses between 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 DOSAGE AND ADMINISTRATION – Impaired Renal Function).

ADVERSE REACTIONS

In clinical studies, the following adverse effects were considered related to CEFOTAN therapy. Those appearing in italics have been reported during postmarketing experience.

Gastrointestinal: symptoms occurred in 1.5% of patients, the most frequent were diarrhea (1 in 80) and nausea (1 in 700); *pseudomembranous colitis*. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment or surgical prophylaxis. (See WARNINGS.)

Hematologic: laboratory abnormalities occurred in 1.4% of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300); *agranulocytosis, hemolytic anemia, leukopenia, thrombocytopenia*, and *prolonged prothrombin time with or without bleeding.*

Hepatic: enzyme elevations occurred in 1.2% of patients and included a rise in ALT (SGPT) (1 in 150), AST (SGOT) (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).

Hypersensitivity: reactions were reported in 1.2% of patients and included rash (1 in 150) and itching (1 in 700); *anaphylactic reactions and urticaria.*

Local: effects were reported in less than 1% of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500).

Renal*: Elevations in BUN and serum creatinine have been reported.*

Urogenital: *Nephrotoxicity has rarely been reported.*

Miscellaneous: *Fever*

In addition to the adverse reactions listed above which have been observed in patients treated with cefotetan, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics: pruritus, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, vomiting, abdominal pain, colitis, superinfection, vaginitis including vaginal candidiasis, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemorrhage, elevated bilirubin, pancytopenia, and neutropenia.

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

Information on overdosage with CEFOTAN in humans is not available. If overdosage should occur, it should be treated symptomatically and hemodialysis considered, particularly if renal function is compromised.

DOSAGE AND ADMINISTRATION

Treatment

Cefotetan injection in Galaxy® plastic container should not be used for intramuscular administration.

CEFOTAN in the ADD-Vantage Vial is intended for intravenous infusion only, after dilution with the appropriate volume of ADD-Vantage diluent solution.

The usual adult dosage is 1 or 2 grams of CEFOTAN (cefotetan disodium for injection) administered intravenously or intramuscularly or CEFOTAN (cefotetan injection) in the Galaxy® plastic container (PL 2040) administered intravenously every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

General Guidelines for Dosage of CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1 - 4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Skin & Skin Structure		
Mild - Moderate[a]	2 grams	2 g every 24 hours IV 1 g every 12 hours IV or IM
Sever	4 grams	2 g every 12 hours IV
Other Sites	2 - 4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6 grams[b]	3 g every 12 hours IV

[a]*Klebsiella pneumoniae* skin and skin structure infections should be treated with 1 or 2 grams every 12 hours IV or IM.

[b]Maximum daily dosage should not exceed 6 grams.

If *Chlamydia trachomatis* is a suspected pathogen in gynecologic infections, appropriate antichlamydial coverage should be added, since cefotetan has no activity against this organism.

Prophylaxis:

To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.

Impaired Renal Function:

When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dosage*	Every 12 hours
10 - 30	Usual Recommended Dosage*	Every 24 hours
<10	Usual Recommended Dosage*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Alternatively, the dosing interval may remain constant at 12 hour intervals, but the dose reduced to one-half the usual recommended dose for patients with a creatinine clearance of 10-30 mL/min, and one-quarter the usual recommended dose for patients with a creatinine clearance of less than 10 mL/min.

When only serum creatinine levels are available, creatinine clearance may be calculated from the following formula. The serum creatinine level should represent a steady state of renal function.

Males: $\frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$

Females: 0.9 x value for males

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

CEFOTETAN DISODIUM FOR INJECTION

Preparation of Solution From Cefotetan Disodium For Injection

For Intravenous Use: Reconstitute with Sterile Water for Injection. Shake to dissolve and let stand until clear.

Vial Size	Amount of Diluent Added (mL)	Approximate Withdrawable Vol (mL)	Approximate Average Concentration (mg/mL)
1 gram	10	10.5	95
2 gram	10-20	11-21	182-95

Infusion bottles (100 mL) may be reconstituted with 50 to 100 mL of Dextrose Injection 5% or Sodium Chloride Injection 0.9%.

NOTE: ADD-VANTAGE VIALS ARE NOT TO BE USED IN THIS MANNER

For ADD-Vantage Vials: ADD-Vantage Vials of CEFOTAN are to be reconstituted only with Sodium Chloride Injection 0.9% or Dextrose Injection 5% in the 50 mL, 100 mL or 250 mL Flexible Diluent Containers. CEFOTAN supplied in single-use ADD-Vantage Vials should be prepared as directed.

Directions for Use of CEFOTAN (cefotetan disodium for injection) in ADD-Vantage Vials:

To Open Diluent Container: Peel overwrap from the corner and remove container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually.

To Assemble ADD-Vantage Vial and Flexible Diluent Container: (Use Aseptic Technique)

1. Remove the protective covers from the top of the vial and the vial port on the diluent container as follows:

Fig. 1

a. To remove the breakaway vial cap, swing the pull ring over the top of the vial and pull down far enough to start the opening (See Figure 1), then pull straight up to remove the cap. (See Figure 2.) **NOTE:** Once the breakaway cap has been removed, do not access vial with syringe.


Fig. 2

b. To remove the vial port cover, grasp the tab on the pull ring, pull up to break the three tie strings, then pull back to remove the cover. (See Figure 3.)


Fig. 3

2. Screw the vial into the vial port until it will go no further. THE VIAL MUST BE SCREWED IN TIGHTLY TO ASSURE A SEAL. This occurs approximately 1/2 turn (180°) after the first audible click. (See Figure 4.) The clicking sound does not assure a seal; the vial must be turned as far as it will go. **NOTE:** ONCE VIAL IS SEATED, DO NOT ATTEMPT TO REMOVE. (See Figure 4.)

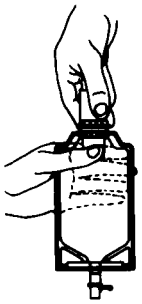


Fig. 4

3. Recheck the vial to assure that it is tight by trying to turn it further in the direction of assembly.

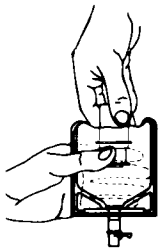
4. Label appropriately.

To Prepare Admixture:

1. Squeeze the bottom of the diluent container gently to inflate the portion of the container surrounding the end of the drug vial.

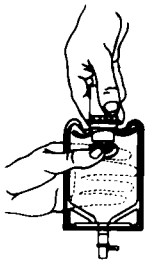
2. With the other hand, push the drug vial down into the container telescoping the walls of the container. Grasp the inner cap of the vial through the walls of the container. (See Figure 5.)

Fig. 5



3. Pull the inner cap from the drug vial. (See Figure 6.) Verify that the rubber stopper has been pulled out and invert the system several times, allowing the drug and diluent to mix.

Fig. 6



4. Mix contents thoroughly and use within the specified time.

Preparation For Administration: (Use Aseptic Technique)

1. Confirm the activation and admixture of vial contents.

2. Check for leaks by squeezing container firmly. If leaks are found, discard unit as sterility may be impaired.

3. Close flow control clamp of administration set.

4. Remove cover from outlet port at bottom of container.

5. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly seated.
   NOTE: See full directions on administration set carton.

6. Lift the free end of the hanger loop on the bottom of the vial, breaking the two tie strings. Bend the loop outward to lock it in the upright position, then suspend container from hanger.

7. Squeeze and release drip chamber to establish proper fluid level in chamber.

8. Open flow control clamp and clear air from set. Close clamp.

9. Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.

10. Regulate rate of administration with flow control clamp.

WARNING: Do not use flexible container in series connections.

For Intramuscular Use: Reconstitute with Sterile Water for Injection; Bacteriostatic Water for Injection; Sodium Chloride Injection 0.9%, USP; 0.5% Lidocaine HCl; or 1% Lidocaine HCl. Shake to dissolve and let stand until clear.

Vial Size	Amount of Diluent Added (mL)	Approximate Withdrawable Vol (mL)	Approximate Average Concentration (mg/mL)
1 gram	2	2.5	400
2 gram	3	4	500

Intravenous Administration:

The intravenous route is preferable for patients with bacteremia, bacterial septicemia, 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 intravenous administration, a solution containing 1 gram or 2 grams of CEFOTAN (cefotetan disodium for injection) in Sterile Water for Injection can be injected over a period of three to five minutes. Using an infusion system, the solution may also be given over a longer period of time through the tubing system by which the patient may be receiving other intravenous solutions. Butterfly® or scalp vein-type needles are preferred for this type of infusion. However, during infusion of the solution containing CEFOTAN (cefotetan disodium for injection), it is advisable to discontinue temporarily the administration of other solutions at the same site.

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

Intramuscular Administration:

As with all intramuscular preparations, CEFOTAN (cefotetan disodium for injection) should be injected well within the body of a relatively large muscle such as the upper outer quadrant of the buttock (ie, gluteus maximus); aspiration is necessary to avoid inadvertent injection into a blood vessel.

CEFOTETAN INJECTION

Directions for Use of CEFOTAN (cefotetan injection) in Galaxy® Plastic Container (PL 2040)

CEFOTAN (cefotetan injection) in Galaxy® plastic container (PL 2040) is for intravenous administration only.

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 (25°C/77°F) or in a refrigerator (5°C/41°F). **[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.

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.

PREPARATION OF INTRAVENOUS USE (USE ASEPTIC TECHNIQUE):

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.

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.

Intravenous Administration

The intravenous route is preferable for patients with bacteremia, bacterial septicemia, 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.

Using an infusion system, CEFOTAN (cefotetan injection) in Galaxy® plastic container (PL 2040) should be given over 20 to 60 minutes through the tubing system by which the patient may be receiving other intravenous solutions. Butterfly® or scalp vein-type needles are preferred for this type of infusion. However, during infusion of the solution containing CEFOTAN (cefotetan injection) in Galaxy® plastic container (PL 2040), it is advisable to discontinue temporarily the administration of other solutions at the same site.

Compatibility and Stability of CEFOTAN Products

Frozen samples should be thawed at room temperature before use. After the periods mentioned below, any unused solutions or frozen material should be discarded. **DO NOT REFREEZE.**

NOTE: Solutions of CEFOTAN must not be admixed with solutions containing aminoglycosides. If CEFOTAN and aminoglycosides are to be administered to the same patient, they must be administered separately and not as a mixed injection. **DO NOT ADD SUPPLEMENTARY MEDICATION.**

CEFOTETAN DISODIUM FOR INJECTION

CEFOTAN (cefotetan disodium for injection) reconstituted as described above (PREPARATION OF SOLUTION) maintains satisfactory potency for 24 hours at room temperature (25°C/77°F), for 96 hours under refrigeration (5°C/41°F), and for at least 1 week in the frozen state (-20°C/-4°F). After reconstitution and subsequent storage in disposable glass or plastic syringes, CEFOTAN (cefotetan disodium for injection) is stable for 24 hours at room temperature and 96 hours under refrigeration.

ADD-Vantage Vials:

Ordinarily, ADD-Vantage Vials should be reconstituted only when it is certain that the patient is ready to receive the drug. However, ADD-Vantage Vials of CEFOTAN reconstituted as described in Preparation of Solution, for ADD-Vantage Vials, maintains satisfactory potency for 24 hours at room temperature (25°C/77°F).

(DO NOT REFRIGERATE OR FREEZE CEFOTAN IN ADD-VANTAGE VIALS.)

CEFOTETAN INJECTION

The thawed solution in Galaxy® plastic container (PL 2040) remains chemically stable for 48 hours at room temperature (25°C/77°F) or for 21 days under refrigeration (5°C/41°F).

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

HOW SUPPLIED

CEFOTAN (cefotetan disodium for injection) is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The vials should not be stored at temperatures above 22°C (72°F) and should be protected from light.

1 g ADD-Vantage Vial (NDC 0310-0376-31)

2 g ADD-Vantage Vial (NDC 0310-0377-32)

1 g Vial (NDC 0310-0376-10)

2 g Vial (NDC 0310-0377-20)

1 g Piggyback Vial (NDC 0310-0376-11)

2 g Piggyback Vial (NDC 0310-0377-21)

CEFOTAN is also available as a 10 g pharmacy bulk package.

10 g in 100 mL Vial (NDC 0310-0375-10)

CEFOTAN (cefotetan injection) is supplied as a frozen, iso-osmotic, premixed solution in single dose Galaxy® plastic containers (PL 2040) as follows:

1 g in 50 mL plastic container (NDC 0310-0378-51)

2 g in 50 mL plastic container (NDC 0310-0379-51)

Store containers at or below -20°C/-4°F. **[See DIRECTIONS FOR USE OF CEFOTAN (cefotetan injection) IN GALAXY® PLASTIC CONTAINER (PL 2040)].**

REFERENCES

1. 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.

2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests -- Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December 1993.

3. National Committee for Clinical Laboratory Standards. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria - Third Edition. Approved Standard NCCLS Document M11-A3, Vol 13, No. 26, NCCLS, Villanova, PA, December 1993.

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CEFOTAN® (cefotetan disodium for injection) is manufactured by GlaxoSmithKline for:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850