CEFOTAN- cefotetan disodium injection, powder, for solution
Teligent Pharma, Inc

CEFOTAN® (Cefotetan for injection, USP)

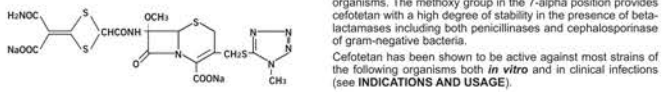
Rx only

For Intravenous or Intramuscular Use

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

DESCRIPTION

CEFOTAN® (cefotetan for Injection, USP), as cefotetan disodium, is a sterile, semisynthetic, broad-spectrum, beta-lactamase resistant, cephalosporin (cephamycin) antibiotic for parenteral administration. It is the disodium salt of [6*R*-(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. Structural formula:



$C_{17}H_{15}N_7Na_2O_8S_4$ M.W. 619.57

CEFOTAN® (cefotetan for Injection, USP) 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 for Injection, USP) 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® (cefotetan for Injection, USP) is available in two vial strengths. Each 1 gram vial contains cefotetan disodium equivalent to 1 gram cefotetan activity. Each 2 gram vial contains cefotetan disodium equivalent to 2 grams cefotetan activity.

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 (mcg/mL)

	Time After Injection						
Route	15 min	30 min	1 h	2 h	4 h	8 h	12 h
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 (mcg/mL)

	Time After Injection						
Route	5 min	10 min	1 h	3 h	5 h	9 h	12 h
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 mcg/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 pharmacokinetic studies of eight elderly patients (greater than 65 years) with normal renal function and six healthy volunteers (aged 25 to 28 years), mean (± 1 sd) 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 cephalosporinase 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 (e.g., *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, e.g., *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 (MICs). These MICs 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 of cefotetan powder. The MIC values should be interpreted according to the following criteria:

MIC (mcg/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 (mcg/mL)
E. coli ATCC 25922	0.06 to 0.25
S. aureus ATCC 29213	4 to 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 mcg 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 mcg cefotetan should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥ 16	Susceptible (S)
13 to 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 mcg cefotetan disk should provide the following zone diameters in these laboratory test quality control strains.

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

Anaerobic Techniques

For anaerobic bacteria, the susceptibility to cefotetan as MICs can be determined by standardized test methods[3]. 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 cefotetan powder should provide the following MIC values:

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

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of CEFOTAN® and other antibacterial drugs, CEFOTAN® 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.

Treatment

CEFOTAN® (cefotetan for Injection, USP) 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 (e.g., 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 a 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. THERE APPEARS TO BE AN INCREASED RISK OF DEVELOPING HEMOLYTIC ANEMIA ON CEFOTETAN RELATIVE TO OTHER CEPHALOSPORINS OF AT LEAST 3 FOLD. IF A PATIENT DEVELOPS ANEMIA ANYTIME WITHIN 2 TO 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 COURSES OF CEFOTETAN FOR TREATMENT OR PROPHYLAXIS OF INFECTIONS SHOULD HAVE PERIODIC MONITORING FOR SIGNS AND SYMPTOMS OF HEMOLYTIC ANEMIA INCLUDING A MEASUREMENT OF HEMATOLOGICAL PARAMETERS WHERE APPROPRIATE.

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

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

Prescribing CEFOTAN® in the absence of 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.

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

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.

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

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® (cefotetan for Injection, USP) 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 Jaffé 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 as found in standard laboratory tests.

Cefotetan has adverse affects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approximately 8 to 16 times the usual adult human dose) on days 6 to 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-dependant; at 120 mg/kg/day (approximately 2 to 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 reproduction 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 pediatric patients 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.

To report **SUSPECTED ADVERSE REACTIONS**, contact Teligent Pharma, Inc. at 1-856-697-1441, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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
The usual adult dosage is 1 or 2 grams of CEFOTAN® (cefotetan for Injection, USP) administered intravenously or intramuscularly. 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® (cefotetan for Injection, USP)

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1 to 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
Severe	4 grams	2 g every 12 hours IV
Other Sites	2 to 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® (cefotetan for Injection, USP) 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 to 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 to 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: $\frac{\text{Weight (kg) x (140 - age)}}{\text{72 x serum creatinine (mg/100 mL)}}$

Females: 0.85 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.

Preparation of Solution
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 to 20	11 to 21	182 to 95

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 for Injection, USP) 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 for Injection, USP), it is advisable to discontinue temporarily the administration of other solutions at the same site.

NOTE: Solutions of cefotetan 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 for Injection, USP) 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.

Compatibility and Stability
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® (cefotetan for Injection, USP) must not be admixed with solutions containing aminoglycosides. If CEFOTAN® (cefotetan for Injection, USP) 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.**
CEFOTAN® (cefotetan for Injection, USP) reconstituted as described above (see **DOSAGE AND ADMINISTRATION, *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 for Injection, USP) is stable for 24 hours at room temperature and 96 hours under refrigeration.
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 for Injection, USP) 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 be stored at 20° to 25° C (68° to 77° F) [see USP Controlled Room Temperature] and should be protected from light.

The following packages are available:

NDC No.	Strength	
52565-052-10	1 gram	10 mL vial, packaged in a tray of 10.
52565-053-10	2 grams	20 mL vial, packaged in a tray of 10.

Vial stoppers do not contain natural rubber latex.

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.

‡Clinitest® is a registered trademark of Ames Division, Miles Laboratories, Inc.

CEFOTAN® is a registered trademark of Teligent Pharma, Inc.

Manufactured for:
Teligent Pharma, Inc.,
Buena NJ 08310

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