DESCRIPTION: Cefotetan for Injection, as cefotetan disodium, is a sterile, semisynthetic, broad-spectrum, beta-lactamase resistant, cephalosporin (cephamycin) antibiotic for parenteral administration. It is the disodium salt of [6R-(6S,7aR)-7-[[4-[(2-amino-1-carboxy-2-oxoethylidene)-3-diethan-2-yl][carboxy][amino]]-7-methoxy-3-[(1-methyl-1H-1,4,3-oxid-5-yl]thio][methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. Structural formula:

\[
\text{C}_{17}H_{15}N_{7}Na_{2}O_{8}S_{4} \quad \text{M.W. 619.57}
\]

Cefotetan 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 cefotetan 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.

Cefotetan for Injection is available in two vial strengths. Each 1 gram vial contains cefotetan dihydrogen 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 OR IM DOSE**

<table>
<thead>
<tr>
<th>Time After Injection</th>
<th>Mean Plasma Concentration (mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Route</strong></td>
<td></td>
</tr>
<tr>
<td>15 min</td>
<td>82†</td>
</tr>
<tr>
<td>30 min</td>
<td>59†</td>
</tr>
<tr>
<td>1 h</td>
<td>103†</td>
</tr>
<tr>
<td>2 h</td>
<td>72†</td>
</tr>
<tr>
<td>4 h</td>
<td>42†</td>
</tr>
<tr>
<td>8 h</td>
<td>18†</td>
</tr>
<tr>
<td>12 h</td>
<td>9†</td>
</tr>
<tr>
<td>TI</td>
<td>47†</td>
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<tr>
<td>M</td>
<td>70†</td>
</tr>
<tr>
<td>1 h 30 min infusion</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>237</td>
</tr>
<tr>
<td>30 min</td>
<td>227</td>
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<tr>
<td>1 h</td>
<td>135</td>
</tr>
<tr>
<td>3 h</td>
<td>74†</td>
</tr>
<tr>
<td>5 h</td>
<td>48†</td>
</tr>
<tr>
<td>9 h</td>
<td>22†</td>
</tr>
<tr>
<td>12 h</td>
<td>179†</td>
</tr>
<tr>
<td>M</td>
<td>199†</td>
</tr>
</tbody>
</table>

*Injection over 3 minutes

*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 cefotetan 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 cefotetan is excreted unchanged by the kidneys over a 24 hour period, which results in high and prolonged urinary concentrations. Following intravenous dosages 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).

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.

For Intravenous or Intramuscular Use

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

**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*

*Haemophillus influenzae* (including ampicillin-resistant strains)

*Klebsiella species* (including *K. pneumoniae*)

*Morganella morgani*

*Neisseria gonorrhoeae* (nonpenicillinase-producing strains)

*Proteus mirabilis*

*Proteus vulgaris*

*Providencia rettgeri*

*Serratia marcescens*

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

**Anaerobes**

*Prevotella bivia* (formerly *Bacteroides bivius*)

*Prevotella disiens* (formerly *Bacteroides disiens*)

*Bacteroides fragilis* species

*Prevotella melaninogenicus* (formerly *Bacteroides melaninogenicus*)

*Bacteroides vulgatus* species

*Fusobacterium* species

*Gram-positive bacilli* (including *Clostridium* species; see WARNINGS)

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

**Peptostreptococcus 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*)

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

- skin
- muscle
- bladder
- fat
- maxillary sinus mucosa
- myometrium
- endometrium
- bile
- cervix
- peritoneal fluid
- ovary
- amniotic fluid

For Intravenous or Intramuscular Use

To reduce the development of drug-resistant bacteria and maintain the effectiveness of cefotetan and other antibacterial drugs, cefotetan should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.
**Bacteroides fragilis**
*Clostridium difficile* (see **WARNINGS**)
Proteus mirabilis 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 according to standard procedures. Standardized procedures are based on a 24-hour incubation of test organisms with standardized inoculum concentrations and standardized concentrations of cefotetan powder. The MIC values should be interpreted according to the following criteria:

<table>
<thead>
<tr>
<th>MIC (mcg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 16</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>16-32</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≥ 64</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

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 an agent normally classifiable as susceptible, further examination should be considered. A report of ‘Resistant’ indicates that the microorganism is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

#### Diffusion Techniques

Quantitative methods that require measurement of growth inhibition in dilution techniques also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure is the disk susceptibility test. This procedure utilizes a disk impregnated with the test compound to produce a local concentration of the antigen in the immediate surrounding environment above the disk. The MIC values should be interpreted according to the following criteria:

<table>
<thead>
<tr>
<th>Zone Diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 12</td>
<td>Resistant (R)</td>
</tr>
<tr>
<td>13-15</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≥ 16</td>
<td>Susceptible (S)</td>
</tr>
</tbody>
</table>

#### Anaerobic Techniques

For anaerobic bacteria, the susceptibility of *C. difficile* can be determined by standardized procedures. The MIC values should be interpreted according to the following criteria:

<table>
<thead>
<tr>
<th>MIC (mcg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 32</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>32-64</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≥ 64</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

### Indications and Usage

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

**Urinary Tract Infections** caused by:
- *E. coli*
- *Klebsiella* spp.
- *Proteus* mirabilis
- *Proteus* vulgaris
- *Provi-
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cancer. Prothrombin time should be monitored and exogenous vitamin K administered as indicated.

PRECAUTIONS:

General: Prescribing cefotetan in the absence of proven or strongly suspected bacterial infection or when infection is unlikely to benefit the patient and increases the risk of the development of drug-resistant bacteria.

Drug class: Cefotetan is a broad-spectrum antibiotic, prolonged use of cefotetan 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.

Cefotetan 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 cefotetan, patients can develop watery andbloody 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 cefotetan, should only be used to treat bacterial infections. They do not treat viral infections and should not be used in patients with viral infections.

Drug Interactions: Increases in serum creatinine have occurred when cefotetan was given alone. If cefotetan and another drug are used concurrently, renal function should be carefully monitored, because nephrotoxicity may be potentiated.

Drug Laboratory Test Interactions: 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 reduced renal function, the drug should be used in dose in elderly patients, 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 cefotetan 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% of patients and included eosinophilia (1 in 200), positive direct Coombs’ test (1 in 250), and thrombocytopenia (1 in 300); agranulocytosis, hemolytic anemia, leukopenia, thrombocytopenia, and prolonged prothrombin time with or without bleeding.

Hepatic: elevation of liver enzymes 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 100) and bilirubin (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 laboratory abnormalities have been reported for cephalosporin-class antibiotics: pruritus, Stevens-Johnson syndrome, erythema multiforme, thrombocytopenia, anaphylaxis, vomiting, abdominal pain, colitis, superinfection, vaginitis including vaginal candidiasis, renal dysfunction, toxic nephritis, aspirin triad, respiratory dysfunction including chloroethanol, aplastic anemia, hemorrhage, elevated bilirubin, pancytopenia, and neutropenia.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with a history of seizures. If 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 cefotetan 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:

Recommended Dosage for Cefotetan for Injection

The usual adult dosage is 0 or 2 grams of Cefotetan for Injection 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.

Dosage for Children

The dosage of cefotetan for injection for the treatment of infections due to susceptible organisms in children, 4 days or older, should be determined by the susceptibility of the causative organism.

Dosage and Route

The usual adult dosage is 1 or 2 grams of Cefotetan for Injection 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.

Dosage in Renal Impairment

Cefotetan is primarily eliminated by the kidneys. The dosage should be reduced in patients with decreased renal function.

Dosage in Hyperkalemia

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

Dosage and Administration

For Intramuscular Use

Reconstitute with Sterile Water for Injection. Shake to dissolve and let stand.

For Intramuscular Use

Reconstitute with 10 mL of sterile water for injection. Shake to dissolve and let stand.

Dosage and Administration

For Intramuscular Use

Reconstitute with sterile water for injection. It is recommended that glucose tests be performed using Clinitest® ‡, Benedict's solution, or Fehling's solution.
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 cefotetan 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 cefotetan for injection, 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 cefotetan 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, cefotetan for injection 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 cefotetan for injection must not be admixed with solutions containing aminoglycosides. If cefotetan for injection 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 for injection 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, cefotetan for injection 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:

Cefotetan 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.

The following packages are available:

Product NDC No. No. Strength
308510 63323-385-10 1 gram 10 mL vial, packaged in a tray of 10.
308620 63323-386-20 2 grams 20 mL vial, packaged in a tray of 10.

Vial stoppers do not contain natural rubber latex.

REFERENCES:


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