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**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**NDA 50-792**

**Medical Review(s)**

## Clinical Review of Original NDA 50-792

B. Braun Medical Inc.  
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Irvine, CA 92623

Regulatory Contact: Richard Bourne

Date of Submission: November 28, 2003

Date of Review: March 11, 2004

### Executive summary

Claforan<sup>®</sup> (cefotaxime for injection, USP) is a cephalosporin antibiotic which is marketed worldwide. This new drug application (NDA) is submitted in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. A 505(b)(2) application may include results of investigations necessary for approval but were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted [21 U.S.C. 355(b)(2)]. These applications are regulated under 21 CFR 314.54 which allow an applicant to rely on the Agency's finding of safety and effectiveness for an approved, reference listed drug to the extent such reliance would be permitted under the generic drug approval provisions at Section 505(j) of the Act.

The NDA concerns a new delivery system for cefotaxime and diluent (dextrose) that utilizes a two chamber container system. The review of this NDA relies on prior FDA determination of safety and effectiveness for the reference listed drug, Claforan<sup>®</sup>. It does not contain any new clinical data, but rather a review of the proposed product label.

### Background

Cefotaxime has been marketed in the U.S. for many years. The NDA for Claforan<sup>®</sup> (NDA 50-547) was approved on January 1, 1982. Cefotaxime is currently manufactured by four companies worldwide. The applicant is seeking approval for the Duplex<sup>®</sup> Container with Cefotaxime for Injection for the same indications approved for Claforan<sup>®</sup>.

On June 12, 1997, representatives from B. Braun Medical Inc. met with members of the Division of Anti-Infective Drug Products to discuss the DUPLEX<sup>®</sup> container system and plans to market numerous cephalosporin drug products in this system. On July 27, 2000, NDA 050-779, Cefazolin for Injection USP and Dextrose for Injection USP in the DUPLEX<sup>®</sup> Container was approved. Subsequently, on February 21, 2001, NDA 50-780, Cefuroxime and Dextrose for Injection in the DUPLEX<sup>®</sup> Container, was approved.

**Chemistry and Manufacturing Controls**Drug Product Information

Proprietary Name: Cefotaxime for Injection USP and Dextrose Injection in the DUPLEX<sup>®</sup> Container

Established Name: Cefotaxime for Injection USP and Dextrose Injection USP

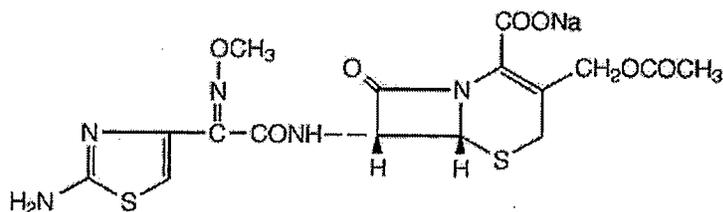
Dosage Form: Dry powder packaged with dextrose solution

Route of Administration: Intravenous (IV)

**Cefotaxime sodium USP**

Chemical Name: Sodium salt of 7-[2-(2-amino-4-thiazolyl) glyoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylate 7<sup>2</sup> (Z)-(o-methyloxime), acetate (ester)

Chemical Structure:



Chemical Formula: C<sub>16</sub>H<sub>16</sub>N<sub>5</sub>NaO<sub>7</sub>S<sub>2</sub>

Molecular Weight: 477.44

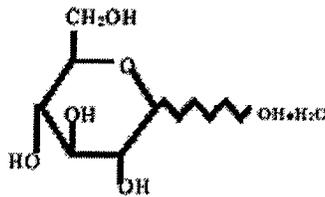
Drug Category: Cephalosporin antibiotic

Dosage Strength: 1 g or 2 g

**Dextrose USP**

Chemical Name: D-glucose monohydrate

Chemical Structure:



Chemical Formula:  $C_6H_{12}O_6 \cdot H_2O$

Molecular Weight: 198.17

Dosage Strength: Dextrose 5% for 1 gram dose and dextrose 3.9% for 2 gram dose

Please see the CMC review by Dr. Andrew Yu, Ph.D., review chemist, for detailed descriptions of the drug product and manufacturing process. A deficiency letter regarding limited stability data was issued to the sponsor on November 25, 2003.

The active pharmaceutical ingredient in this product is cefotaxime, which is obtained from [redacted]. The manufacturer has given right of reference to the drug master file [redacted] for this drug product. The DUPLEX<sup>®</sup> container is a dual chamber delivery system manufactured by B. Braun Medical Inc. at its facility in Irvine, CA. It is composed of two chambers, one for the sterile, lyophilized cefotaxime powder (1 gram or 2 grams), and the other for the dextrose injection diluent. The chambers are separated by a peelable seal which is removed to allow mixing of the cefotaxime with the dextrose containing diluent. After mixing, a second seal which separates the reconstituted drug and a forward compartment containing the administration port is then removed. The reconstituted cefotaxime is then administered to the patient.

### Pharmacology/Toxicology Information

The pharmacology/toxicology review for this product was written by Dr. Terri Peters, D.V.M., HFD-520. No new non-clinical pharmacology or toxicology information was included in the submission. The applicant refers to information found in the labeling for the reference listed drug, Claforan<sup>®</sup>, in accordance with regulations found under 21 CFR 314.51(a)(3).

### Clinical Pharmacokinetics and Biopharmaceutics

The biopharmaceutics review for this product was written by Dr. Paul Buehler, Ph.D., Pharm.D. and Dr. Venkateswar Jarugula, Ph.D., Biopharmaceutics Team Leader. The applicant has not provided any new clinical pharmacokinetic or biopharmaceutical information concerning cefotaxime in the application. The information found in the CLINICAL PHARMACOLOGY section of the label is taken from the label for the reference listed drug, Claforan<sup>®</sup>. Provisions found under 21 CFR 320.22(b)(1)(i) allow for a waiver of the requirement of bioavailability/bioequivalence data when the formulation is intended solely for administration by IV injection. Therefore, all

references to other types of administration, e.g., intramuscular, intraperitoneal, should be deleted.

**Clinical Reviewer's Comment:** *All references to pharmacokinetic data, e.g.,  $C_{max}$ , half-life, etc., associated with intramuscular administration should be eliminated.*

### **Microbiology**

The applicant has not submitted any additional information concerning any changes to the Microbiology section of the labeling. The information found in the current labeling for the reference listed drug, Claforan<sup>®</sup> will be used, as permitted under 21 CFR 314.54(a)(3). Please see the microbiology review by Ms. Connie Mahon, HFD-520 microbiologist, for additional details.

### **Clinical Data**

#### Efficacy

The applicant has not submitted any new clinical data regarding this product, but is relying on the efficacy data provided for the reference listed drug, Claforan<sup>®</sup>.

**Clinical Reviewer's Comment:** *The current labeling for Claforan<sup>®</sup> includes indications for gonorrhea to be treated with a single, intramuscular (IM) injection of 0.5 – 1.0 gram of cefotaxime. Since the delivery system for this product does not allow for any IM administration of the drug, all indications for gonorrhea should be deleted from the INDICATIONS AND USAGE section of the label.*

*The use of product information regarding the other indications from the labeling for Claforan<sup>®</sup> is permitted by provisions found under 21 CFR 314.54(a)(3). The information must be identical to that found with the reference listed drug.*

#### Safety

The applicant is using the safety database provided by the reference listed drug, Claforan<sup>®</sup>. Since there are several differences between that product and the DUPLEX<sup>®</sup> container delivery system manufactured by B. Braun Medical Inc., several changes to the labeling are required. The DUPLEX<sup>®</sup> container system is a single-use product to deliver a 1 gram or 2 gram dose of cefotaxime sodium in 50 mL of dextrose in water. The following revisions to the product's labeling are required:

1. The product is designed for intravenous administration only. Thus, all references to intramuscular or intraperitoneal administration must be deleted. The product's label should only contain pharmacokinetic information related to the intravenous administration of cefotaxime.

2. The product is designed for single-use and not designed to deliver a dose of less than 1 gram or 2 grams. The product should not be used in pediatric patients who require less than a 1 gram dose to prevent accidental overdose.
3. The product contains dextrose which may cause serious adverse reactions in some patients or should not be used in diabetics without monitoring blood glucose levels.

**Clinical Reviewer's Comment:** *A statement has been added to the CONTRAINDICATIONS section warning clinicians of a possible hypersensitivity of some patients to corn products containing dextrose. In support of this addition, the applicant has submitted copies of three references from the literature. The articles describe 10 cases of patients who developed symptoms of an allergic reaction after ingesting corn products or receiving intravenous injections of 5% dextrose in sodium chloride.<sup>1-3</sup>*

In order to provide an update of new safety information regarding cefotaxime, the applicant conducted a literature search covering the time period from 2000 to the present. This time frame covers the period since the last printing of the package insert for the reference listed drug, Aventis Pharmaceutical's Claforan<sup>®</sup> Sterile Cefotaxime for Injection (NDA 50-547). Three adverse reactions were identified that are not in the current labeling for Claforan<sup>®</sup>. These events are encephalopathy in patients with renal insufficiency, angina, and faintness.

In the current labeling for Claforan<sup>®</sup>, under the PRECAUTIONS section, there is a paragraph concerning the need to reduce the dosage in renally impaired patients. The applicant would like to add another sentence that reads: "Reversible encephalopathy with psychosis has been reported, even with reduced dosage." In support of this addition, the applicant included a copy of an abstract from a Swedish paper that describes a patient with severe renal failure who experienced a reversible encephalopathy in spite of reduced doses of cefotaxime.<sup>4</sup>

**Clinical Reviewer's Comment:** *A computerized search of the FDA's Adverse Event Reporting System retrieved 21 reports of patients who developed encephalopathy while receiving cefotaxime. One report was a duplicate and another was a triplicate, for a total of 18 patients. There were eight deaths among them. Of the 18 case reports, eight were unconfounded and had enough information to show a possible association between cefotaxime therapy and the development of encephalopathy.*

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<sup>1</sup>Sandberg, DH. 1977. Persistent vomiting due to sensitivity to corn sugar or dextrose present in intravenous fluids. *Ped. Res.* 11(4):449 (#466).

<sup>2</sup>Randolph, TG, JP Rollins, and CK Walter. 1950. Allergic reactions following the intravenous injection of corn sugar (Dextrose). *Arch. Surg.* 61:554-564.

<sup>3</sup>Randolph, TG, JP Rollins, and CK Walter. 1949. Allergic reactions following the intravenous injection of corn sugar (Dextrose or Glucose). *J. Lab. & Clin. Med.* 34:1741.

<sup>4</sup>Brink, B, E Kimland, and M von Euler. 2003. An unusual case of a side effect. Cefotaxime-induced confusion in a patient with renal failure. *Lakartidningen.* 100(28-29):2370-1.

Since the applicant limited its literature search to the last three years, another search was conducted without any time limitations. Two additional references were retrieved. One was a French paper that described a case of encephalopathy due to cefotaxime in an aged patient with renal failure.<sup>5</sup> The second article was a letter to the editor that described a 68 year-old patient with renal impairment who developed neurotoxic symptoms while receiving cefotaxime.<sup>6</sup>

Under the ADVERSE REACTIONS section, the applicant would like to add ( ) the Cardiovascular System paragraph, ( ) and ( ) encephalopathy to the Central Nervous System subsection. A review article was included that contains a table of serious adverse events induced by antibiotics where ( ) were listed for cefotaxime.<sup>7</sup>

**Clinical Reviewer's Comment:** *A computerized search of the FDA's Adverse Event Reporting System for reports of angina and faintness associated with cefotaxime therapy retrieved no reports. The review article provided by the applicant did not contain any information to support a possible association between cefotaxime therapy and either of these adverse events.*

#### Review of the labeling.

The proposed labeling for this product was compared to the most recently approved label for the reference listed drug Claforan<sup>®</sup>. All references to the administration of cefotaxime through routes other than the intravenous route or to neonates or pediatric patients not requiring a full adult dose should be deleted from the labeling. Additional statements required by recent notices published in the Federal Register, e.g., bacterial resistance, geriatric use, will be added where appropriate.

Note: Additions to the labeling are represented by text with an underline, while deletions to the labeling are represented by a ~~strikethrough~~.

Appears This Way  
On Original

<sup>5</sup> Vincent, JP, P Dervanian, and A Bodak. 1989. Encephalopathy caused by cefotaxime. A case in an aged patient with renal failure. Ann. Med. Interne. (Paris). 140:322.

<sup>6</sup> Pascual, J, F liano, and J Ortuno. 1990. Cefotaxime-induced encephalopathy in an uremic patient. Nephron. 54:92.

<sup>7</sup> Gallelli, L, G. Ferreri, M. Colosimo, *et al.* 2002. Adverse drug reactions to antibiotics observed in two pulmonary divisions of Catanzaro, Italy: A six-year retrospective study. Pharmacol. Res. 46(5):395-400.

Y36-002-528  
Package Insert

## CefOTAXime for Injection USP and Dextrose Injection

**Clinical Reviewer's Comment:** *The following statement should be added after the product name:*

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

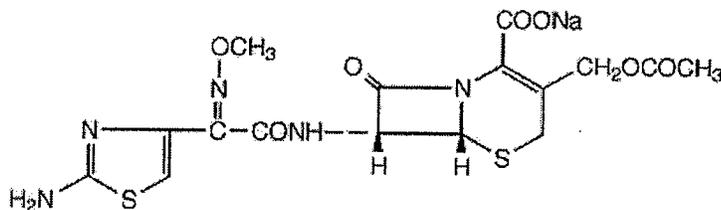
### DESCRIPTION

**Rx only**

Cefotaxime for Injection USP and Dextrose Injection is a sterile, nonpyrogenic, single use, packaged combination of Cefotaxime Sodium and Dextrose Injection (diluent) in the DUPLEX sterile container. The DUPLEX Container is a flexible dual chamber container.

The drug chamber is filled with sterile Cefotaxime Sodium USP, a semisynthetic, broadspectrum, cephalosporin antibiotic for parenteral administration. It is the sodium salt of 7-[2-(2-amino-4-thiazolyl) glyoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo [4.2.0] oct- 2-ene-2-carboxylate 7<sup>2</sup> (Z)-(o-methyloxime), acetate (ester). The CAS Registry Number is 64485-93-4.

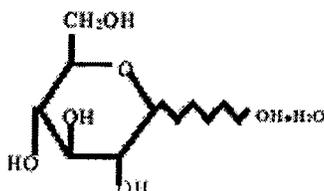
Cefotaxime Sodium has the following structural formula:



The empirical formula of Cefotaxime Sodium is  $C_{16}H_{16}N_5NaO_7S_2$ , representing a molecular weight of 477.45.

Cefotaxime Sodium contains approximately 50.5 mg (2.2 mEq) of sodium per gram of cefotaxime activity.

The diluent chamber contains Dextrose Injection. The concentration of Hydrous Dextrose in Water for Injection USP has been adjusted to render the reconstituted drug product iso-osmotic. Dextrose Injection is sterile, nonpyrogenic, and contains no bacteriostatic or antimicrobial agents. Hydrous Dextrose USP has the following structural (molecular) formula:



The molecular weight of Hydrous Dextrose USP is 198.17.

Cefotaxime Sodium is supplied as a dry powder form equivalent to either 1 g or 2 g of cefotaxime.

Dextrose hydrous USP has been added to the diluent to adjust osmolality (approximately 1.95 g and 1.2 g to 1 g and 2 g dosages, respectively).

After removing the peelable foil strip, activating the seals, and thoroughly mixing, the reconstituted drug product is intended for single intravenous use. When reconstituted, the approximate osmolality for the reconstituted solution for Cefotaxime for Injection USP and Dextrose Injection is 290 mOsm/kg.

The DUPLEX dual chamber container is made from a specially formulated material. The product (diluent and drug) contact layer is a mixture of thermoplastic rubber and a polypropylene ethylene copolymer that contains no plasticizers. The safety of the container system is supported by USP biological evaluation procedures.

## CLINICAL PHARMACOLOGY

There was a dose-dependent increase in serum levels after the IV administration of 500 mg, 1 g, and 2 g of cefotaxime (38.9, 101.7, and 214.4  $\mu\text{g/mL}$  respectively) without alteration in the elimination half-life. There is no evidence of accumulation following repetitive IV infusion of 1 g doses every 6 hours for 14 days as there are no alterations of serum or renal clearance. About 60% of the administered dose was recovered from urine during the first 6 hours following the start of the infusion.

Approximately 20-36% of an intravenously administered dose of  $^{14}\text{C}$ -cefotaxime is excreted by the kidney as unchanged cefotaxime and 15-25% as the desacetyl derivative, the major metabolite. The desacetyl metabolite has been shown to contribute to the bactericidal activity. Two other urinary metabolites (M2 and M3) account for about 20-25%. They lack bactericidal activity.

A single 50 mg/kg dose of cefotaxime was administered as an intravenous infusion over a 10- to 15- minute period to 29 newborn infants grouped according to birth weight and age. The mean half-life of cefotaxime in infants with lower birth weights ( $\leq 1500$  grams), regardless of age, was longer (4.6 hours) than the mean half-life (3.4 hours) in infants whose birth weight was greater than 1500 grams. Mean serum clearance was also smaller in the lower birth weight infants. Although the differences in mean half-life values are statistically significant for weight, they are not clinically important. Therefore, dosage should be based solely on age. (See **DOSAGE AND ADMINISTRATION** section.)

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

**Clinical Reviewer's Comment:** *Since the DUPLEX<sup>®</sup> Container product is designed for intravenous administration only, the reference to intramuscular pharmacokinetic data found in the first sentence of the Claforan<sup>®</sup> label has been deleted.*

### **Microbiology**

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

#### **Aerobes, Gram-positive:**

*Enterococcus* spp.

*Staphylococcus aureus*\*, including  $\beta$ -lactamase-positive and negative strains

*Staphylococcus epidermidis*

*Streptococcus pneumoniae*

*Streptococcus pyogenes* (Group A beta-hemolytic streptococci)

*Streptococcus* spp.

\*Staphylococci which are resistant to methicillin/oxacillin must be considered resistant to cefotaxime sodium.

#### **Aerobes, Gram-negative:**

*Acinetobacter* spp.

*Citrobacter* spp.

*Enterobacter* spp.

*Escherichia coli*

*Haemophilus influenzae* (including ampicillin-resistant strains)

*Haemophilus parainfluenzae*

*Klebsiella* spp. (including *Klebsiella pneumoniae*)  
*Morganella morganii*  
*Neisseria gonorrhoeae* (including  $\beta$ -lactamase positive and negative strains)  
*Neisseria meningitidis*  
*Proteus mirabilis*  
*Proteus vulgaris*  
*Providencia rettgeri*  
*Providencia stuartii*  
*Serratia marcescens*

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

**Clinical Reviewer's Comment:** *All references to Neisseria gonorrhoeae have been removed from the Microbiology and Susceptibility Tests subsections by Ms. Connie Mahon, because the recommended therapy for gonorrhea is an IM injection of cefotaxime.*

**Anaerobes:**

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

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

**Aerobes, Gram-negative:**

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

Cefotaxime sodium is highly stable *in vitro* to four of the five major classes of  $\beta$ -lactamases described by Richmond et al.<sup>1</sup>, including type IIIa (TEM) which is produced by many gram negative bacteria. The drug is also stable to  $\beta$ -lactamase (penicillinase) produced by staphylococci. In addition, cefotaxime sodium shows high affinity for penicillin-binding proteins in the cell wall, including PBP: Ib and III.

**Clinical Reviewer's Comment:** *The word "5-lactamases" should be changed to "β-lactamases".*

Cefotaxime sodium and aminoglycosides have been shown to be synergistic *in vitro* against some strains of *Pseudomonas aeruginosa* but the clinical significance is unknown.

### ***Susceptibility Tests***

#### **Dilution techniques:**

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

**Clinical Reviewer's Comment:** *The superscript "1" should be a "2".*

When testing organisms<sup>a</sup> other than *Haemophilus* spp., *Neisseria gonorrhoeae*, and *Streptococcus* spp.

<u>MIC (μg/mL)</u>	<u>Interpretation</u>
≤8	Susceptible (S)
16-32	Intermediate (I)
≥64	Resistant (R)

When testing *Haemophilus* spp.<sup>b</sup>

<u>MIC (μg/mL)</u>	<u>Interpretation<sup>c</sup></u>
≤2	Susceptible (S)

When testing *Streptococcus*<sup>d</sup>

<u>MIC (μg/mL)</u>	<u>Interpretation</u>
≤0.5	Susceptible (S)
1	Intermediate (I)
≥2	Resistant (R)

When testing *Neisseria gonorrhoeae*<sup>e</sup>

<u>MIC (μg/mL)</u>	<u>Interpretation<sup>e</sup></u>
≤0.5	Susceptible (S)

- <sup>a</sup> Staphylococci exhibiting resistance to methicillin/oxacillin, should be reported as also resistant to cefotaxime despite apparent *in vitro* susceptibility.
- <sup>b</sup> Interpretive criteria is applicable only to tests performed by broth microdilution method using *Haemophilus* Test Media<sup>2</sup>
- <sup>c</sup> The absence of resistant strains precludes defining any interpretations other than susceptible.
- <sup>d</sup> *Streptococcus pneumoniae* must be tested using cation-adjusted Mueller-Hinton broth

with 2-5% lysed horse blood.

~~<sup>e</sup> Interpretive criteria applicable only to tests performed by agar dilution method using GC agar base with 1% defined growth supplement.<sup>2</sup>~~

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal and if the microorganism is not fully susceptible to alternative clinically feasible drugs the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable, other therapy should be selected.

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

<u>Microorganism</u>	<u>MIC (<math>\mu\text{g/mL}</math>)</u>	
<i>Escherichia coli</i> ATCC 25922	0.06-0.25	<u>0.03-0.12<sup>3</sup></u>
<i>Staphylococcus aureus</i> ATCC 29213	1-4	
<i>Pseudomonas aeruginosa</i> ATCC 27853	4-16	<u>8-12<sup>3</sup></u>
<i>Haemophilus influenzae</i> <sup>a</sup> ATCC 49247	0.12-0.5	
<i>Streptococcus pneumoniae</i> <sup>b</sup> ATCC 49619 0.	0.06-0.25	<u>0.03-0.12<sup>3</sup></u>
<i>Neisseria gonorrhoeae</i> <sup>e</sup> ATCC 49226	0.015-0.06	

<sup>a</sup>. Ranges applicable only to tests performed by broth microdilution method using Haemophilus Test Media.<sup>2</sup>

<sup>b</sup>. Ranges applicable only to tests performed by broth microdilution method using cation adjusted Mueller-Hinton broth with 2-5% lysed horse blood.<sup>2</sup>

~~<sup>e</sup>. Ranges applicable only to tests performed by agar dilution method using GC agar base with 1% defined growth supplement.<sup>2</sup>~~

#### **Diffusion Techniques:**

Quantitative methods that require measurements of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure<sup>34</sup> requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30  $\mu\text{g}$  cefotaxime sodium to test the susceptibility of microorganisms to cefotaxime sodium. Reports from the laboratory providing results of the standard single-disk susceptibility test using a 30  $\mu\text{g}$  cefotaxime sodium disk should be interpreted according to the following criteria:

When testing organisms<sup>a</sup> other than *Haemophilus* spp., *Neisseria gonorrhoeae*, and

*Streptococcus* spp.

<u>MIC (µg/mL)</u>	<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥23		Susceptible (S)
15-22		Intermediate
≤14		Resistant (R)

**Clinical Reviewer's Comment:** *The MIC (µg/mL) should be changed to Zone Diameter (mm).*

When testing *Haemophilus* spp.<sup>b</sup>

<u>Zone Diameter (mm)</u>	<u>Interpretation<sup>c</sup></u>
≥26	Susceptible (S)

When testing *Streptococcus* other than *Streptococcus pneumoniae*

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

When testing *Neisseria gonorrhoeae*<sup>d</sup>

<u>Zone Diameter (mm)</u>	<u>Interpretation<sup>e</sup></u>
≥31	Susceptible (S)

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

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

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

<u>Microorganism</u>	<u>Zone Diameter (mm)</u>
<i>Escherichia coli</i> ATCC 25922	29-35
<i>Staphylococcus aureus</i> ATCC 25923	25-31
<i>Pseudomonas aeruginosa</i> ATCC 27853	18-22
<i>Haemophilus influenzae</i> <sup>a</sup> ATCC 49247	31-39

~~*Neisseria gonorrhoeae*<sup>b</sup> ATCC 49226~~ ~~38-48~~

<sup>a</sup> Ranges applicable only to tests performed by disk diffusion method using Haemophilus Test Media.<sup>34</sup>

~~<sup>b</sup> Ranges applicable only to tests performed by disk diffusion method using GC agar base with 1% defined growth supplement.<sup>3</sup>~~

#### Anaerobic Techniques:

For anaerobic bacteria, the susceptibility to cefotaxime sodium as MICs can be determined by standardized test methods.<sup>45</sup> The MIC values obtained should be interpreted according to the following criteria:

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

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

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

<u>Microorganism</u>	<u>MIC (µg/mL)</u>
<i>Bacteroides fragilis</i> <sup>a</sup> ATCC 25285	8-32
<i>Bacteroides thetaotaomicron</i> ATCC 29741	16-64
<i>Eubacterium lanthem</i> ATCC 43055	64-256

<sup>a</sup> Ranges applicable only to tests performed by agar dilution method.

## INDICATIONS AND USAGE

### Treatment

Cefotaxime for Injection USP and Dextrose Injection is indicated for the treatment of patients with serious infections caused by susceptible strains of the designated microorganisms in the diseases listed below.

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

**Clinical Reviewer's Comment:** *The words "(formerly Diplococcus pneumoniae)" should be deleted.*

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

**Clinical Reviewer's Comment:** *The approved therapy for the treatment of uncomplicated gonorrhea involves the administration of an intramuscular dose of cefotaxime, which is not possible with this system. Therefore, this indication should be removed from the INDICATIONS AND USAGE section.*

**(3) Gynecologic infections,** including pelvic inflammatory disease, endometritis and pelvic cellulitis caused by *Staphylococcus epidermidis*, *Streptococcus* species, *Enterococcus* species, *Enterobacter* species\*, *Klebsiella* species\*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides* species (including *Bacteroides fragilis*\*), *Clostridium* species, and anaerobic cocci (including *Peptostreptococcus* species and *Peptococcus* species) and *Fusobacterium* species (including *F. nucleatum*\*). Cefotaxime, like other cephalosporins, has no activity against *Chlamydia trachomatis*. Therefore, when cephalosporins are used in the treatment of patients with pelvic inflammatory disease and *C. trachomatis* is one of the suspected pathogens, appropriate anti-chlamydial coverage should be added.

**(4) Bacteremia/Septicemia** caused by *Escherichia coli*, *Klebsiella* species, and *Serratia marcescens*, *Staphylococcus aureus* and *Streptococcus* species (including *S. pneumoniae*).

**Clinical Reviewer's Comment:** *An "e" should be added to "S. pneumoniae."*

**(5) Skin and skin structure infections** caused by *Staphylococcus aureus* (penicillinase and non-penicillinase producing), *Staphylococcus epidermidis*, *Streptococcus pyogenes* (Group A streptococci) and other streptococci, *Enterococcus* species, *Acinetobacter* species\*, *Escherichia coli*, *Citrobacter* species (including *C. freundii* \*), *Enterobacter* species, *Klebsiella* species, *Proteus mirabilis*, *Proteus vulgaris*\*, *Morganella morganii*, *Providencia rettgeri* \*, *Pseudomonas* species, *Serratia marcescens*, *Bacteroides* species, and anaerobic cocci (including *Peptostreptococcus*\* species and *Peptococcus* species).

**(6) Intra-abdominal infections** including peritonitis caused by *Streptococcus* species\*, *Escherichia coli*, *Klebsiella* species, *Bacteroides* species, and anaerobic cocci (including *Peptostreptococcus*\* species and *Peptococcus*\* species) *Proteus mirabilis*\*, and *Clostridium* species\*.

**(7) Bone and/or joint infections** caused by *Staphylococcus aureus* (penicillinase and nonpenicillinase producing strains), *Streptococcus* species (including *S. pyogenes*\*), *Pseudomonas* species (including *P. aeruginosa*\*), and *Proteus mirabilis*\*.

**(8) Central nervous system infections**, e.g., meningitis and ventriculitis, caused by *Neisseria meningitidis*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*\* and *Escherichia coli*\*.

(\*) Efficacy for this organism, in this organ system, has been studied in fewer than 10 infections. Although many strains of enterococci (e.g., *S. E. faecalis*) and *Pseudomonas* species are resistant to cefotaxime sodium *in vitro*, cefotaxime has been used successfully in treating patients with infections caused by susceptible organisms.

**Clinical Reviewer's Comment:** *The "S" in "S. faecalis" should be changed to an "E".*

Specimens for bacteriologic culture should be obtained prior to therapy in order to isolate and identify causative organisms and to determine their susceptibilities to cefotaxime. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

In certain cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, cefotaxime may be used concomitantly with an aminoglycoside. The dosage recommended in the labeling of both antibiotics may be given and depends on the severity of the infection and the patient's condition. Renal function should be carefully monitored, especially if higher dosages of the aminoglycosides are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. It is possible that nephrotoxicity may be potentiated if cefotaxime is used concomitantly with an aminoglycoside.

### ***Prevention***

The administration of cefotaxime preoperatively reduces the incidence of certain infections in patients undergoing surgical procedures (e.g., abdominal or vaginal hysterectomy, gastrointestinal and genitourinary tract surgery) that may be classified as contaminated or potentially contaminated.

In patients undergoing cesarean section, intraoperative (after clamping the umbilical cord) and postoperative use of cefotaxime may also reduce the incidence of certain postoperative infections. See **DOSAGE AND ADMINISTRATION** section.

Effective use for elective surgery depends on the time of administration. To achieve effective tissue levels, cefotaxime should be given 1/2 or 1 1/2 hours before surgery. See **DOSAGE AND ADMINISTRATION** section.

For patients undergoing gastrointestinal surgery, preoperative bowel preparation by mechanical cleansing as well as with a non-absorbable antibiotic (e.g., neomycin) is recommended.

If there are signs of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapy may be instituted.

**Clinical Reviewer's Comments:** *The following statement should be added to this section:*

*"To reduce the development of drug-resistant bacteria and maintain the effectiveness of Cefotaxime for Injection USP and Dextrose Injection and other antibacterial drugs, Cefotaxime for Injection USP and Dextrose Injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy."*

#### CONTRAINDICATIONS

Cefotaxime for Injection USP and Dextrose Injection is contraindicated in patients who have shown hypersensitivity to cefotaxime sodium or the cephalosporin group of antibiotics.

Solutions containing dextrose may be contraindicated in patients with hypersensitivity to corn products.

**Clinical Reviewer's Comment:** *The applicant has provided copies of three articles from the literature to support the addition of the last statement. Also, the statement is found in the current labeling for Dextrose and Sodium Chloride Injection, USP.*

#### WARNINGS

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

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

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

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

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

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

## PRECAUTIONS

### *General*

**Clinical Reviewer's Comment:** *The following statement should be added to this subsection:*

*"Prescribing Cefotaxime for Injection USP and Dextrose Injection in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria."*

Cefotaxime for Injection USP and Dextrose Injection should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

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

~~Although there is no clinical evidence supporting the necessity of changing the dosage of~~

~~cefotaxime sodium in patients with even profound renal dysfunction, it~~ It is suggested that, based upon the data available from published studies until further data are obtained, the dose of cefotaxime sodium be halved in patients with estimated creatinine clearances of less than 20 mL/min/1.73 m<sup>2</sup>.

**Clinical Reviewer's Comment:** *The revisions to paragraph three were recommended by Dr. Jarugula, based on a review of the current scientific literature.*

When only serum creatinine is available, the following formula<sup>56</sup> (based on sex, weight, and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

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

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

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

As with other beta-lactam antibiotics, granulocytopenia and, more rarely, agranulocytosis may develop during treatment with cefotaxime, particularly if given over long periods. For courses of treatment lasting longer than 10 days, blood counts should therefore be monitored.

Cefotaxime, like other parenteral anti-infective drugs, may be locally irritating to tissues. In most cases, perivascular extravasation of cefotaxime responds to changing of the infusion site. In rare instances, extensive perivascular extravasation of cefotaxime may result in tissue damage and require surgical treatment. To minimize the potential for tissue inflammation, infusion sites should be monitored regularly and changed when appropriate.

As with other dextrose-containing solutions, Cefotaxime for Injection USP and Dextrose Injection should be prescribed with caution in patients with overt or known subclinical diabetes mellitus or carbohydrate intolerance for any reason.

If administration is controlled by a pumping device, care must be taken to discontinue pumping action before the container runs dry or air embolism may result.

Use only if solution is clear and container and seals are intact.

**Clinical Reviewer's Comment:** *An "Information for Patients" subsection should be added here, along with the following statement:*

*"Patients should be counseled that antibacterial drugs including Cefotaxime for Injection USP and Dextrose Injection should only be used to treat bacterial*

infections. They do not treat viral infections (e.g., the common cold). When Cefotaxime for Injection USP and Dextrose Injection 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 Cefotaxime for Injection USP and Dextrose Injection or other antibacterial drugs in the future."

#### **Drug Interactions**

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

#### **Drug/Laboratory Test Interactions**

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

#### **Carcinogenesis, Mutagenesis**

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

#### **Pregnancy: Teratogenic Effects: Pregnancy Category B:**

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

#### **Nonteratogenic Effects**

Use of the drug in women of child-bearing potential requires that the anticipated benefit be weighed against the possible risks.

In perinatal and postnatal studies with rats, the pups in the group given 1200 mg/kg/day of cefotaxime were significantly lighter in weight at birth and remained smaller than pups in the control group during the 21 days of nursing.

#### **Nursing Mothers**

Cefotaxime is excreted in human milk in low concentrations. Caution should be exercised

when cefotaxime is administered to a nursing woman.

#### ***Pediatric Use***

See **PRECAUTIONS** above regarding perivascular extravasation.

**Clinical Reviewer's Comments:** *The following statement should be added to the Pediatric Use subsection:*

"Cefotaxime for Injection USP and Dextrose Injection in the DUPLEX Container is designed to deliver a 1 g or 2 g dose of cefotaxime. To prevent unintentional overdose, this product should not be used in pediatric patients who require less than the full adult dose of cefotaxime."

*A Geriatric Use subsection should be added to the label at this point. Based on the recently approved labeling for Claforan<sup>®</sup>, it should contain the following statement:*

#### **Geriatric Use**

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

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

#### **ADVERSE REACTIONS**

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

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

Local (4.3%)—Injection site inflammation with IV administration.

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

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

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

Nausea and vomiting have been reported rarely.

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

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

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

Genitourinary System—Moniliasis, vaginitis.

Central Nervous System—Headache, encephalopathy.

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

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

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

**Clinical Reviewer's Comment:** "Encephalopathy" should be added to the Central Nervous System statement.

#### **Cephalosporin Class Labeling**

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

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

#### **OVERDOSAGE**

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

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

**DOSAGE AND ADMINISTRATION**

**This product is intended for intravenous administration only.**

**Adults**

**Clinical Reviewer's Comment:** *The following subsection and paragraph should be added to this section, in order to conform to the reference listed drug labeling:*

*“Geriatric Use*

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

Dosage and route of administration should be determined by susceptibility of the causative organisms, severity of the infection, and the condition of the patient (see table for dosage guideline). Cefotaxime for Injection USP and Dextrose Injection is intended for IV administration after reconstitution. The maximum daily dosage should not exceed 12 grams.

**GUIDELINES FOR DOSAGE OF CEFOTAXIME FOR INJECTION USP  
AND DEXTROSE INJECTION**

Type of Infection	Daily Dose (grams)	Frequency
Uncomplicated infections	2	1 gram every 12 hours
Moderate to severe infections Infections commonly needing antibiotics	3-6	1-2 grams every 8 hours
in higher dosage (e.g., septicemia)	6-8	2 grams every 6-8 hours
Life-threatening infections	up to 12	2 grams every 4 hours
<del>If <i>C. trachomatis</i> is a suspected pathogen, appropriate anti-chlamydial coverage should be added, because cefotaxime sodium has no activity against this organism.</del>		

**Clinical Reviewer's Comment:** *The statement regarding *C. trachomatis* should be deleted, since dosage recommendations for the treatment of gonorrhea have been deleted as they referred to the intramuscular administration of cefotaxime.*

To prevent postoperative infection in contaminated or potentially contaminated surgery, the recommended dose is a single 1 gram IV administered 30 to 90 minutes prior to start of surgery.

***Cesarean Section Patients***

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

**Neonates, Infants, and Children**

The following dosage schedule is recommended:

Neonates (birth to 1 month):

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

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

**Clinical Reviewer's Comment:** *The dosage schedule for neonates should be deleted, along with the sentence concerning premature and normal gestational age infants. None of these infants could receive a full adult dose of 1 g in the DUPLEX system*

~~Infants and Pediatric Patients(1 month to 12 years):~~

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

**Clinical Reviewer's Comment:** *In the statement above, "IV" should be deleted.*

*The following statement should be added to this paragraph:*

*"Cefotaxime for Injection USP and Dextrose Injection in the DUPLEX Container is designed to deliver a 1 g or 2 g dose of cefotaxime. To prevent unintentional overdose, this product should not be used in pediatric patients who require less than the full adult dose of cefotaxime."*

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

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

[

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**Clinical Reviewer's Comment:** *The above paragraph is not needed and should be deleted, because the product can only be administered through the intravenous route.*

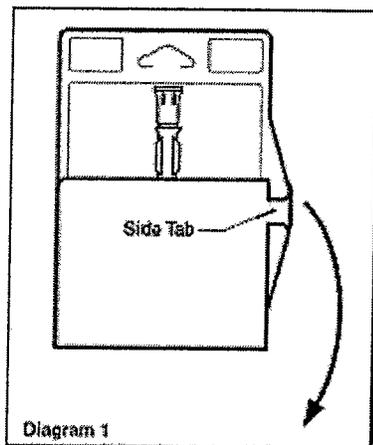
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

**DUPLEX® Drug Delivery System Directions for Use**  
**Removal from Multi-Pack Tray**

- Tear tape strips from one or both sides of the tray.  
Remove top tray.
- To avoid inadvertent activation, DUPLEX Container should remain in the folded position until activation is intended.

**Patient Labeling and Drug Powder/Diluent Inspection**

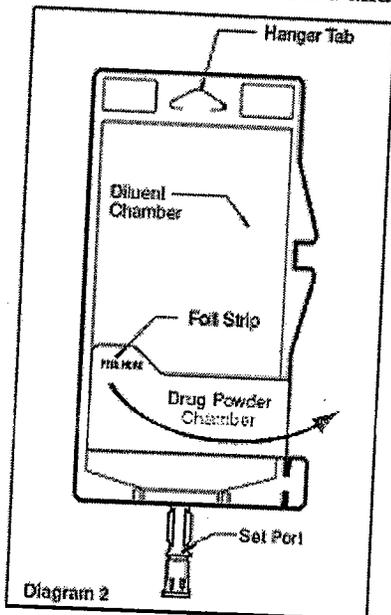
- Apply patient-specific label on foil side of container.  
USE CARE to avoid activation. Do not cover any portion of foil strip with patient label.
- Unlatch side tab and unfold DUPLEX Container.  
(See Diagram 1.)



- Visually inspect diluent chamber for particulate matter.
- Use only if container and seals are intact.
- To inspect the drug powder for foreign matter or discoloration, peel foil strip from drug chamber.  
(See Diagram 2.)
- Protect from light after removal of foil strip.

**Note: If foil strip is removed, product must be used within 30 days, but not beyond the labeled expiration date.**

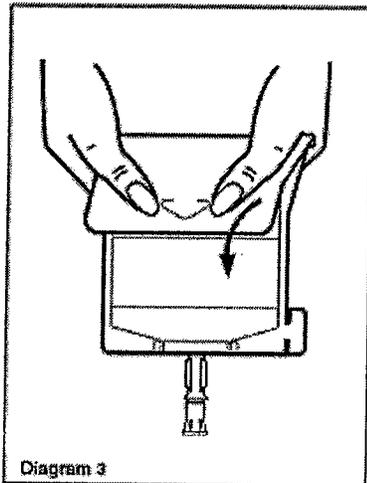
- The product should be re-folded and the side tab latched until ready to activate.



### Reconstitution (Activation)

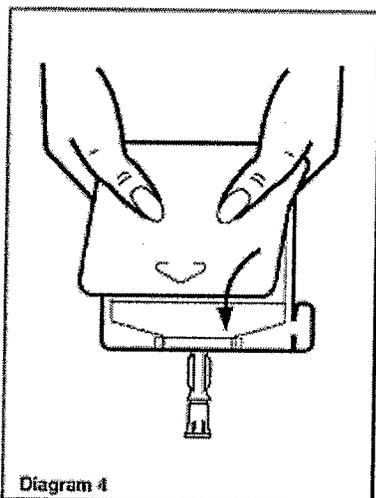
- Do not use directly after storage by refrigeration; allow the product to equilibrate to room temperature before patient use.
- Unfold the DUPLEX Container and point the set port in a downward direction. Starting at the hanger tab end, fold the DUPLEX Container just below the diluent meniscus trapping all air above the fold. To activate, squeeze the folded diluent chamber until the seal between the diluent and powder opens, releasing diluent into the drug powder chamber.  
(See Diagram 3.)
- Agitate the liquid-powder mixture until the drug powder is completely dissolved.

**Note: Following reconstitution (activation), product must be used within 12 hours if stored at room temperature or within 5 days if stored under refrigeration.**



### Administration

- Visually inspect the reconstituted solution for particulate matter.
- Point the set port in a downwards direction. Starting at the hanger tab end, fold the DUPLEX Container just below the solution meniscus trapping all air above the fold. Squeeze the folded DUPLEX Container until the seal between reconstituted drug solution and set port opens, releasing liquid to set port. (See Diagram 4.)



- Prior to attaching the IV set, check for minute leaks by squeezing container firmly. If leaks are found, discard container and solution as sterility may be impaired.
- Using aseptic technique, remove the set port cover from the set port and attach sterile administration set.
- Refer to Directions for Use accompanying the administration set.

### Precautions

- As with other cephalosporins, reconstituted Cefotaxime for Injection USP and Dextrose

Injection tends to darken depending on storage conditions, within the stated recommendations. However, product potency is not adversely affected.

- Use only if prepared solution is clear and free from particulate matter.
- Do not use in series connection.
- Do not introduce additives into the DUPLEX Container.
- Do not freeze.

### HOW SUPPLIED

Cefotaxime for Injection USP and Dextrose Injection in the DUPLEX<sup>®</sup> Drug Delivery System is a flexible dual chamber container supplied in two concentrations. After reconstitution, the concentrations are equivalent to 1 g and 2 g cefotaxime. The diluent chamber contains approximately 50 mL of Dextrose Injection. Dextrose Injection has been adjusted to 3.9% and 2.4% for the 1 g and 2 g doses, respectively, such that the reconstituted solution is iso-osmotic.

Cefotaxime for Injection USP and Dextrose Injection is supplied sterile and nonpyrogenic in the DUPLEX Drug Delivery System Containers packaged 12 units per tray, 2 trays per case.

NDC	Cat. No.	Dose	Volume
Cefotaxime for Injection USP and Dextrose Injection 0264-3133-11	3133-11	1 g	50 mL
Cefotaxime for Injection USP and Dextrose Injection 0264-3135-11	3135-11	2 g	50 mL

Store the unactivated unit at 20-25°C (68-77°F). Excursions permitted to 15-30°C (59-86°F).

### REFERENCES

- 1) Richmond, M. H. and Sykes R. B.: The  $\beta$ -Lactamases of Gram-Negative Bacteria and their Possible Physiological Role, *Advances in Microbial Physiology* 9:31-88, 1973.
- 2) National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - Third Edition.* Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December, 1993.
- 3) National Committee for Clinical Laboratory Standards. *MIC Testing Supplemental Tables* NCCLS Document M100- S14, Vol. 24, No. 1, NCCLS, Wayne, PA, January, 2004.
- 4) National Committee for Clinical Laboratory Standards. *Performance Standard for Antimicrobial Disk Susceptibility Tests - Fifth Edition.* Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December, 1993.
- 5) National Committee for Clinical Laboratory Standards. *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria - Third Edition.* Approved Standard NCCLS Document M11-A3, NCCLS, Villanova, PA, December, 1993.
- 6) Cockcroft, D.W. and Gault, M.H.: Prediction of Creatinine Clearance from Serum Creatinine, *Nephron* 16:31-41, 1976.

**Clinical Reviewer's Comment:** *Reference #3 has been added as a result of a change in the NCCLS quality control standards.*

DUPLEX® is a registered trademark of B. Braun Medical Inc.  
U.S. Patent Nos. D388,168, D397,789, D402,366, D407,816, 5,944,709, and 6,165,161;  
additional patents pending.  
Made in USA  
Issued: September 2003

**B. Braun Medical Inc.**  
Irvine, CA USA 92614-5895

### Conclusion

The NDA for the DUPLEX Container with Cefotaxime for Injection is the third in a series of cephalosporin products developed by B. Braun Medical, Inc. All have been submitted in accordance with Section 505 (b)(2) of the Food, Drug, and Cosmetic Act, as regulated under 21 CFR 314.54. The DUPLEX Container described in this application is identical to the previously approved delivery systems with the exception that it is slightly larger in order to accommodate a larger amount of cefotaxime, 1 – 2 grams.

It is recommended that this product be approved contingent upon concurrence from the other reviewing disciplines.

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James Blank, Ph.D.

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Sumathi Nambiar, M.D., M.P.H.

**cc:**

Orig. NDA  
HFD-520  
HFD-520/actMTL/SNambiar  
ClinRev/JBlank  
Micro/CMahon  
CSO/RPeat  
Pharm/ROsterberg  
Chem/JVidra

**concurrence only:**

HFD-520/DivDir/JSoreth  
HFD-520/actMTL/SNambiar

Word/50-792; draft; 6-17-04;6-25-04;7-20-04;7-22-04;7-29-04

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/s/

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