

may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS

General

Prescribing cefotaxime 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 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 is suggested that, until further data are obtained, the dose of cefotaxime sodium be halved in patients with estimated creatinine clearances of less than 20 mL/min/1.73 m².

When only serum creatinine is available, the following formula⁵ (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.

$$\begin{aligned} \text{Males: } & \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine}} \\ \text{Females: } & 0.85 \times \text{above value} \end{aligned}$$

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.

Information for Patients

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

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Drug Interactions

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 mg/m²) or in mice when administered intravenously at doses up to 2000 mg/kg/day (0.7 times the recommended human dose based on mg/m²).

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 mg/m²) or in pregnant rats when administered intravenously at doses up to 1200 mg/kg/day (0.8 times the recommended human dose based on mg/m²). No evidence of embryotoxicity or teratogenicity was seen in these studies. Although cefotaxime has been reported to cross the placental barrier and appear in cord blood, the effect on the human fetus is not known. There are no well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects

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

In perinatal and postnatal studies with rats, the pups in the group given 1200 mg/kg/day of 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.

Geriatric Use

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

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

ADVERSE REACTIONS

Clinical Trials Experience

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

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

Local (4.3%) - Injection site inflammation with IV administration. Pain, induration, and tenderness after IM injection.

Hypersensitivity (2.4%) - Rash, pruritus, fever, eosinophilia.

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

Symptoms of pseudomembranous colitis can appear during or after antibiotic treatment. Nausea and vomiting have been reported rarely.

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

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

Genitourinary System - Moniliasis, vaginitis.

Central Nervous System - Headache.

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

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

Post-Marketing Experience

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

Cardiovascular System - Potentially life-threatening arrhythmias following rapid (less

than 60 seconds) bolus administration via central venous catheter have been observed. Cutaneous - As with other cephalosporins, isolated cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme have been reported.

Hematologic System - Hemolytic anemia, agranulocytosis, thrombocytopenia.

Hypersensitivity - Anaphylaxis, urticaria.

Kidney - Interstitial nephritis, transient elevations of creatinine.

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

Cephalosporin Class Labeling

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

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced. See **DOSE 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 EVENTS contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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. There is a risk of reversible encephalopathy in cases of administration of high doses of beta-lactam antibiotics including cefotaxime. No specific antidote exists. Patients who receive an acute overdosage should be carefully observed and given supportive treatment.

DOSE AND ADMINISTRATION

Adults

Dosage and route of administration should be determined by susceptibility of the causative organisms, severity of the infection, and the condition of the patient (see table for dosage guideline). Cefotaxime for injection may be administered IM or IV after reconstitution. The maximum daily dosage should not exceed 12 grams.

GUIDELINES FOR DOSAGE OF CEFOTAXIME FOR INJECTION

Type of Infection	Daily Dose (grams)	Frequency and Route
Gonococcal urethritis/cervicitis in males and females	0.5	0.5 gram IM (single dose)
Rectal gonorrhea in females	0.5	0.5 gram IM (single dose)
Rectal gonorrhea in males	1	1 gram IM (single dose)
Uncomplicated infections	2	1 gram every 12 hours IM or IV
Moderate to severe infections	3-6	1 to 2 grams every 8 hours IM or IV
Infections commonly needing antibiotics in higher dosage (e.g., septicemia)	6-8	2 grams every 6 to 8 hours IV
Life-threatening infections	up to 12	2 grams every 4 hours IV

If *C. trachomatis* is a suspected pathogen, appropriate anti-chlamydial coverage should be added, because cefotaxime sodium has no activity against this organism.

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

Cesarean Section Patients

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

Neonates, Infants, and Children

The following dosage schedule is recommended:

Neonates (birth to 1 month):

0 to 1 week of age 50 mg/kg per dose every 12 hours IV

1 to 4 weeks of age 50 mg/kg per dose every 8 hours IV

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

Infants and Children (1 month to 12 years):

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

Geriatric Use

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

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

NOTE: As with antibiotic therapy in general, administration of 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.

Preparation of Cefotaxime

Cefotaxime for injection for IM or IV administration should be reconstituted as follows:

Strength	Diluent (mL)	Withdrawable Volume (mL)	Approximate Concentration (mg/mL)
500 mg vial* (IM)	2	2.2	230
1 g vial* (IM)	3	3.4	300
2 g vial* (IM)	5	6	330
500 mg vial* (IV)	10	10.2	50
1 g vial* (IV)	10	10.4	95
2 g vial* (IV)	10	11	180

(* in conventional vials)

Shake to dissolve; inspect for particulate matter and discoloration prior to use. Solutions of cefotaxime for injection range from very pale yellow to light amber, depending on concentration, diluent used, and length and condition of storage.

For intramuscular use: Reconstitute vials with Sterile Water for Injection or Bacteriostatic Water for Injection as described above.

For intravenous use: Reconstitute vials with at least 10 mL of Sterile Water for Injection. A 1 gram and 2 gram dose should be further diluted with 50 or 100 mL of 0.9% Sodium Chloride Injection or 5% Dextrose Injection. For other diluents, see **Compatibility and Stability** section.

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

A SOLUTION OF 1 G CEFOTAXIME IN 14 ML OF STERILE WATER FOR INJECTION IS ISOTONIC.

IM Administration: As with all IM preparations, cefotaxime 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. Individual IM doses of 2 grams may be given if the dose is divided and administered in different intramuscular sites.

IV Administration: The IV route is preferable for patients with bacteremia, bacterial septicemia, peritonitis, meningitis, or other severe or life-threatening infections, or for patients who may be poor risks because of lowered resistance resulting from such debilitating conditions as malnutrition, trauma, surgery, diabetes, heart failure, or malignancy, particularly if shock is present or impending.

For intermittent IV administration, a solution containing 1 gram or 2 grams in 10 mL of Sterile Water for Injection can be injected over a period of three to five minutes. Cefotaxime should not be administered over a period of less than three minutes. (See **WARNINGS**.) With an infusion system, it may also be given over a longer period of time through the tubing system by which the patient may be receiving other IV solutions. However, during infusion of the solution containing cefotaxime, it is advisable to discontinue temporarily the administration of other solutions at the same site.

For the administration of higher doses by continuous IV infusion, a solution of cefotaxime may be added to IV bottles containing the solutions discussed below.

Compatibility and Stability

Solutions of cefotaxime sterile reconstituted as described above (**Preparation of Cefotaxime**) remain chemically stable (potency remains above 90%) as follows when stored in original containers and disposable plastic syringes:

Strength	Reconstituted Concentration mg/mL	Stability at or below 22°C	Stability under Refrigeration (at or below 5°C) Original Containers	Plastic Syringes
500 mg vial IM	230	12 hours	7 days	5 days
1 g vial IM	300	12 hours	7 days	5 days
2 g vial IM	330	12 hours	7 days	5 days
500 mg vial IV	50	24 hours	7 days	5 days
1 g vial IV	95	24 hours	7 days	5 days
2 g vial IV	180	12 hours	7 days	5 days

Reconstituted solutions stored in original containers and plastic syringes remain stable for 13 weeks frozen.

Reconstituted solutions may be further diluted up to 1000 mL with the following solutions and maintain satisfactory potency for 24 hours at or below 22°C, and at least 5 days under refrigeration (at or below 5°C): 0.9% Sodium Chloride Injection; 5 or 10% Dextrose Injection; 5% Dextrose and 0.9% Sodium Chloride Injection; 5% Dextrose and 0.45% Sodium Chloride Injection; 5% Dextrose and 0.2% Sodium Chloride Injection; Lactated Ringer's Solution; Sodium Lactate Injection (M/6); 10% Invert Sugar Injection; 8.5% TRAVASOL[®] (Amino Acid) Injection without Electrolytes.

Solutions of cefotaxime sterile reconstituted in 0.9% Sodium Chloride Injection or 5% Dextrose Injection in small volume plastic bags for intravenous use maintain satisfactory potency for 24 hours at or below 22°C, 5 days under refrigeration (at or below 5°C) and 13 weeks frozen.

NOTE: Cefotaxime solutions exhibit maximum stability in the pH 5 to 7 range. Solutions of cefotaxime should not be prepared with diluents having a pH above 7.5, such as Sodium Bicarbonate Injection.

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

HOW SUPPLIED

Cefotaxime for Injection USP, is off-white to pale yellow crystalline powder supplied in vials containing cefotaxime sodium equivalent to 500 mg, 1 gram or 2 grams of cefotaxime.

The following packages are available:

Cefotaxime for Injection USP, 500 mg vials in a Box of 10 NDC 0069-0003-02

Cefotaxime for Injection USP, 1 g vials in a Box of 10 NDC 0069-0044-04

Cefotaxime for Injection USP, 2 g vials in a Box of 10 NDC 0069-0037-21

Store dry powder at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. The dry material as well as solutions tend to darken depending on storage conditions and should be protected from elevated temperatures and excessive light.

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