PRODUCT MONOGRAPH

[Pr] CEFOTAXIME SODIUM FOR INJECTION BP

(sterile cefotaxime sodium, 0.5 g, 1g, 2 g)

β-lactam Antibiotic

Sponsor:
Aurobindo Pharma Limited (Unit VI)
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PRODUCT MONOGRAPH

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ACTION AND CLINICAL PHARMACOLOGY

Cefotaxime Sodium for Injection BP is a semi-synthetic, 2-aminothiazolyl cephalosporin antibiotic for parenteral use. *In vitro* studies indicate that the antibacterial action of Cefotaxime Sodium for Injection results from inhibition of cell wall synthesis. It is stable against the action of most β-lactamases.

INDICATIONS AND CLINICAL USE

Treatment

Cefotaxime Sodium for Injection BP may be indicated for the treatment of infections caused by susceptible strains of the designated micro-organisms in the diseases listed below.

Lower Respiratory Tract Infections:

Pneumonia and lung abscess caused by *Streptococcus pneumoniae* (formerly *Diplococcus pneumoniae*), other streptococci (excluding enterococci, e.g. *S. faecalis*), *Staphylococcus aureus* (penicillinase and non-penicillinase producing), *Escherichia coli*, *Hemophilus influenzae*, (including ampicillin resistant strains) and unspecified *Klebsiella* species.

Urinary Tract Infections:

Caused by *Escherichia coli*, unspecified *Klebsiella* species (including *K. pneumoniae*), *Proteus mirabilis*, indole positive *Proteus*, *Serratia marcescens* and *Staphylococcus epidermidis*. Also, uncomplicated gonorrhea caused by *N. gonorrhoeae* including penicillin resistant strains.

Bacteremia/Septicemia:

Caused by *Escherichia coli*, unspecified *Klebsiella* strains and *Serratia marcescens*.

Skin Infections:

Caused by *Staphylococcus aureus* (penicillinase and non-penicillinase producing), *S. epidermidis*, group A streptococci, *Escherichia coli*, *Proteus mirabilis* and indole positive *Proteus*.

Intra-abdominal Infections:

Caused by *Escherichia coli*, and unspecified *Klebsiella* species.

Gynecological Infections:

Including pelvic inflammatory disease, endometritis and pelvic cellulitis caused by *E. coli*, group A streptococci and *Staphylococcus epidermidis*; anaerobic bacteria including unspecified *Peptococcus* and *Peptostreptococcus* strains and some strains of *Bacteroides fragilis*. In several cases, although clinical cures were achieved, bacteriological follow-up was not available.

Cefotaxime Sodium for Injection, 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.

Central Nervous System Infections:

Meningitis and ventriculitis caused by *Haemophilus influenzae*, *Neisseria meningitidis*, *Streptococcus pneumoniae, Klebsiella pneumoniae* and *Escherichia coli*. Cefotaxime Sodium for Injection is not active against *Listeria monocytogenes*.

Clinical experience with Cefotaxime Sodium for Injection in anaerobic infections is limited. Cefotaxime Sodium for Injection has been used with some success in wound and intra-abdominal infections against some strains of unidentified *Bacteroides* and anaerobic cocci.

Cefotaxime Sodium for Injection has been shown to be active against some strains of *Pseudomonas.*

In the treatment of infections encountered in immunosuppressed and granulocytopenic patients, results of therapy with Cefotaxime Sodium for Injection have not been impressive.

Cefotaxime Sodium for Injection should not be considered in the treatment of enterococcal infections, i.e. *Streptococcus faecalis.*

Specimens for bacteriologic culture should be obtained prior to therapy in order to isolate and identify the causative organisms and to determine their susceptibilities to Cefotaxime Sodium for Injection. Therapy may be instituted before results of susceptibility studies are known; antibiotic treatment should be re-evaluated once these results become available.

Prophylactic use

The administration of Cefotaxime Sodium for Injection perioperatively (preoperatively, intra-operatively and postoperatively) may reduce the incidence of certain infections in patients undergoing elective 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 caesarian section who are considered to be at increased risk of infection, intra-operative (after clamping the umbilical cord) and postoperative use of Cefotaxime Sodium for Injection may also reduce the incidence of certain postoperative infections.

Effective use for elective surgery depends on the time of administration (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.

CONTRAINDICATIONS

Cefotaxime Sodium for Injection is contraindicated in patients who have shown hypersensitivity to cefotaxime sodium, the cephalosporin or the penicillin groups of antibiotics.

WARNINGS

Anaphylactic reactions

BEFORE THERAPY WITH CEFOTAXIME SODIUM FOR INJECTION IS INSTITUTED, IT MUST BE CAREFULLY DETERMINED WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFOTAXIME, CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS. SINCE CROSS ALLERGY EXISTS BETWEEN PENICILLINS AND CEPHALOSPORINS IN 5 TO 10 % OF CASES, CEFOTAXIME SODIUM FOR INJECTION SHOULD BE GIVEN WITH EXTREME CAUTION TO PATIENTS WITH TYPE 1 HYPERSENSITIVITY REACTIONS TO PENICILLIN. ANTIBIOTICS, INCLUDING CEFOTAXIME SODIUM FOR INJECTION SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO CEFOTAXIME SODIUM FOR INJECTION OCCURS, THE DRUG SHOULD BE DISCONTINUED AND THE PATIENT TREATED WITH THE USUAL AGENTS (E.G. EPINEPHRINE, ANTIHISTAMINES, PRESSOR AMINES OR CORTICOSTEROIDS).

Speed of I.V injection

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

Gastrointestinal
***Clostridium difficile* -associated disease**

Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including Cefotaxime Sodium for Injection. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *Clostridium difficile*. *Clostridium difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridium difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile*. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases (see **ADVERSE REACTIONS** section).

PRECAUTIONS

Cefotaxime Sodium for Injection should be prescribed with caution in individuals with a history of lower gastrointestinal disease, particularly colitis.

General

Prolonged use of Cefotaxime Sodium for Injection may result in the overgrowth of non-susceptible organisms. Constant evaluation of the patient's condition is essential. If superinfection occurs, therapy should be discontinued and appropriate measures taken.

As with other β-lactam antibiotics, granulocytopenia and, more rarely, agranulocytosis may develop during treatment with Cefotaxime Sodium for Injection, particularly if given

over long periods. For courses of treatment lasting longer than 10 days, blood counts should therefore be monitored and treatment stopped in the event of neutropenia.

Cefotaxime Sodium for Injection, like other parenteral anti-infective drugs, may be locally irritating to tissues. In most cases, perivascular extravasation of Cefotaxime Sodium for Injection responds to changing of the infusion site. In rare instances, extensive perivascular extravasation of Cefotaxime Sodium for Injection 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.

Use In Obstetrics

Cefotaxime crosses the placental barrier. However, the safety of Cefotaxime Sodium for Injection in pregnancy has not been established and it should not be used during pregnancy.

Use of Cefotaxime Sodium for Injection in women of child-bearing potential requires that the anticipated benefits be weighed against the possible risks.

Nursing Mothers

Since cefotaxime is excreted in human milk in low concentrations, either breast feeding or treatment of the mother should be discontinued as necessary.

Patients with Special Diseases and Conditions

Although Cefotaxime Sodium for Injection rarely produces alterations in kidney function, evaluation of renal status is recommended, especially in severely ill patients receiving high doses.

Patients with markedly impaired renal function should be placed on the special dosage schedule recommended under **DOSAGE AND ADMINISTRATION** section, because normal dosage in these individuals is likely to produce excessive and prolonged serum antibiotic concentrations. If Cefotaxime Sodium for Injection and aminoglycosides are to be administered to the same patient, these antibiotics should be administered separately and not as a mixed injection (see **Reconstitution, Incompatibilities** section). Renal function must be monitored in all such cases.

The sodium content of cefotaxime sodium (48.2 mg/g) should be taken into account in patients necessitating sodium restriction.

Drug Interactions

Probenecid interferes with the renal tubular transfer of cephalosporins, thereby delaying their excretion and increasing their plasma concentrations.

As with other cephalosporins, cefotaxime may potentiate the nephrotoxic effects of nephrotoxic drugs.

Laboratory Tests

Positive direct Coombs' test is known to develop in individuals during treatment with the cephalosporin group of antibiotics, including cefotaxime sodium.

In laboratory tests a false positive reaction to glucose may occur with reducing substances but not with the use of specific glucose oxidase methods.

ADVERSE REACTIONS

Clinical Trials

The most frequent adverse reactions with their frequency of occurrence are:

Central Nervous System (0.2%):
Headache

Gastrointestinal (1.7%):
Colitis, diarrhea, nausea and vomitings. Symptoms of pseudomembranous colitis can appear during or after Cefotaxime Sodium for Injection treatment.

Genitourinary System (<1%):
Moniliasis, vaginitis

Hematologic System (<1%):
As with other β-lactam antibiotics, neutropenia and, more rarely, agranulocytosis may develop during treatment with Cefotaxime Sodium for Injection, particularly if given over long periods. Furthermore, transient leukopenia, eosinophilia and thrombocytopenia have also been reported.

Some individuals have developed positive direct Coombs' test during treatment with Cefotaxime Sodium for Injection and other cephalosporin antibiotics (see **PRECAUTIONS, Laboratory tests** section). Rare cases of hemolytic anemia have been reported.

Hypersensitivity (1.8%):
Rash, pruritus, fever

Kidney (<1%):
Increased BUN has occasionally been observed.

Liver (<1%):
Transient elevations in SGOT, SGPT, serum LDH, and serum alkaline phosphatase levels have been reported.

Local (5%):
Injection site inflammation with intravenous administration. Pain, induration and tenderness after intramuscular injection

Other Adverse Events including Post-Marketing Surveillance Data

Anaphylactic reactions:
Angioedema, bronchospasm, malaise possibly culminating in shock, may rarely occur (see **WARNINGS, Anaphylactic reactions** section).

Cardiovascular:
Potentially life-threatening arrythmia following rapid bolus infusion has been reported in very few patients who received rapid intravenous administration of Cefotaxime Sodium for Injection through a central venous catheter (see **WARNINGS, Speed of I.V injection** section).

Central Nervous System:
Administration of high doses of β-lactam antibiotics, including Cefotaxime Sodium for Injection, particularly in patients with renal insufficiency may result in encephalopathy (e.g. impairment of consciousness, abnormal movements and convulsions).

Cutaneous:
Rash, pruritis and less frequently urticaria. As with other cephalosporins, isolated cases of bullous eruptions (erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis) have been reported.

Gastrointestinal:
During treatment with Cefotaxime Sodium for Injection, abdominal pain may occur. As with all other broad spectrum antibiotics diarrhea may sometimes be a symptom of enterocolitis, which may, in some cases, be accompanied by blood in stools. A particular form of enterocolitis that can occur with antibiotics, including Cefotaxime Sodium for Injection, is *Clostridium difficile*-associated disease **(see WARNINGS, Gastrointestinal, *Clostridium difficile* associated disease section).**

Kidney:
Decreases in renal function (increase of creatinine) have been observed with cephalosporins including Cefotaxime Sodium for Injection, particularly when co-prescribed with aminoglycosides.

As with some other cephalosporins, rare cases of interstitial nephritis have been reported in patients treated with Cefotaxime Sodium for Injection.

Liver:

Increase in liver enzymes (ALT, AST, LDH, gamma-GT and/or alkaline phosphatase) and/or bilirubin have been reported. These laboratory abnormalities, which may also be explained by the infection, may rarely exceed twice the upper limit of the normal range and elicit a pattern of liver injury, usually cholestatic and most often asymptomatic. Hepatitis (sometimes with jaundice) has been reported.

Other:

Superinfection: as with other antibiotics, the use of Cefotaxime Sodium for Injection, especially if prolonged, may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

As reported with other antibiotics for the treatment of borreliosis a Jarisch-Herxheimer reaction may develop during the first days of treatment.

The occurrence of one or more of the following symptoms has been reported after several weeks of treatment of borreliosis: skin rash, itching, fever, leucopenia, increase in liver enzymes, difficulty of breathing, and joint discomfort. To some extent, these manifestations are consistent with the symptoms of the underlying disease for which the patient is being treated.

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701C
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guideline are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is a risk of reversible encephalopathy in cases of administration of high doses of β-lactam antibiotics including Cefotaxime Sodium for Injection

For management of a suspected drug overdose, contact your regional Poison Control Centre Immediately.

DOSAGE AND ADMINISTRATION

Cefotaxime Sodium for Injection may be administered intramuscularly or intravenously after reconstitution (see **Tables 3 and 4** with recommended mode of reconstitution according to route of administration).

Dosage

Treatment for adults and children with body weight of 50 kg or more:
The dosage of Cefotaxime Sodium for Injection should be determined by susceptibility of the causative organisms, severity of the infection and condition of the patient.

Table 1:Guidelines for dosage of Cefotaxime Sodium for Injection for adults and children with body weight of 50 kg or more.

Type of Infection	*Daily Dose (g)*	*Frequency and Route*
Uncomplicated gonorrhea	1	1 g i.m. single dose
Uncomplicated infections	2	1 g every 12 hours i.m. or i.v.
Moderately severe to severe infections	3 - 6	1-2 g every 8 hours i.m. or i.v.
Very severe infections (e.g. septicemia, CNS)	6 - 8	2 g every 6-8 hours i.v.
Life-threatening infections	up to 12	2 g every 4 hours i.v.

THE MAXIMUM DAILY DOSAGE SHOULD NOT EXCEED 12 GRAMS.

Treatment for 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 I.V every 12 hours
1-4 weeks of age: 50 mg/kg per dose I.V every 8 hours

Infants and children (1 month to 12 years)

For body weights less than 50 kg, the recommended daily dose is 50 to 100 mg/kg i.m. or i.v. divided into 4 to 6 equal doses, or up to 180 mg/kg/day for severe infections (including central nervous system infections).

For body weights of 50 kg or more, the usual adult dosage should be used; THE MAXIMUM DAILY DOSAGE SHOULD NOT EXCEED 12 GRAMS.

Table 2: Guidelines for dosage of Cefotaxime Sodium for Injection for neonates, infants and children.

Patients	**Age or weight**	**Dose**	**Route**	**Dose interval**
Neonates	0 to 1 week	50 mg/kg/**dose**	IV	Every 12 hours
Neonates	1 to 4 weeks	50 mg/kg/**dose**	IV	Every 8 hours
Infants and Children	< 50 kg	50 to 100 mg/kg/**day** (up to 180 mg/kg/day for severe infections, including meningitis)	IV or IM	Divided into 4 to 6 equal doses
Children	≥ 50 kg	adult dosage		

Duration of Treatment:

Administration of Cefotaxime Sodium for Injection 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 infections and may be required for several months after therapy has been completed; persistent infections may require prolonged treatment. Doses less than those recommended should not be employed.

Prophylactic use:

Surgery patients

To prevent postoperative infection in contaminated or potentially contaminated surgery, recommended doses are as follows:

- 1 g i.m. or i.v. administered 1/2 to 1 1/2 hours prior to the initial surgical incision to ensure that adequate antibiotic levels are present in the serum and tissues at the start of surgery
- 1 g i.m. or i.v. administered 1 1/2 to 2 hours following the first dose; for lengthy operative procedures, additional intraoperative doses may be administered, if necessary, at appropriate intervals (1 1/2 to 2 hours) during surgery
- 1 g i.m. or i.v. administered within 2 hours following completion of surgery

The total cumulative prophylactic dose should not exceed 6 g in a 12-hour period.

Caesarian Section Patients

The first dose of 1 g is administered i.v. as soon as the umbilical cord is clamped. The second and third doses should be given as 1 g i.m. or i.v. at 6 and 12 hours after the first dose.

Dosage for Patients with Impaired Renal Function:
In patients with estimated creatinine clearance of less than 20 mL/min/1.73m^2 the dose of Cefotaxime Sodium for Injection should be halved (see **PRECAUTIONS, Patients with Special Disease and Conditions** section).

If serum creatinine values alone are available, the following formula (based on sex, weight, and age of the patient) may be used to convert these values into creatinine clearance.

Males: Cl_{Cr} (ml/min) = $\frac{\text{Weight (kg) x (140 - age in years)}}{\text{72 x serum creatinine (mg/dl)}}$

Females: Cl_{Cr} (ml/min) = 0.85 x above value

In hemodialysed patients

1 to 2 g daily, depending on the severity of the infection; on the day of haemodialysis, Cefotaxime Sodium for Injection must be administered after the dialysis session.

Administration

Intramuscular:
Cefotaxime Sodium 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.

Intravenous:
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 bolus administration, the solution containing Cefotaxime Sodium for Injection must be injected over a period of 3 to 5 minutes (see **WARNINGS, Speed of i.v. injection** section).

Using 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 intravenous solutions. Butterfly[1]*or scalp vein type needles are preferred for this type of infusion. However, during infusion of the solution containing Cefotaxime Sodium for Injection, it is advisable to discontinue temporarily the administration of other solutions at the same site (see **Reconstitution**, **Incompatibilities** section).

Reconstitution

For Intramuscular Use:

Cefotaxime Sodium for Injection should be reconstituted with Sterile Water for injection or Bacteriostatic Water for injection in accordance with the volumes recommended in the following table.

Table 3: Reconstitution table for intramuscular use

	Volume to be Added to Vial (mL)*	Approximate Available vol. (mL)	Approx. Average Concentration (mg/mL)
500 mg vial	2	2.2	230
1 g vial	3	3.4	300
2 g vial	5	6.0	330

* shake to dissolve

For Intravenous Use:

For intravenous bolus use

500 mg, 1 g and 2 g vials should be reconstituted with at least 10 mL of Sterile Water for injection.

For intravenous infusion use

Reconstituted solution may be further diluted with 50 to 1000 mL of the fluids recommended for i.v. infusion.

Table 4: Reconstitution table for intravenous use

	Volume to be Added to Vial (mL)*	Approximate Available vol. (mL)	Approx. Average Concentration (mg/mL)
500 mg vial	10	10.2	50
1 g vial	10	10.4	95
2 g vial	10	11.0	180

* shake to dissolve

A solution of 1 g of Cefotaxime Sodium for Injection in 14 mL of Sterile Water for Injection is isotonic.

[1]*Reg'd TM of Abott Laboratories

Solutions For i.v. Infusion:
Cefotaxime Sodium for Injection is compatible with the following infusion fluids:

- 0.9% NaCl injection
- 5% Dextrose injection
- 0.9% NaCl and 5% Dextrose injection
- 0.45% NaCl and 5% Dextrose injection
- 0.2% NaCl and 5% Dextrose injection
- Sodium Lactate injection
- 5% Dextrose and 0.15% KCl injection
- Plasma-Lyte 56 Electrolyte Solution in 5% Dextrose injection
- Ringer's injection
- Lactated Ringer's solution
- Lactated Ringer's with 5% Dextrose injection

Incompatibilities:
Solutions of Cefotaxime Sodium for Injection must not be admixed aminoglycoside solutions. If Cefotaxime Sodium for Injection and aminoglycosides are to be administered to the same patient, they must be administered separately and not as a mixed injection.

Solutions of Cefotaxime Sodium for Injection should not be prepared with diluents having a pH above 7.5 such as Sodium Bicarbonate Injection.

STABILITY AND STORAGE RECOMMENDATIONS

Solutions of Cefotaxime Sodium for Injection range from light yellow to amber, depending on concentration and the diluent used. The solutions tend to darken depending on storage conditions and should be protected from elevated temperatures and excessive light. Cefotaxime Sodium for Injection in the dry state should be stored at room temperature (15ºC to 25ºC), protected from light and heat.

Reconstituted solution in water for injection is stable up to 12 hours at room temperature (15ºC to 25ºC) and 24 hrs, at 2 – 8°C. Only freshly prepared reconstituted solutions may be further diluted with 50 to 1000 mL of the recommended infusion fluids in VIAFLEX* intravenous bags. Such solutions maintain satisfactory potency for 24 hours at room temperature (15ºC to 25ºC) and for 72 hours under refrigeration (2-8ºC). Any unused solutions should be discarded.

Cefotaxime Sodium for Injection solutions exhibit maximum stability in the pH 5-7 range

Special Instructions

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Solutions of Cefotaxime Sodium for Injection range

from light yellow to amber, depending on concentration and diluent used. The dry powder as well as solutions tends to darken, depending on storage conditions.

AVAILABILITY OF DOSAGE FORMS

Dosage Forms

Cefotaxime sodium for injection 0.5 g

A white or slightly yellow powder filled in 15 ml moulded Type I (Ph.Eur.) clear glass vials with 20 mm grey bromo butyl rubber stoppers and sealed with aluminium seal having 20 mm yellow colour PP disc.

Cefotaxime sodium for injection 1 g

A white or slightly yellow powder filled in 15 ml moulded Type I (Ph.Eur.) clear glass vials with 20 mm grey bromo butyl rubber stoppers and sealed with aluminium seal having 20 mm lime green colour PP disc.

Cefotaxime sodium for injection 2 g

A whi*te or slightly yellow powder filled in 15 ml moulded Type I (Ph.Eur.) clear glass vials with 20 mm grey bromo butyl rubber stoppers and sealed with aluminium seal having 20 mm pink colour PP disc.

Composition:

Cefotaxime Sodium for Injection BP does not contain any additives or other inactiv ingredients

* Reg'd TM of Baxter-Travenol Laboratories

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

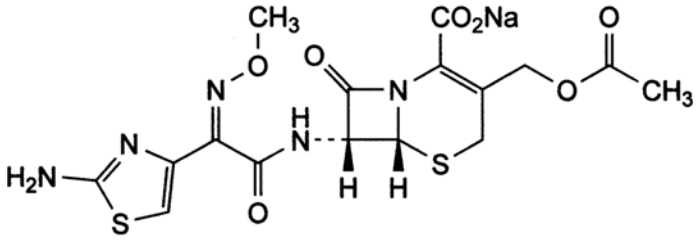
Proper Name : Cefotaxime sodium

Chemical Name : Sodium (6R, 7R)-3-[(acetyloxy) methyl]-7-[[(2Z)-2-(2-aminothiazol -4 -yl)-2-(methoxyimino) acetyl] amino]-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylate.

Molecular Formula : $C_{16}H_{16}N_5NaO_7S_2$

Molecular Mass : 477.5

Structural Formula :



Physico-chemical properties:

Description : White or slightly yellow powder

Solubility : It is soluble in water at about 20%, but poorly soluble in common organic solvents including ethanol.

MICROBIOLOGY

Cefotaxime has *in vitro* activity against a wide range of Gram-positive and Gram-negative organisms as observed in the following table.

Table 5: Summary for sensitivity of aerobic and anaerobic bacteria to cefotaxime

MICROORGANISMS	No. of strains	CUMULATIVE PERCENTAGE OF STRAINS INHIBITED AT INDICATED CONCENTRATIONS[a] (µg/mL)									
		≤0.1	0.5	1.0	2.0	4.0	8.0	16	32	64	≥128
AEROBES GRAM-NEGATIVE											
Acinetobacter spp.	39	5	10	18	28	38	62	72	87	90	100
Acinetobacter anitratum	154				6	13	43	71	83	87	100
Acinetobacter Iwoffii	15			50	90		100				
Citrobacter spp.	47	60	74	74	77	79	85	89	94	98	100
Citrobacter diversus	25	100									
Citrobacter freundii	28	79	93	96				100			
Enterobacteriacae spp.	6083		91	95	99	100					
Enterobacter spp.	61	79	90	95	98					100	
Enterobacter aerogenes	57	88	89	91		95		98		100	
Enterobacter cloacae	80	63	69	74	84	88				94	100
Escherichia colib	657	95	98	99						100	
Haemophilus spp.b	294	97	99	100							
Haemophilus influenza [b]	113	96	98	99						100	
Klebsiella spp.	101	91	97	100							
Klebsiella oxytoca	10			20	50	60	70	80	90	100	
Klebsiella pneumoniae[b]	226	88	98	99	100						
Neisseria spp.	12	75	100								
Neisseria gonorrhoeae[b]	472	100									
Neisseria meningitidis	150				50	90					
Proteus indole (+)	102	64	75	85	94	96		97		100	
Proteus indole (-)	20	90				95				100	
Proteus mirabilis (-)	186	98	99		100						
Providencia spp.	37	35	54	78	86	95		100			
Pseudomonas spp.	136		1		3	9	28	57	72	85	100
Pseudomonas aeruginosa	1412				1	6	30	69	85	97	100
Pseudomonas maltophilia	12								50	90	100
Pseudomonas putida	10							50		90	100
Salmonella spp.	33	79	97		100						
Salmonella typhi	30	100									
Serratia spp.	93	29	43	47	52	54	58	63	78	95	100
Serratia marcescens[b]	86	35	41	44	50	65	81	97	100		
Shigella spp.	19	74	84	95	100						
AEROBES GRAM-POSITIVE											
Staphylococcus aureus	1686		5	16	89	95	100				
Staphylococcus epidermidis	175	20	45	57	73	89	99			100	
Streptococcus group A	12	100									
Streptococcus group B	20	90	100								

MICROORGANISMS	No. of strains	CUMULATIVE PERCENTAGE OF STRAINS INHIBITED AT INDICATED CONCENTRATIONS[a] (µg/mL)									
Streptococcus enterococcus	146		1	5	10	14	17	20	21	25	100
Streptococcus group D non-enterococcus	23	70	87	98	100						
Streptococcus pneumoniae	67	91									
ANAEROBES GRAM-NEGATIVE											
Bacteroides spp	51		4		20	26	38	60	82	94	100
Bacteroides fragilis	28						50	90			
Bacteroides thetaiotaomicron	13							50		90	
ANAEROBES GRAM-POSITIVE											
Clostridum spp. (Other than C. difficile)	13	15			61	84	100				
Clostridium perfringens	19		50			90					
Cocci	11	50	90								
Propionibacterium	11	90									

a Serial dilutions (broth and agar methods)
b Includes producers and non-producers of β-lactamases.

The sensitivity to β-lactamases was determined by a cell-free *in vitro* test system using characteristic β-lactamases of various Richmond classes. Evidence was found of the stability of cefotaxime against the inactivating effect of cephalosporinases from *Enterobacter cloacae* P 99 (class Ia) and *Pseudomonas* HS 18 (Id), as well as against that of the β-lactamase from *Escherichia coli* TEM (IIIa). The test compound was mildly sensitive to the effects of the enzyme formed by *Klebsiella aerogenes* 1082 E (Ivc).

Table 6: Effect of ß-lactamase on cefotaxime

	E. cloacae P99		Ps. Aeruginosa HS18		K1. aerogenes 1082E		E. coli TEM	
	Relative ß-lactamase sensitivity	MIC	Relative ß-lactamase sensitivity	MIC	Relative ß-lactamase sensitivity	MIC	Relative ß-lactamase sensitivity	MIC
Cefotaxime	0%	125 µg	0%	1.0 µg	2.5%	12.5 µg	0%	0.078 µg

Initial count for each organism about 5 x 10^{-4} CFU per mL in each tube. There is *in vitro* evidence of synergy between cefotaxime and aminoglycoside antibiotics (gentamicin and tobramycin) against some strains of *Pseudomonas*.

A broth dilution checkerboard synergy assay was used to assess the activity of cefoperazone, cefotaxime, moxalactam, and carbenicillin, in combination with tobramycin, against 38 strains of *Pseudomonas aeruginosa*. Synergy occurred significantly more often ($p < 0.001$) when tobramycin was combined with cefotaxime (63%) than when it was combined with carbenicillin (26%), cefoperazone (21%), or moxalactam (18%). Of the 25 synergistically inhibited strains, the combination cefotaxime-tobramycin was synergistic against 24 and was the only synergistic

combination against 10. Of six strains initially resistant to cefotaxime, five were susceptible to this agent (minimum inhibitory concentration, 32 μg /mL) when it was combined with tobramycin.

Table 7: Results of synergy testing against 38 strains of *Pseudomonas aeruginosa*

Antibiotic combination[a]	No. (%) synergistic
T + CT[b]	24 (63.2)
T + CB	10 (26.3)
T + CP	8 (21.1)
T + ML	7 (18.4)

[a] T (tobramycin)
CT (cefotaxime)
CB (carbenicillin)
CP (cefoperazone)
ML (moxalactam)

[b] $p < 0.001$ for T + CT vs each of the other combinations (McNemar test). Differences among the other antibiotic combinations were not statistically significant.

In another study the combination cefotaxime/gentamicin was tested agains 111 clinical isolates of *Pseudomonas aeruginosa* and was found to have a synergistic effect against 73.9% of the strains tested.

Susceptibility Tests

With the Bauer-Kirby-Sherris-Turck method of disc susceptibility testing, a disc containing 30 μg of cefotaxime should give a zone of at least 20 mm for microorganisms to be considered susceptible to Cefotaxime Sodium for Injection , 15-19 mm for organisms of intermediate susceptibility and a zone of 14 mm or less for cefotaxime resistant organisms.

Because certain strains of enterobacteriaceae have been shown to be resistant to the cephalosporin class disc, only the cefotaxime discs must be used for testing the susceptibility of Cefotaxime Sodium for Injection.

PHARMACOLOGY

Animal Pharmacology

Animal pharmacology studies demonstrate that cefotaxime has no significant effect on the central nervous system, cardiovascular system, respiratory system, kidneys, blood clotting mechanisms and blood glucose levels.

Human Pharmacology and Kinetics

Intramuscular administration:

Single dose
Following intramuscular administration of a single 500 mg or 1 g dose of Cefotaxime Sodium for Injection to normal volunteers, mean peak serum concentrations of 11.7 and 20.5 μg/mL respectively, are attained within 30 minutes and decline with an elimination half-life of approximately 1 hour.

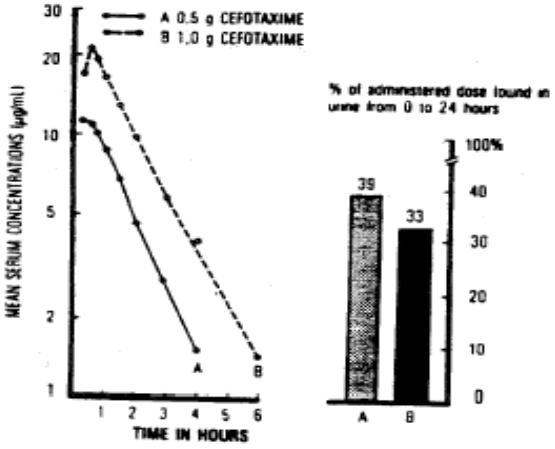


Fig. 1: Mean serum concentrations and urinary excretion data of cefotaxime administered intramuscularly as a single dose of 0.5 g and 1.0 g in 14 healthy male volunteers

Table 8: Pharmacokinetic parameters of cefotaxime after single intramuscular administration in 14 healthy male volunteers (mean)

	Cefotaxime	
KINETIC PARAMETERS	**500 mg**	**1000 mg**
Peak serum level (μg/mL)	11.7	20.5
Time to peak (h)	0.4	0.5
AUC $_{(0-\infty)}$ (μg/mL/h)	24.1	48.4
$t_{1/2}$ ß (h)	1.2	1.3
Cl $_S$ (mL/min/1.73m^2)	315.6	318.5
% unchanged drug in urine / 0-24 h	38.8	33.3
Cl $_r$ (mL/min/1.73m^2)	122.4	103.8

Multiple doses

Following multiple intramuscular injections, serum levels at 30 minutes after a dose of 500 mg every 8 hours, ranged from 9.2 to 11.9 µg/mL. There was no difference between the half-life (h) at Day 1 and Day 11, but differences were noted in the $AUC_{0\text{-}8\ h}$, fractional serum clearance and renal clearance; the latter probably being related to significantly lower recovery of the drug on Day 11.

Drug administration time

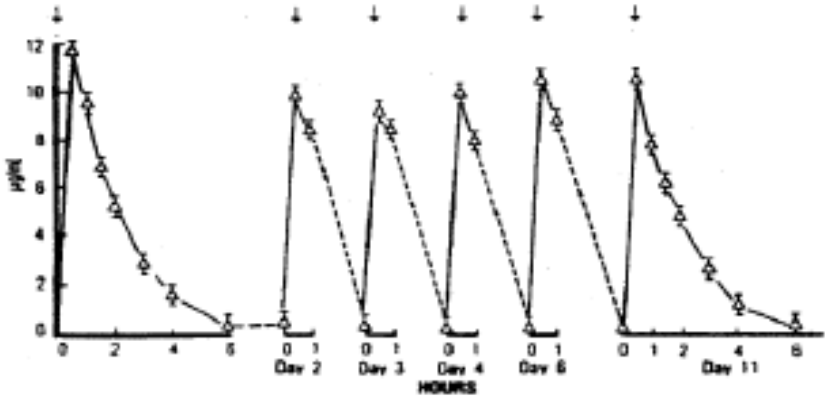


Fig. 2: Mean serum levels ± SE of cefotaxime administered intramuscularly after multiple doses of 500 mg every 8 hours in 30 healthy male volunteers.

Table 9: Pharmacokinetic parameters of cefotaxime after multiple intramuscular injections of 500 mg (mean ± *SE*) in 30 healthy male volunteers

	Day 1	**Day 11**
Elimination rate constant (ß) (h^{-1})	0.778 ± 0.04	0.784± 0.04
$t_{1/2}$ (h)	0.93 ± 0.05	0.92± 0.05
$AUC_{(0\text{-}8\ h)}$ (µg /mL/h)	24.28 ± 1.18	19.9 ±1.25
Serum clearance (mL/min/1.73m^2)	304.8 ±13.49	377.3 ± 23.61
Volume of distribution (L/1.73m^2)	23.96 ±1.07	29.68 ± 2.58
Renal clearance (mL/min/1.73m^2)	194.4 ±18.35	146.6 ±13.86
Drug excreted (0-6 h) (%)	62.6 ±5.09	39.1± 3.77

Intravenous administration:

Single dose (bolus over 5 minutes)

Following intravenous administration (bolus) of a single 500 mg, 1 g and 2 g dose of Cefotaxime Sodium for Injection to healthy adult male volunteers, the serum levels were 38.9, 101.7, and 214.4 µg/mL respectively, without alteration in the elimination half-life.

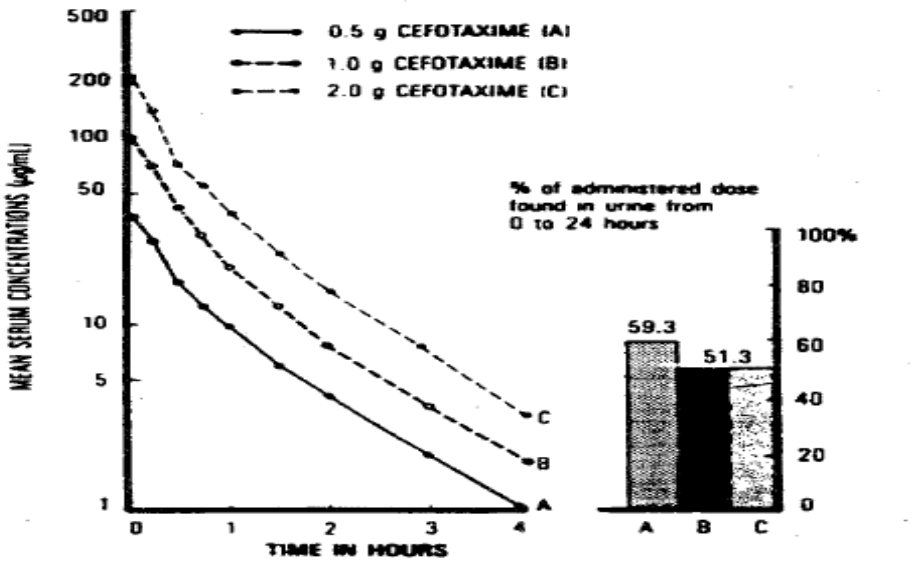


Fig 3. Mean serum concentrations and urinary excretion data of cefotaxime administered intravenously (over a 5 min. period) as a single dose of 0.5 g, 1 g and 2 g in 15 healthy male volunteers.

Table 10: Pharmacokinetic parameters of cefotaxime after intravenous administration of a single dose of 0.5 g, 1 g and 2 g in 15 healthy male volunteers (mean).

	Cefotaxime		
KINETIC PARAMETERS	**500 mg**	**1000 mg**	**2000 mg**
Peak serum level (µg/mL)	38.9	101.7	214.4
AUC $_{(0-\infty)}$ (µg /mL/h)	30.6	70.4	134.1
$t_{1/2}$ ß (h)	1.04	1.05	0.86
Cl_s (mL/min/1.73m^2)	245.3	206.8	215.1
% unchanged drug in urine/0-24 h	59.3	51.3	51.3
Cl_r (mL/min/1.73m^2)	146.8	104.0	110.4

Single dose (infusion over 30 minutes)

Administration of 1 g of Cefotaxime Sodium for Injection infused intravenously over 30 minutes gave mean peak serum concentrations at the end of the 30 minutes of 41.1 µg/mL with an elimination half-life of 1.13 h.

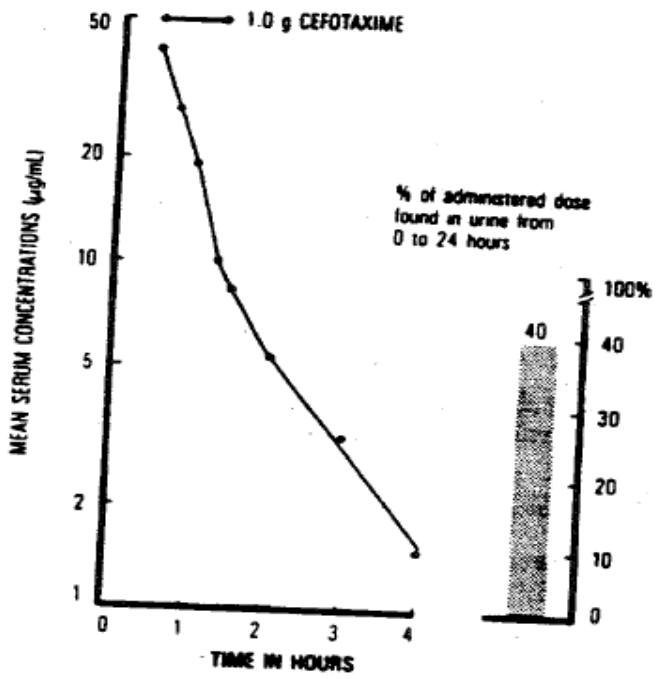


Fig 4. Mean serum concentrations and urinary excretion data of cefotaxime infused intravenously over 30 min. as a single dose of 1.0 g in 10 healthy male volunteers.

Table 11: Pharmacokinetic parameters after single intravenous infusion over 30 min. of 1 g cefotaxime in 10 healthy male volunteers (mean)

	Cefotaxime
KINETIC PARAMETERS	**1000 mg**
Peak serum level at the end of 30 min. infusion (µg/mL)	41.1
AUC $_{(0-\infty)}$ (µg/mL/h)	44.3
$t_{1/2}$ ß (h)	1.13
Cl_s (mL/min/1.73m^2)	341.6
% unchanged drug in urine/0-24 h	40.0
Cl_r (mL/min/1.73m^2)	130.1

Multiple dose (repetitive i.v infusion over 30 minutes)

There was no evidence of drug accumulation following repetitive i.v. infusions over 30 minutes of 1 g doses every 6 hours for 14 days.

The biological half-life was approximately 1.0 hour and the 24 hours urinary excretion of unchanged drug amounted to 62.6% of the administered dose (almost all of it in the first 6 hours).

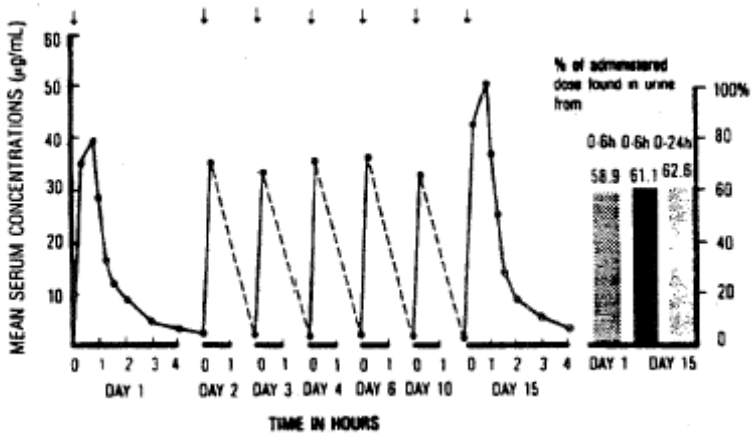


Fig. 5. Mean serum concentrations and urinary excretion data of cefotaxime infused intravenously over 30 min. as a single dose of 1.0 g, every 6 hours for 14 days in 16 healthy male volunteers.

Table 12: Pharmacokinetic parameters of cefotaxime after repetitive intravenous infusion (over 30 min.) of 1.0 g doses every 6 hours, for 14 days in 16 healthy male volunteers (mean)

KINETIC PARAMETERS	1000 mg Cefotaxime	
	Day 1	Day 15
AUC $_{(0-\infty)}$ (µg /mL/h)	57.4	68.9
$T_{1/2}$ ß (h)	1.2	1.0
Cl_s (mL/min/1.73m^2)	259.3	219.5
% unchanged drug in urine/0-6 h	58.9	61.1
Cl_r (mL/min/1.73m^2)	154.5	132.9

Cerebrospinal Fluid Penetration:

Children

In 13 children (9 days to 5 years) successfully treated for bacterial meningitis with a dose of 40 mg/kg, iv, every 6 hours for 14 days, cefotaxime diffused consistently and in therapeutic levels into the cerebrospinal fluid. Cerebrospinal fluid levels of 6.0 µg/ mL (after 36-48 h) and 1.2 µg/mL (after 14 days) in treatment were 17 to 275 - fold the MBCs for the infecting organisms. After a single 40 mg/kg dose to each of 5 infants (1 to 19 months) with ventriculostomies, mean cerebrospinal fluid levels of cefotaxime were 6.4, 5.7 and 4.5 µg/mL at 2, 4 and 6 hours, respectively. Cefotaxime mean half-life in 4 infants was 1.15 ± 0.58 h in plasma and 4.3 ± 3.1 h in cerebrospinal fluid.

Table 13: Cefotaxime and desacetyl cefotaxime plasma and CSF levels after i.v. injection in 13 children with bacterial meningitis

Drug level (µg/ml)*						
Drug	Early (36 to 48 h)			Late (14 days)		
	Plasma	CSF	Diffusion ratio (%)	Plasma	CSF	Diffusion ratio (%)
Cefotaxime	5.1-55.7 (16.7 ± 14.7)	0.74-38.8 (6.0 ± 10.2)	7.0-69.7 (27.7 ± 16.2)	1.7-13.6 (6.6 ± 4.3)	0.6-3.1 (1.2 ± 0.9)	4.5-64.7 (25.7 ± 21)
Desacetyl cefotaxime	2.5-20.1 (8.1 ± 4.2)	0.89-27.4 (4.6 ± 7.0)	12.2-219 (51.9 ± 54.5)	1.5-9.5 (5.4 ± 1.9)	0.5-2.1 (1.1 ± 0.8)	8.9-40.0 (20.8 ± 9.3)

* Values in parentheses represent the mean ± standard deviation.

Adult

Thirty-two (32) cases of adult meningitis received cefotaxime, 2 g every 8 hours by bolus injection (3-5 minutes). Mean concentration of cefotaxime in cerebrospinal fluid ranged from 0.8 µg/mL (aseptic meningitis), to 6.4 µg/mL (Gram-negative and Listeria monocytogenes), and from 0.5 to 5.4 µg/mL for the metabolite.

Paediatric Pharmacokinetics:

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 weight (less than or equal to 1500 g), 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 g. 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, Treatment for Neonates, Infants and Children:** section).

Table 14: Pharmacokinetic parameters in 29 newborns receiving single intravenous dose of 50 mg/kg cefotaxime (mean)

	Group I (≤1500 g at birth and < 5 days old)	**Group II** (> 1500 g at birth and < 5 days old)	**Group III** (varying birth weight and ≥ 5 days old)	**Group A** (≤ 1500 g)	**Group B** (> 1500 g)
Peak serum concentration (µg/ml)	116	127	122	133	117
AUC $_{0\text{-}6\ h}$ (µg/ml/h)	394	418	375	400	392
AUC $_{0\text{-}\infty}$ (µg/ml/h)	683	620	551	675	561 (1)

Half-life (h)	4.9 (1) 3.7 (2) 3.5	4.6 (2) 3.4
Vd (L/kg)	0.53 (2) 0.44 (1) 0.45	0.51 (2) 0.44
Cl_s (ml/min/1.73 m^2)	22.5 (1) 38.8 (1) 39.1	23.0 (3) 43.9

(1) $p \leq 0.05$; (2) $p \leq 0.01$; (3) $p \leq 0.001$

Renal insufficiency:

1 g of cefotaxime was injected intravenously b.i.d. for 4 to 7 days in 9 patients with renal insufficiency whose creatinine clearances ranged from 5.0 to 25.5 mL/min/1.73m^2.

Table 15: Pharmacokinetic parameters of cefotaxime and its metabolites in 9 patients with renal insufficiency after repeated intravenous administration (mean)

	CEFOTAXIME		**DACM**		**UP1**		**UP2**	
	First dose	**last dose**	**First dose**	**last dose**	**First dose**	**last dose**	**First dose**	**last dose**
Peak plasma level (µg/mL)			19.3	37.3	5.0	17.2	4.5	14.7
C max *last dose* / *C* max *first dose*	1.2		2.0		4.2		3.9	
Time-to-peak (h)			5.1	3.7	6.5	6.0	6.2	6.0
Distribution half-life (h)	0.5	0.7						
Biological half-life (h)	2.9	3.1	10.4	11.5	6.2	16.6	8.1	21.1
AUC $_{0-\infty}$ (µg /mL/h)	280	351	331	722	106	605	115	538
$AUC_{(0-12h)}$ *last dose* / $AUC_{(0-12h)}$ *first dose*	1.3		1.7		3.1		3.0	
Renal clearance (mL/min)	13.0		14.8		30.2		30.9	
Cumulative urinary excretion (mg)	171.4	137.7	127.8	154.4	84.5	142.0	75.3	133.7

The half-lives of cefotaxime, desacetyl cefotaxime (DACM), and UP1 and UP2 were longer and renal clearances were decreased in these patients. The biological half-life of cefotaxime was 2.9 hours after the first dose and 3.1 hours after the 5th dose. Neither the

drug nor its metabolites accumulated even when clearances were as low as 20 mL/min/1.73m^2.

However, in patients with creatinine clearances approaching 5 mL/min/1.73m^2, accumulation of the metabolites becomes apparent.

Consequently, until further clinical experience is obtained in such patients, it is recommended that the dose of cefotaxime be halved when creatinine clearance is lower than 20 mL/min/1.73m^2 (see **DOSAGE AND ADMINISTRATION, Dosage for Patients with Impaired Renal Function:** section).

Metabolism and Excretion:

Cefotaxime is partially metabolized in humans by non-specific esterases which desacetylate the acetoxymethyl side chain to form desacetyl cefotaxime (DACM). Desacetylation is followed by formation of the lactone and subsequent conversion to open β-lactam ring structures (UP1 and UP2).

Approximately 20-36% of an intravenous dose of ^{14}C cefotaxime is excreted by the kidney as unchanged cefotaxime and 15-25% as the DACM derivative, the major metabolite. Two other urinary metabolites (UP1 and UP2) account together for about 20-25%. Faecal recovery accounts for approximately 10% of the administered dose.

The DACM has been shown to contribute to 10-15% of the bactericidal activity of the parent compound. It has no activity against Pseudomonas. UP1 and UP2 lack antibacterial activity.

In a study conducted on 22 healthy volunteers administered Cefotaxime Sodium for Injection and alcohol, there was no disulfiram-like reaction.

Protein binding:

In an *in vitro* study using the dialysis chambers method, it was found that about 51% (range 35-64%) of cefotaxime was bound to human serum proteins when concentrations ranged from 6.25 to 50 μg/mL. The bound percentage of the desacetyl metabolite was 16% to 32%, which is approximately half of the parent compound. At a concentration of 100 μg/mL in serum, only a small percentage of both the parent compound and its metabolite were bound; most probably the portion of the protein molecules which bind them is saturated at this concentration.

TOXICOLOGY

Acute Toxicity

The acute toxicity of cefotaxime was determined in mice, rats, rabbits and dogs. The order of toxicity by various routes was: i.v. > i.p. > s.c. No LD_{50}s were found for per os or intramuscular administration.

Common signs of toxicity were clonic and tonic convulsions, dyspnea, hypothermia and cyanosis. There were almost no differences in sex or species. Cefotaxime was found to be twice as toxic for new borns as it was for adults. The LD_{50} of the desacetyl derivative of cefotaxime was determined in mice and found to be similar to cefotaxime with similar signs of intoxication.

Short-term Toxicity

In a 6-day acute toxicity study, cefotaxime was given intravenously to 3 groups of beagle dogs, each consisting of 2 males and 2 females, at doses of 500 mg/kg for 2 days followed by 100 mg/kg for 4 days; and in a second group, 1000 mg/kg for 2 days followed by 250 mg/kg for 4 days. A third group of 4 dogs receiving physiological saline under the same conditions served as control. The results of biochemical tests were unremarkable although there were transient increases in urea and SGPT in a few treated males and in SGPT and alkaline phosphatase in 2 treated females.

At autopsy, microscopic examinations revealed superficial hemorrhages in the urethra of one high dose male and a similar finding in the bladder of a female of the same group. The hemorrhages were the apparent result of catheterization. The other high dose male had a scar on the kidney and two scars on the bladder. Histological examination of the livers showed a few areas of Kupffer cell hyperplasia in all treated males. A male and a female of the high dose group had an abundance of glycogen in the hepatic parenchyma. Microscopic examination of the kidneys showed slightly dilated proximal convoluted tubules without epithelial changes in one male from each of the treated groups. Inflammatory and histocytic cells were noted in the kidneys of one male from both treated groups.

Long-term Toxicity (30 days and 13 weeks)

The long-term toxicity of cefotaxime was investigated in 3 groups of 17 rats each of both sexes receiving single daily subcutaneous doses of 300, 1000 and 3000 mg/kg for 1 month. At the lowest dose, cefotaxime caused slight dilation of the cecum and very slight inflammatory changes in the subcutaneous tissue at the sites of injection. In the 1000 mg/kg/day group, dilation of the cecum, inflammatory changes at the injection sites accompanied by histopathological change of the spleen and bone marrow, and tubular changes of the kidneys were observed. These changes were seen infrequently and had a slight degree of severity. In rats treated with the highest concentration of 3000 mg/kg/day, there was dilation of the cecum and extensive subcutaneous hemorrhage at

the injection sites. Secondary to the hemorrhagic and inflammatory changes were an increase in neutrophils and a decrease in RBC count, hematocrit and hemoglobin values, lymphoid hyperplasia of the spleen and increased erythropoiesis in the bone marrow. Correspondingly, spleen weights were increased. After 2 weeks of reversal of treatment, these changes were reduced. Fragments of epithelial cells and amorphous salts were observed in urine sediment. Kidney weights were increased in all females. The kidneys had dilated tubules and eosinopositive granular material in the proximal tubule epithelial cells.

In another study, cefotaxime was given under the same conditions to 3 groups of 15 rats each of both sexes at dose levels of 400, 800 and 1600 mg/kg/day for 13 weeks. Different parameters such as urinalysis, hematology, clinical chemistry and post-mortem examination of macroscopic and microscopic examination of lesions showed similar results as observed above.

The intravenous toxicity of cefotaxime was studied in 4 groups of 15 male and 15 female rats who received 0 to 1000 mg/kg/day in the caudal tail vein for 1 month. Except for some of the animals given the highest dose of 1000 mg/kg who squeaked, tried to escape from the drug injection and developed inflammatory changes at the sites of injection, cefotaxime administration caused neither remarkable change in behavior nor fatal cases in any of the drug treated groups. In the hematological tests, plasma recalcification time and prothrombin time were slightly shorter and the platelet count was decreased to a slight degree in the high dose rats in both sexes although not statistically significant. Autopsies of both males and females exhibited dose-dependent dilation of the cecum with retention of contents.

In some of these cases, hemorrhage, inflammatory changes and attenuation of the wall of the cecum were observed microscopically. There were no spleen abnormalities except that lymphoid hyperplasia was observed in all of the drug treated and control groups. However, in another study done under the same conditions dose-related increases in spleen weights were reported. Histologically, the spleens of some of the animals treated with 100 or 300 mg/kg for 30 days were observed to have a moderate degree of white pulp activation.

The long-term intravenous and intramuscular toxicity of cefotaxime was further investigated in groups of 3 male and 3 female beagle dogs treated with doses ranging from 0 to 300 mg/kg/day for 30 consecutive days. When injected intravenously at 300 mg/kg/day, all dogs salivated profusely and showed a clear nasal discharge. In dogs, the weight of the kidneys was increased. One male and all 3 females of the high dose group had hyperemia with slight edema in the cortical areas of the kidneys. Hemorrhage and hemorrhagic residues were seen at the site of injection. Cefotaxime when given intramuscularly at doses of 72 or 179 mg/kg/day caused pain at the site of injection in a few animals. The intensity of the lesions at the site of injection and the frequency of their occurrences appear to be dose-related. Diarrhea was also noted in several dogs treated with cefotaxime at these two doses.

In another study, cefotaxime was injected intravenously to beagle dogs - 3 animals/sex/group - at doses of 500, 1000 and 1500 mg/kg/day for 13 weeks. As observed earlier, the mid- and highdose dogs salivated during the injection of the compound and had occasionally soft stools. At week 11, one female treated with 1500 mg/kg/day showed signs of anemia; palpation suggested a hemorrhagic disorder in the area of the spleen. The hemograms were consistent with an acute hemorrhage. Renal lesions graded minimal to slight were reported to occur in all drug groups but not in all dogs. Some dogs treated with 1000 and 1500 mg/kg/day showed a slight increase of extra medullary hematopoiesis in the spleens. In prescapular lymph nodes, an increase of focal lymphadenitis and erythrophagocytosis were seen in treated dogs. In male dogs, the lymph nodes showed increased activity of the germinal centers and hyperplasia of medullary plasmacytes.

Groups of 4 male and 4 female beagle pups further received subcutaneous injections of cefotaxime at doses of 0 to 1500 mg/kg/day for 30 consecutive days. A dose-related response to pain, both in intensity and duration was observed. Post-mortem examinations revealed hemorrhage and edema at the injection site.

The long-term toxicity of cefotaxime was compared with that of cephaloridine and cephalothin in 6 groups of 3 male and 3 female rabbits treated intravenously, daily for 30 days.

Cefotaxime doses ranged from 0 to 120 mg/kg/day while cephaloridine and cephalothin were given at the daily dose of 120 mg/kg/day. In the cefotaxime group, one rabbit died at 30 mg/kg, three at 60 mg/kg and two at 120 mg/kg. Two rabbits died in the cephaloridine and one in the cephalothin group. Diarrhea was observed in all treated groups. Neither cefotaxime nor cephalothin produced microscopic lesions. Two rabbits given cephaloridine had myocardial necrosis.

Chronic Toxicity

The chronic toxicity of cefotaxime was investigated in rats and dogs over a period of 6 months.

Groups of 25 male and 25 female rats received subcutaneous injections of cefotaxime at doses of 0, 40, 100 and 250 mg/kg/day 7 days a week for 26 weeks. On the whole, chronic administration of cefotaxime for 6 months was well tolerated. Rats treated with 250 mg/kg/day showed a slight and transient depression of body weight gain in both males and females. Local tolerance reactions were noted in animals treated with 100 or 250 mg/kg from the third week to the end of the study. Microscopic examination of these tissues taken from the high dose animals showed marked inflammatory subcutaneous sclerosis often accompanied by the presence of hematomas and muscular atrophy.

One male treated with 250 mg/kg had to be killed after 4 months of treatment because of sudden deterioration of its general condition. Histopathological examination revealed

ulceration of the stomach mucosa, congestion of the liver and a subcapsular interstitial scar in the kidney. Otherwise, there was no mortality in any of the groups.

The chronic toxicity of cefotaxime was further examined in dogs (4 animals/sex/group) when given intramuscularly at doses of 0, 40, 100 or 250 mg/kg/day 7 days a week for 26 weeks.

Reaction of pain was observed in all dogs in the highest dosage groups immediately following the injection. Histopathologic lesions at the injection sites showed a dose-related inflammatory response. No dogs died during the treatment. Numerous variations in hematology, coagulation and biochemical values were observed in individual animals. The variations were, however, within normal limits and the distribution in the two groups did not suggest an effect of the compound.

Fertility and Reproduction

Cefotaxime was administered intravenously at doses of 0, 100, 400 and 2000 mg/kg/day to groups of 22-24 male mice for 9 weeks prior to and including mating and to groups of 23-24 females for 2 weeks before mating and through Day 6 of gestation. Under these conditions the copulation and conception rate in the treated groups were comparable to those in the control.

Treated groups did not differ from controls in the number of corpora lutea, resorptions and live and dead fetuses. Body and placental weights, crown-rump lengths and sex ratio of the live fetuses from treated females corresponded with those found in the control group. The live fetuses at each dosage level showed no external, visceral or skeletal abnormalities considered to be related to the administration of the compound.

In a similar study done in rats with 20-25 animals/sex/group, cefotaxime at doses of 0, 40, 100 or 250 mg/ kg/day did not alter the sexual behavior and reproductive function of the parents (F0) or of the F1 offspring.

Peri and Postnatal Behavior

Two perinatal and postnatal studies were conduced with cefotaxime in 104 mated rats. In the first study, dosage levels of 150, 300 and 600 mg/kg were administered by intravenous injection twice daily at a minimum of 6 hours apart beginning on the 15th day of gestation and continuing throughout gestation and lactation.

No effects attributable to treatment with cefotaxime were observed on maternal appearance, behavior, survival, fertility, length of gestation or number of live and non-viable pups. Maternal body weights were comparable during the gestation and lactation periods for cefotaxime-treated groups and the control groups with the exception of slightly reduced body weight gains in the 1200 mg/kg/day treated rats during the first 5 days of treatment and Days 12 through 21 of lactation. Reduced mean pup body weights were noted in this group at birth through weaning. No other biologically meaningful

effects were noted from intravenous injections of cefotaxime at 1200 mg/kg/day or less during the later portion of gestation through weaning.

Under a similar protocol, cefotaxime was given intramuscularly at doses of 0, 40, 100 or 250 mg/kg/day. At these doses, no effects of cefotaxime were observed on the peri and postnatal behaviour of the mothers and the general condition and viability of the offspring.

Teratology

Cefotaxime was given intravenously at doses of 300, 600 and 1200 mg/kg/day to groups of 20-23 pregnant mice, and to pregnant rats intravenously (300, 600 and 1200 mg/kg/day) or intramuscularly (40, 95 or 210 mg/kg/day) from Day 6 through Day 15 or 18 of gestation. No findings indicative of a compound-related teratogenic effect were noted in any of the fetuses at necropsy or during the visceral and skeletal examinations. On the basis of these studies, cefotaxime was not considered embryotoxic or teratogenic when administered parenterally in mice and rats at levels up to 1200 mg/kg/day.

The teratogenic effect of cefotaxime was further studied in pregnant rabbits treated intramuscularly with daily doses of 25, 50 and 90 mg/kg for sequential periods of 4-7 days throughout the phase of embryogenesis. Maternal toxicity and embryotoxicity were recorded in groups dosed with 50 mg/kg and higher. Lower fetal weights were recorded in the groups dosed with 90 mg/kg/day and a few malformations or simple abnormalities appeared in all groups, including the controls. Rabbits are particularly sensitive to cephalosporins in general and are therefore inappropriate to test the reproductive and teratogenic effects of these compounds.

Mutagenicity

Possible mutagenic effects of cefotaxime were investigated using the micronucleus test in mice and the Ames test in bacterial strains. No mutagenicity could be attributed to cefotaxime using these two standard methods.

Carcinogenicity

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of cefotaxime.

Nephrotoxicity

The potential nephrotoxicity of cefotaxime was compared with that of cephaloridine and cephalothin in rabbits (2 males and 2 females per group) when given daily intramuscularly at doses of 220, 200 and 190 mg/kg, respectively for 7 consecutive days. The 3 antibiotics induced emaciation in some animals and death of one rabbit in each treated group. Only in the animals treated with cephaloridine did the histological

examination reveal tubular necrosis. No morphological substance-induced organ changes were detected in the rabbits treated with cefotaxime or cephalothin.

A potent diuretic agent, furosemide, has been shown to enhance the nephrotoxicity of cephaloridine in animals. Studies were conducted in mice and rats to evaluate the effect of a single parenteral dose of 20 mg/kg furosemide given 15 minutes before the injection of cefotaxime on renal function and renal histology. Cefotaxime concentrations were 2000 and 4000 mg/kg in mice and 2500 and 5000 mg/kg in rats. Microscopic examination of the kidneys revealed some dilated tubules in the cortex and the medulla and some hyalin casts in control and all treated groups regardless of furosemide administration.

The nephrotoxicity of the combined administration of cefotaxime (1000 mg/kg/day i.v.) with gentamicin (30 mg/kg/day i.m.) or furosemide (100 mg/kg/day p.o.) was studied in groups of 16 female rats for 28 consecutive days. Single treatments with each drug, alone or in combination with cefotaxime produced neither death nor abnormalities in behavior or appearance, nor did they affect body weight gain and food consumption. Main histopathological findings were: occurrence of eosinpositive material (slight degeneration) in the epithelial cells of the proximal convoluted tubules, considered to be due to a change in the lysosomes, in the group given cefotaxime alone; interstitial inflammation and slight focal necrosis in the proximal tubules in rats injected only with gentamicin; and calcification of the distal convoluted tubules in animals administered furosemide alone. The concurrent administration of cefotaxime with gentamicin or furosemide produced combinations of the above described changes, each of which was not enhanced either in incidence or in extent.

Tolerance studies

The local intravenous tolerance of cefotaxime was investigated in rats and dogs. Rats (15 animals/sex/ group) injected intravenously in the caudal vein daily for 30 days with cefotaxime at doses of 125, 500 and 1000 mg/kg in physiological saline and those being used as controls showed a slight but dose-related degeneration of the epidermis, hemorrhage, perifollicular edema and inflammatory cell infiltration of the dermis and subcutaneous tissues. In dogs, however, the intravenous tolerance was not dose-related and did not differ from that of controls. The minimal lesions observed at the injection sites following a 13 week administration of 0 to 1500 mg/kg/day were interpreted as being caused by the trauma of repeated i.v. injections rather than by cefotaxime itself.

The local intramuscular tolerance of cefotaxime was compared with that of cephaloridine in 2 groups of 10 male rats given a single injection of 100 mcg per rat. Cefotaxime caused only minor and transient local tissue damage - necrotic areas, fragmentation of muscle fibers and inflammation - while similar doses of cephaloridine produced more severe and persistent damage.

The local intramuscular tolerance of 1000 mg/kg cefotaxime was further investigated in groups of 3 male and 3 female rabbits when given in a single injection with or without

1% lidocaine. One rabbit of each group died of diarrhea and no substance-induced organ lesions were observed at the end of a 3 week follow-up period. This study showed that the tolerance to 1000 mg/kg cefotaxime in rabbits was not affected by administration in a 1% lidocaine solution.

The sub-occipital tolerance of cefotaxime was also compared with that of cephaloridine when given as a single sub-occipital injection to groups of 10 rats at doses ranging from 2.5 to 19 mg/kg. Doses of 2.5 and 5 mg/kg cephaloridine and 19 mg/kg cefotaxime caused prostration, respiratory impairment, hyperventilation, tremors, and convulsions. At each of these dosage levels, 40-60% of animals per group died a few minutes following the injections. Doses of 2.5, 5 and 9.5 mg/kg cefotaxime and 1.25 mg/kg cephaloridine were satisfactorily tolerated.

To investigate the intrathecal tolerance, 50 mg cefotaxime was administered as a single dose through the foramen magnum to 2 male and 2 female beagles. All dogs treated with cefotaxime showed slight tetanoid convulsions for about 1 hour towards the end of anesthesia. Histological examinations did not reveal any compound-related impairment of the CNS, the spinal cord and meninges.

The renal tolerance of cefotaxime was further compared with that of cephaloridine in groups of 2 male and 2 female beagle dogs when given as a single 1000 mg/kg i.v. injection. In contrast to cephaloridine, cefotaxime caused only a slight and transient reduction of PAH clearance. Creatinine clearance remained unchanged and the urinary output was not disturbed at any time.

Combination LD_{50} Study

The toxicity of combinations of cefotaxime and gentamicin when studied in rats did not appear very different from the toxicities exhibited by the individual components.

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