CEFOTAXIME

Cefotaxime sodium, powder for injection, equivalent to Cefotaxime 500 mg, 1 g and 2 g

PRESENTATION

Cefotaxime is a white to slightly yellowish powder, which, when dissolved in Water for Injections B.P., forms a straw coloured solution given by intravenous or intramuscular administration.

Each Cefotaxime 500 mg vial contains sterile cefotaxime sodium equivalent to cefotaxime 500 mg.
Each Cefotaxime 1 g vial contains sterile cefotaxime sodium equivalent to cefotaxime 1 g.
Each Cefotaxime 2 g vial contains sterile cefotaxime sodium equivalent to cefotaxime 2 g.

Variations in the intensity of colour of the freshly prepared solution do not indicate change in potency or safety.

USES

Actions

Cefotaxime is a semi-synthetic broad-spectrum bactericidal cephalosporin antibiotic. It is a other β-lactam antibiotic whose mode of action is inhibition of bacterial cell wall synthesis. Cefotaxime is exceptionally active *in vitro* against Gram-negative organisms sensitive or resistant to first or second generation cephalosporins. It is similar to other cephalosporins in activity against Gram-positive bacteria.

Susceptibility Data
Dilution or diffusion techniques – either quantitative minimum inhibitory concentration (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method e.g. NCCLS. Standardised susceptibility test procedures require the use of laboratory control micro-organisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the microbial compound in the blood reaches the concentrations usually achievable. Some strains of *Pseudomonas aeruginosa* (approximately 25%) and *Bacteroides* (approximately 43%) have *in vitro* MIC <16 mg/L.A report of "Intermediate" indicates that the results should be considered equivocal, and if the micro-organism 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 the drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation.A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable and other other should be selected. Cefotaxime shows resistance to many β-lactamases (penicillinases and cephalosporinases)
The following table describes the spectrum of cefotaxime activity under *in* vitro conditions at plasma concentrations achieved at the recommended doses.

Pathogen Group	**Susceptible Micro-organisms**	**Resistant Micro-organisms**

Gram Positive	Staphylococci, including penicillinase-producing strains (15% non-susceptible) Methicillin susceptible *Staph.Aureus* *Strep. pyogenes* *Strep. pneumoniae*	Methicillin-resistant Staphylococci *Clostridium perfringens* *Enterococcus faecalis*
Gram Negative	Various strains of Klebsiella, Enterobacter and Serratia *Haemophilus influenzae* (0.3% non-susceptible) Neisseria species Gonococcus (including penicillin-resistant strains) Proteus genera (including *P. vulgaris,* *P. rettgeri, P. mirabilis* (2.6% non-susceptible) *and P. morganii*) *E. coli* (0.1% non-susceptible) (including many gentamicin and cephalothin-resistant strains)	*Enterobacter cloacae* (39.6% non-susceptible

There is *in vitro* evidence of synergy between cefotaxime and aminoglycoside antibiotics e.g. gentamicin against some species of Gram-negative bacteria including some strains of *Serratia marcescens, E, coli, Pseudomonas aeruginosa,* Klebsiella sp., *P.mirabilis* and *Staph.aureus.*. .

Pharmacokinetics

AbsorptionCefotaxime is administered by intramuscular and intravenous injection but due to poor absorption it is not suitable for oral administration. After administration of a 1 gram dose, the mean plasma concentration is approximately 20 mg/L (intramuscular, t_{max} = 30 minutes), 102 mg/L (intravenous over 2-5 minutes), 27.9 mg/L (30 minute IV infusion).

Single muscular injections of 500 mg and 1 g cefotaxime to normal volunteers gave post-dose mean peak plasma levels of 11.7 and 20.5 mg/L at 30 minutes and 1.4 and 3.36 mg/L at 4 hours respectively. Proportionally higher plasma levels are seen with 2 g doses. Following 8 hourly 500 mg I.M. injections over 10 days in 15 normal volunteers, pre-dose plasma levels of 0.08 to 0.55 mg/L and post-dose levels of 9.2 to 11.9 mg/L were recorded.

Mean plasma levels (mg/L) obtained following I.V. bolus injections of cefotaxime 500 mg, 1 g and 2 g administered over 5 minutes to normal volunteers were

Dose	**Cmax**	**1 hour post-dose**	**4 hours post-dose**
500 mg	38	9.7	1.0
1 g	102	20	1.9
2 g	214	40	3.3

When administered as an infusion over 30 minutes, a 1 g dose gives plasma levels of 27.9, 8.81 and 2.62 mg/L at 30, 90 and 210 minutes post-dose respectively. Steady state trough levels of 1.33 mg/L are obtained following 6 hourly 1 g infusions over 14 days. In patients with normal renal function, there is no evidence of cefotaxime accumulation following multiple I.V. or I.M. dosing. Following administration via I.M., I.V. bolus and I.V. infusion, the mean elimination half lives were1.45, 1.06 amd 1.13 hours respectively.

Distribution
Cefotaxime is 32-44% bound to plasma protein with the desacetyl metabolite displaying half of this binding, High renal clearance indicates that cefotaxime has a low binding affinity.Urinary concentrations vary with the route of administration with 1 g bolus I.V., infusion I.V. and I.M injections giving peak levels 4 hours post-dose of 1309, 599 and 903 mg/L respectively.

Concentrations of Cefotaxime in the CSF are considerably lower than plasma. When meninges are inflamed, cefotaxime displays significant diffusion into the CSF with concentrations obtained following I.V. doses of 1-2 g being above the MIC for susceptible organisms (i.e. those with MIC <0.5 mg/L)

Metabolism
Cefotaxime is rapidly deacetylated in the body with measurable plasma levels obtained 5 minutes post-dose. The desacetyl metabolite of cefotaxime is detectable in blood and urin; after a single I.V. dose of 15 mg.kg to normal volunteers the mean peak serum levels after 10 minutes for cefotaxime and desacetylcefotaxime were 100 µg/mL and 5 µg/mL respectively. Desacetylcefotaxime has a similar antimicrobial spectrum to cefotaxime *in vitro*, but is generally less active ranging from twice as active to 32 times less active depending depon the microbial species. Desacetylcefotaxime undergoes further metabolisation to a microbially inactive open lactone moiety.

Approximately 20-36% of drug is excreted unchanged in the urine, with 15-25 % as the desacetyl metabolite and 20-25% as the open lactone moiety.. 85-90% of the administered dose is recovered in the urine while the faeces accounted for 7-9.5% of the recovery total. 70-80% of the administered dose is recovered in the first 4 hours after administration.

Elimination
Cefotaxime has a high renal clearance. There is no significant evidence of accumulation after repetitive dosing. Following I.M. administration of a 1 g dose, the mean plasma clearance is 318 mL/min/1.73 m^2. In patients with normal renal function, the elimination half-life of Cefotaxime is 0.7-1.3 hours whilst desacetylcefotaxime is approximately 2 hours. Mean elimination half-life is 1.45 hour (I.M.), 1.06 hour (rapid I.V.) and 1.13 hour (30 minute I.V. infusion).

Special patient groups
IN patients with impaired renal function, the terminal half-life of desacetylcefotaxime is prolonged to a greater extent than that of cefotaxime (in patients with creatinine clearance of 5-10 mL/min the terminal half-life of cefotaxime is 3.5 hours c.f. 13.0 hours for desacetylcefotaxime).
Neonatal pharmacokinetics are influenced by birth weight with the elimination half-life being prolonged at lower birth weights. Following a ten minute infusion of 50mg/kg, the mean concentrations shown in the table below were obtained.

Table: Pharmacokinetics following 10 minute infusions of 50mg/kg in low birthweight neonates

Mean birthweight	Peak plasma Conc.	Plasma Conc. 2 hours post-dose	Plasma Conc. 6 hours post-dose	Elimination half-life
1100 g	115.9 mg/L	69.8 mg/L	34.4 mg/L	4.63 hours
2500 g	132.7 mg/L	78.9 mg/L	38.1 mg/L	3.37 hours

Indications

Cefotaxime is indicated in the treatment of the following infections either before the infecting organism has been identified or when caused by bacteria of established sensitivity.

- Septicaemia.
- Respiratory tract infections: acute and chronic bronchitis, bacterial pneumonia, infected bronchiectasis, lung abscess and post-operative chest infections.
- Urinary tract infections: acute and chronic pyelonephritis, cystitis and asymptomatic bacteriuria.
- Soft tissue infections: cellulitis, peritonitis and wound infections.
- Bone and joint infections: osteomyelitis, septic arthritis.
- Obstetric and gynaecological infections: pelvic inflammatory disease.
- Gonorrhoea: particularly if penicillin-resistant.
- Other bacterial infections: meningitis and other sensitive infections suitable for parenteral antibiotic therapy.

The administration of cefotaxime prophylactically may reduce the incidence of certain post-operative infections in patients undergoing surgical procedures that are classified as contaminated or potentially contaminated or in clean operations where infections would have serious effects. Protection is best ensured by achieving adequate local tissue concentrations at the time contamination is likely to occur. Cefotaxime should therefore be administered immediately prior to surgery and if necessary continued in the immediate post-operative period. Administration should usually be stopped within 24 hours since continuing use of any antibiotic in the majority of surgical procedures does not reduce the incidence of subsequent infections.

DOSAGE AND ADMINISTRATION

Cefotaxime should be administered only by the intramuscular or intravenous routes.The dosage route of administration and dosage interval will depend on the site and severity of the infection, sensitivity of the pathogens and condition of the patient.

Cefotaxime has been used with other β-lactam antibiotics e.g. carbenicillin in the treatment of neutropenic patients.

Cefotaxime may also be administered with metronidazole in the treatment of mixed infections caused by anaerobic and aerobic organisms.

The length of treatment depends upon the patient's response. Therapy should be continued for at least 3 days after body temperature normalisation.

Adults

For urinary tract infections:
The recommended dose is 2 g daily in two divided doses.

Other Infections:
For other infections the minimum recommended dosage is 2 g daily in divided doses. This dosage may be increased to 3, 4 or 6 g daily according to the severity of the infection, sensitivity of causative organisms and condition of the patient.

For prevention of post-operative infection:
Cefotaxime should be administered immediately prior to surgery. A single dose of 1 g is suitable for most procedures. For procedures longer than 4 hours a dose of 2 g is recommended. A single 1 g dose in combination with 500 mg metrionidazole is effective in colorectal surgery.

For the treatment of gonorrhoea:
Uncomplicated gonorrhoea due to β-lactamase producing organisms: One single intramuscular dose of 1g.
Uncomplicated gonorrhoea due to β-lactamase producing organisms: One single intramuscular dose of 500 mg of Cefotaxime plus probenecid, 1 g orally, given 1 hour earlier.

Paediatrics

Neonatal meningitis: The following dosage schedule is recommended:
0-1 week of age – 50 mg/kg I.V. every 12 hours
1-4 weeks of age – 50 mg/kg I.V. every 8 hours.

Children

The usual dosage range is 100-150 mg/kg/day in 3 to 4 divided doses. However, in very severe infections doses of up to 200 mg/kg/day may be required.

Impaired renal function

Because of extra-renal elimination, it is only necessary to reduce the dosage of Cefotaxime in severe renal failure (creatinine clearance <10 mL/min). After an initial loading dose of 1 g, the daily dose should be halved without change in the frequency of dosing, e.g. 1 g 12 hourly becomes 500 mg 12 hourly, 1 g 8 hourly becomes 500 mg 8 hourly, 2 g 8 hourly becomes 1 g 8 hourly.

Elderly

There are no specific dose recommendations for the elderly.

Intravenous and intramuscular injection

Dissolve Cefotaxime in Water for Injections B.P. as shown below. Shake well until dissolved and then withdraw the entire contents of the vial into the syringe and use immediately.

Vial Size	Volume of Water for Injections to be added	Final Volume
500mg 1g 2g	2 mL 4 mL 10 mL	2.3 mL 4.5 mL 11.2 mL

Intravenous infusion

Cefotaxime may be administered by intravenous infusion. 1-2 g are dissolved in 40-100 mL of Water for Injections B.P. or in the infusion fluids listed under Pharmaceutical Precautions. The prepared infusion should be administered over 20-60 minutes.

Contraindications

Cefotaxime is contraindicated in patients who have had previous experience of a major allergy or anaphylaxis to a cephalosporin or penicillin.

Cefotaxime is also contraindicated to patients who have experienced hypersensitivity to any components of the product (See the section of Further Information).

Lidocaine should not be used as the diluent for cefotaxime when administered the intravenous route of administration is to be used. Nor should lidocaine be used for patients with a history of hypersensitivity to lidocaine or other amide type local anaesthetics, patients with non-paced heart block, patients with severe heart failure or for infants aged less than 30 months.

Warnings and precautions

Cefotaxime should be given with caution to patients who have experienced symptoms of allergy associated with a cephalosporin or penicillin.

Pseudomembranous colitis and delaying peristalsis-Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It is important to consider this diagnosis in patients who develop diarrhoea in association with the use of Cefotaxime. Drugs which delay peristalsis may prolong and/or worsen the condition and should not be used.

Prothrombin time-Prolonged prothrombin time may occur in patients receiving protracted antimicrobial therapy.

Ability to drive or operate machinery-During treatment with cefotaxime undesirable effects may occur (e.g. dizziness), which may influence the ability to drive and use machines. Patients should be cautious when driving or operating machinery.

Hypersensitivity Reactions:

Patients should be asked about allergies and particularly hypersensitivity to β-lactam antibiotics.

Occurrence of a hypersensitivity reaction requires treatment being stopped.
The use of Cefotaxime is strictly contraindicated in subjects with a previous history of immediate type hypersensitivity to cephalosporins. In any doubt, it is essential that a physician be present at the time of the first administration, in order to treat any possible anaphylactic reaction. As there is cross allergy between penicillins and cephalosporins in 5 to 10% of cases, use of the latter should be undertaken with extreme care in penicillin sensitive subjects; careful monitoring is necessary from the first administration. Hypersensitivity reactions (anaphylaxis) occurring with these two antibiotic families may be serious or even fatal.

In the case of anaphylactic shock immediate counter measures are required. At the first signs of hypersensitivity e.g. cutaneous reactions such as skin rashes or urticarial, headache, nausea, restlessness, cefotaxime therapy should be discontinued. In cases of severe hypersensitivity reactions or analphylactic reactions, emergency treatment should be initiated e.g. administration of adrenaline orepinephrine and/or glucocorticoids. Depebding upon the clinical severity additional therapeutic measures may be required e.g. artificial breathing, application of histamine-receptor antagonists. In cases of respiratory collapse, Resuscitation must be started according to the current guidelines.

Serious bullous reactions:

Cases of serious bullous skin reactions like Stevens-Johnson syndrome to toxic epidermal necrolysis have been reported with cefotaxime (see Adverse Effects). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Pseudomembranous Colitis:

If severe or persistent diarrhoea has been observed during treatment, or in the initial weeks following treatment, it may be indicative of *C. difficile* associated disease. The most severe form of this disease is pseudomembranous colitis.*C. difficile associated disease* can be diagnosed by faecal screening for the pathogen and its cytotoxin. Confimation of the pseudomembranous colitis diagnosis should be made by endoscopic and/or histologic examination

If pseudomembranous colitis is suspected cefotaxime should be stopped immediately and appropriate specific antibiotic therapy started without delay e.g. oral antibacterial agents effective against *C. difficile. Fluids, electrolyte and protein replacement should be provided as required.*. Drugs that delay peristalsis e.g. opiates and diphenoxylate with atropine may prolon and/or worsen the condition and should not be used during cefotaxime therapy, particularly in bed patients.

Renal Insufficiency:

The dosage should be modified according to the creatinine clearance or the serum creatinine where measurement of the former is not possible (see Dosage and Administration)

Cardiac arrhythmia:

Potentially life-threatening arrhythmia has been reported in a few few patients receiving rapid I.V. cefotaxime administration via a central venous catheter. Cefotaxime given by intermittent I.V. injection should be administered over a 3-5 minutes period.

Hepatic and Renal Disease:

Transient rises in hepatic enzymes, urea and creatinine have been seen in some patients given cefotaxime. Careful monitoring of hepatic and renal function is advised where any dysfunction exists. For dosage adjustment in moderate and sevre renal impairment refer to Dosage and Administration.

Severe hepatic insufficiency or reduced hepatic blood flow may inhibit the metabolism of lidocaine causing accumulation and toxicity. In these cases repeated use of lidocaine should be avoided,

Care should be taken to monitor renal finctionduring treatment with other antibiotics that are potentially nephrotoxic e.g. aminoglycosides or potent diuretics e.g. furosemide.

Joint Prescription with other Medicaments:

Care should be taken to monitor renal function during treatment with other antibiotics that are potentially nephrotoxic (notably aminoglycosies) or potent diuretics.

Pregnancy:

Category B1

Although studies in animals have not shown an adverse effect on the developing foetus, the safety of cefotaxime in human pregnancy has not been established. Cefotaxime crosses the placenta and consequently, cefotaxime should not be administered during pregnancy especially during the first trimester, without carefully weighing the expected benefits against the possible risks.

Lactation:

Cefotaxime passes into breast milk and may be present at levels corresponding to approximately 0.3% of the maternal dose. Cephalosporins are considered to be compatible

with breast feeding although there are theorectical risks of alterations to infant bowel flora and allergic sensitisation..

Effects on ability to drive and use machines

During the treatment with cefotaxime, undesirable effects may occur (e.g. dizziness), which my influence the ability to drive and use machine. Patients should be cautions when driving or operating machinery.

Adverse effects

Hypersensitivity:

Rash, pruritus, fever, and less frequently: urticaria, anaphylactic reactions.

Gastrointestinal:

Nausea, vomiting, abdominal pain, diarrhoea, candidias, rarely pseudomembranous colitis (see Warnings and Precautions). Diarrhoea may sometimes be a symptom of entercolitis which may be accompanied by blood stools

Hepatic:

Moderate regressive increase in transaminases (ALT, AST) and/or alkaline phosphatases and/or bilirubin. These laboratory abnormalities which could also be attributed to the infection amy rarely exceed twice the upper limit of the normal range and elict a pattern of liver damage, usually cholestatic and most often asympromatic. Hepatitis.

Haematological:

As with all β-lactam antibiotics, neutropenia and more rarely agranulocytosis may occur, particularly during prolonged treatment. The white cell count should be monitored where treatment lasts more than 10 days and treatment stopped in the event of neutropenia.

Some cases of eosinophilia and thrombocytopenia, rapidly reversible on stopping treatment, have been reported. Rare cases of haemolytic anaemia have also been reported.

Renal Toxicity:

Changes in renal function have been observed with antibiotics of the same group, particularly when co-prescribed with aminoglycosides and/or potent diuretics.

As with some other cephalosporins, rare cases of interstitial nephritis have been reported in patients treated with cefotaxime.

Administration of high doses of β-lactam antibiotics, particularly in patients with renal insufficiency may result in encephalopathy (impairment of consciousness, abnormal movements and convulsions).

Other:

Fever, shivering, headache, dizziness, joint pain and superinfection.
*Superinfection:*As with other antibiotics, the use of cefotaxime, 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.

Phlebitis at the site of injection and cutaneous vasculitis may occur. Pain, phlebitis and tenderness have been reported in approximately 4.8% of cases. Inflammatory reactions at the injection site have also been reported.

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 treatment of borreliosis – skin rash, itching, leucopenia, increase in liver enzymes, difficulty in breathing, joint discomfort. These manifestations are consistent with the symptoms of the underlying disease for which the patient is being treated.

Interactions

Medicine Interactions:

Cefotaxime exhibits an additive microbiological effect with gentamicin. However, because of physical incompatibility, cefotaxime should not be mixed with an aminoglycoside antibiotic into a single preparation.

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

Cefotaxime may potentiate the renal toxicity of nephrotoxic drugs

Cefotaxime may decrease the efficacy of oral contraceptives and additional contraceptive methods should be used.

Cefotaxime should not be combined with bacteriostatic antibiotics e.g. tetracycline, erythromycin and chloramphenicol as an antagonistic effect is possible.

Interactions with Laboratory Tests:

Appearance of a positive Coombs' test may be seen during treatment with cefotaxime.

In urine glucose testing with non-specific reducing agents, a false positive reaction may occur in patients treated with cefotaxime. This phenomenon is not seen when a glucose-oxidase specific method is used.

Overdosage

Animal evidence suggests that cefotaxime has a very low toxic potential. LD50 studies in mice and rats administered cefotaxime intravenously have shown no mortality or signs of intoxication up to doses of 716 mg/kg and 2000 mg/kg, respectively. As with all cephalosporins, there is a risk of reversible encephalopathy. Serum levels of cefotaxime may be reduced by peritoneal dialysis or haemodialysis.

Pharmaceutical precautions

The dry powder in vials should be stored below 25 ^{O}C and protected from light. The pH of the formulated material is 4.5 to 6.5. Whilst it is preferable to use only freshly prepared solutions for both intravenous and intramuscular injection, cefotaxime is compatible with several commonly used intravenous fluids and will retain satisfactory potency for up to 24 hours when stored under refrigeration (2-8 ºC) in the following solutions:

- Water for Injections B.P.
- 0.9% Sodium Chloride B.P.
- 5% Dextrose Injection B.P.
- 5% Dextrose and 0.9% Sodium Chloride Injection B.P.
- Compound Sodium Lactate Injection B.P (Ringer-Lactate Injection)5% Metronidazole solution
- Dextran 40 in 0.9% Sodium Chloride Solution
- Dextran 40 in 5% Dextrose solution
- 1% Lidocaine – for I.M. administration only.

After 24 hours any unused solution should be discarded.

Freshly prepared solutions should be used. Cefotaxime does not contain any anti-microbial preservative. Some increase in colour of prepared solutions may occur on storage. However, provided the recommended storage conditions are observed, this does not indicate change in potency or safety.

Incompatibilities:

Cefotaxime is incompatible with aqueous solutions of sodium bicarbonate and infusion solutions with a pH greater than 7.

Cefotaxime is physically incompatible with aminoglycosides. Where combination therapy is required the drugs should be administered separately and not mixed together as a single preparation.

Medicine classification

Prescription Medicine.

Package quantities

Single vials containing 500 mg or 1 g cefotaxime as cefotaxime sodium (for use by intramuscular or intravenous injection).
Single vials containing 2 g cefotaxime as cefotaxime sodium (for intravenous use only).

Further information

Each gram of cefotaxime contains approximately 48 mg (2.09 mmol) of sodium.

Cefotaxime has been used with other β-lactam antibiotics such as carbenicillin in the treatment of neutropenic patients.

Cefotaxime may also be administered with metronidazole in the treatment of mixed infections caused by anaerobic and aerobic organisms. Cefotaxime usually passes the blood-brain barrier in levels above the MIC of common sensitive pathogens when the meninges are inflamed.

Name and address

AFT Pharmaceuticals Ltd
PO Box 33-203
Takapuna
Auckland

Ph (09) 488 0232
Fax (09) 488 0234
E:mail customer.service@aftpharm.com

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