

CEFOTAXIME

Cefotaxime sodium

PRESENTATION

Vials containing 500mg, 1g or 2g of cefotaxime as cefotaxime sodium.

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

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

USES

Actions

Cefotaxime is a broad-spectrum bactericidal cephalosporin antibiotic. 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 bacterial.

The following organisms have shown *in vitro* sensitivity to Cefotaxime.

Gram-positive:

Staphylococci spp, including coagulase-positive, coagulase-negative and penicillinase-producing strains.

Streptococci spp, including β -haemolytic and other streptococci such as *Streptococcus mitis* (*viridans*), *Streptococcus pneumoniae*. (Many strains of enterococci, e.g. *Streptococcus faecalis*, are relatively resistant).

Clostridium perfringens.

Gram negative:

Escherichia coli,

Haemophilus influenzae including ampicillin-resistant strains,

Klebsiella spp.,

***Proteus* spp. both indole-positive and indole-negative,**

Enterobacter spp.,

Providencia spp.,

Serratia spp.,

Citrobacter spp.,

Neisseria spp, including β -lactamase producing strains of *Neisseria gonorrhoeae*

Salmonella spp. including *Salmonella typhi*, *Shigella* spp.

Cefotaxime has frequently exhibited useful *in vitro* activity against *Pseudomonas* and *Bacteroides* species although some strains of *Bacteroides fragilis* are resistant.

There is *in vitro* evidence of synergy between cefotaxime and aminoglycoside antibiotics such as gentamicin against some species of Gram-negative bacteria including some strains of *Pseudomonas*. No *in vitro* antagonism has been noted. In severe infections caused by *Pseudomonas* spp, the concurrent use of an aminoglycoside antibiotic may be indicated.

Pharmacokinetics

Cefotaxime is administered by intramuscular and intravenous injection. After administration of a 1 gram dose, the mean plasma concentration is approximately 20mg/L (intramuscular, t_{max} = 30 minutes), 102mg/L (intravenous over 2-5 minutes), 40mg/L (30 minute IV infusion). There is no significant evidence of accumulation after repetitive dosing. Mean elimination half life is 1.45 hour (IM), 1.06 hour (rapid IV) and 1.13 hour (30 minute IV infusion).

The desacetyl metabolite of cefotaxime is detectable in blood and urine and is microbiologically active against a similar spectrum of bacteria, but is less active by a factor of 2 to 3. Approximately 20-36% of drug is excreted unchanged in the urine.

Cefotaxime is 32-44% bound to plasma protein and has a high renal clearance. 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. The elimination half-life of Cefotaxime is 0.7-1.3 hours whilst that of the metabolites is approximately 2 hours. Mean peak urinary concentrations obtained after 1 gram administration of Cefotaxime IM, IV and IV infusion at 4 hours were 903 mg/L, 1309 mg/L and 599 mg/L, respectively.

Concentrations of Cefotaxime in the CSF are considerably lower than plasma.

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.

Adults

For urinary tract infections:

The recommended dose is 2g daily in two divided doses.

Other Infections:

For other infections the minimum recommended dosage is 2g daily in divided doses. This dosage may be increased to 3, 4 or 6g 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 1g is suitable for most procedures. For procedures longer than 4 hours a dose of 2g is recommended. A single 1g dose in combination with 500mg metronidazole 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 0.5g of Cefotaxime plus probenecid, 1g orally, given 1 hour earlier.

Paediatrics

Neonatal meningitis: The following dosage schedule is recommended:

0-1 week of age – 50mg/kg IV every 12 hours

1-4 weeks of age – 50mg/kg IV 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 200mg/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 <10ml/min). After an initial loading dose of 1g, the daily dose should be halved without change in the frequency of dosing, e.g. 1g 12 hourly becomes 0.5g 12 hourly, 1g 8 hourly becomes 0.5g 8 hourly, 2g 8 hourly becomes 1g 8 hourly.

Intravenous and intramuscular administration

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
500mg	2 ml
1g	4 ml
2g	10 ml

Intravenous infusion

Cefotaxime may be administered by intravenous infusion. 1-2g are dissolved in 40-100mL 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.

Elderly

No specific recommendations for the elderly.

Contraindications

Known allergy to cephalosporins.

Warnings and precautions

This product should not ordinarily be given to those known to be allergic to penicillin or to cephalosporins especially if they have experienced an allergic or urticarial reaction.

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.

Pseudomembranous Colitis:

Severe or persistent diarrhoea has been observed during treatment, or in the initial weeks following treatment, with various antibiotics. It may be indicative of pseudomembranous colitis, the diagnosis of which is confirmed by colonoscopy. This event, rare with cephalosporins, but possibly fatal, requires that cefotaxime be stopped immediately and appropriate specific antibiotic therapy started without delay (e.g. vancomycin or metronidazole). The administration of drugs favouring faecal stasis is strictly forbidden 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 and/or Renal Insufficiency:

The sodium content of cefotaxime sodium (2.09 mmol/g) should be taken into account.

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:

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. Consequently, cefotaxime should not be administered during pregnancy especially during the first trimester, without carefully weighing the expected benefits against the possible risks.

Lactation:

As cefotaxime passes into breast milk either breast feeding or treatment of the mother should be stopped.

Adverse effects

Hypersensitivity:

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

Gastrointestinal:

Nausea, vomiting, abdominal pain, diarrhoea, rarely pseudomembranous colitis (see Warnings and Precautions)

Hepatic:

Moderate regressive increase in transaminases (ALT, AST) and/or alkaline phosphatases.

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:

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. Inflammatory reactions at the IV or IM injection site.

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.

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 716mg/kg and 2000mg/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°C and protected from light. The pH of the formulated material is 4.5 to 6.5. Raising the pH (as by addition of strong base) will result in an intense yellow colour and possible degradation.

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 refrigerated in the following:

Water for Injections B.P.
Sodium Chloride Injection B.P.
5% Dextrose Injection B.P.
Dextrose and Sodium Chloride Injection B.P.
Compound Sodium Lactate Injection B.P.
(Ringer-Lactate Injection).

After 24 hours any unused solution should be discarded.

Cefotaxime is also compatible with 1% lignocaine. Freshly prepared solutions should be used. 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.

Medicine classification

Prescription Medicine.

Package quantities

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

Further information

Each gram of cefotaxime contains approximately 48 mg (2.09mmol) 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 separately 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. The laboratory abbreviation for cefotaxime is CTX.

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

Date of preparation

May 1999