CEFOTAXIME FOR INJECTION USP 1g

1. Name of the medicinal product

Cefotaxime for Injection USP 1g

2. Qualitative and quantitative composition

Each vial Contains:

Cefotaxime Sodium USP Equivalent to Cefotaxime ……1 g

3. Pharmaceutical form

Powder for injection or infusion.

Off white to pale yellow crystalline powder contained in 10 ml clear vials plugged with Grey butylrubber plug with blue colour Flip-off Seal.

4. Clinical particulars

4.1 Indications

Cefotaxime is indicated for the treatment of the following severe infections when known or thought very likely to be due to bacteria that are susceptible to cefotaxime:

- Bacterial pneumonia; cefotaxime is not active against bacteria that cause atypical pneumonia or against several other bacterial species that may cause pneumonia, including P. aeruginosa.
- Complicated infections of the kidneys and upper urinary tract.
- Severe infections of the skin and soft tissue
- Genital infections caused by gonococci, particularly when penicillin has failed or is unsuitable
- Intra-abdominal infections (such as peritonitis). Cefotaxime should be used in combination with an antibiotic that is active against anaerobes in the treatment of intra-abdominal infections.
- Acute bacterial meningitis (particularly if due to H. influenzae, N. meningitides, S. pneumoniae, E. coli, Klebsiella spp.)
- Septicaemia infections originating from the lungs, urinary tract, or bowel (in case of gram-negative organisms a combination with another suitable antibiotic should be considered).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Cefotaxime may be administered by intravenous bolus injection, by intravenous infusion, by intramuscular injection after reconstitution of the solution according to the directions given below.

Dosage and mode of administration should be determined by the severity of the infection, susceptibility of the causative organism and the patient's condition. Therapy may be started before the result of sensitivity tests are known.

Adults and children over 12 years

The usual dose in adults is for mild to moderate infections is 2 to 6g daily. However, dosage may be varied according to the severity of the infection, sensitivity of the causative organisms and conditions of the patient.

Guidelines for dosage:

Typical infection in presence (or suspicion) of a sensitive micro-organism: 1g every 12 hours corresponding to a total daily dosage of 2g intramuscularly or intravenously.

Infection in the presence (or suspicion) of sensitive or moderatively sensitive multiple micro-organisms: 1-2g every 12 hours corresponding to a total daily dosage of 2-4g.

Severe infection by unidentified micro-organisms or for infections that cannot be localized: 2-3g as a single dose every 6 to 8 hours up to a maximum daily dosage of 12 g. A combination of cefotaxime and other antibiotics in indicated in severe infections.

A combination of cefotaxime and other antibiotics in indicated in severe infections. Infants and children up to 12 years

The usual dosage for infants and children <50 kg is 50-150 mg/kg/day in 2 to 4 divided doses. In very severe infections up to 200 mg/kg/day in divided doses may be required. In infants and children >50 kg the usual dose in adults, without exceeding the maximum daily dose of 12 g should be given.

Newborn infants and premature infants

The recommended dosage is 50 mg/kg/day in 2 to 4 divided doses. In case of life threatening situations, it may be necessary to increase the daily dose. In severe infections 150-200 mg/kg/day have been given: in those situations, the following table may serve as a guide, since there are differences in kidney maturation.

Age	Daily dose of Cefotaxime
0-7 days	50 mg/kg every 12 hours
8 days- 1 months	50 mg/kg every 8 hours

Elderly

No dosage adjustment is required, provided that renal and hepatic function are normal.

Other recommendations

Gonorrhoea: For gonorrhoea, a single injection (intramuscularly or intravenously) of 0.5g to 1 g cefotaxime. For complicated infections, consideration should be given to available official guidelines. Syphilis should be excluded before initiating treatment.

Urinary tract infections: In uncomplicated UTI 1 g every 12 hours.

Bacterial meningitis: In adults, daily doses of 6 to 12 g and in children daily doses of 150 to 200 mg/kg divided in equal doses every 6 to 8 hours are recommended. For the new-born, 50 mg/kg of cefotaxime can be given every 12 hours to infants 0-7 days old and every 8 hours to those 7-28 days old.

Intra-abdominal infections: Intra-abdominal infection should be treated with Cefotaxime in combination with other appropriate antibiotics.

Duration of therapy

The duration of therapy with Cefotaxime depends on the clinical condition of the patient and varies according to the course of the disease. Administration of Cefotaxime should be continued until symptoms have subsided or evidence of bacterial eradication has been obtained. Treatment over at least 10 days is necessary in infections caused by Streptococcus pyogenes (parenteral therapy maybe switched to an adequate oral therapy before the end of the 10-day period).

Dosage in renal function impairment

In adult patients with a creatinine clearance of ≤ 5 ml/min, the initial dose is similar to the recommended usual dose should be halved without change in the frequency of dosing.

Dosage in dialysis or peritoneal dialysis

In patients on haemodialysis and peritoneal dialysis an i.v. injection of 0.5-2 g, given at the end of each dialysis session and repeated every 24 hours, is sufficient to treat most infections efficaciously.

Method of administration

In order to prevent any risk of infection, the preparation of the infusion should be done in close aseptic conditions. Do not delay the infusion after the preparation of the solution.

Intravenous infusion

- For short intravenous infusion 1g or Cefotaxime should be dissolved in 40-50 ml Water for Injections or in another compatible fluid (e.g., glucose 10%). After preparation the solution should be given as a 20-minute intravenous infusion.
- For long lasting intravenous infusion 2 g Cefotaxime should be dissolved in 100 ml of Water for Injections or another suitable fluid, e.g., 0.9% sodium chloride or isotonic glucose solutionor other compatible fluids for infusions. After preparation, the solution may be given as a 50-60-minute intravenous infusion.

Intravenous injection

- For intravenous injection Cefotaxime 1 g should be dissolved in 4 ml Water for Injections, Cefotaxime 2 g should be dissolved in 10 ml Water for Injections and should be injected over3-5 minutes.

Intramuscular injection

- Cefotaxime 1.0 g is dissolved in the 4ml Water for Injections. The solution should be administered by deep intramuscular injection. In order to prevent pain from the injection Cefotaxime 1.0 g may be dissolved in 4 ml % Lidocaine Hydrochloride (only for adults). Solutions with lidocaine must not be administered intravenously. If the total daily dose is more than 2g, then intravenous administration should be chosen. In the case of severe infections, intramuscular injection is not recommended.

4.3 Contraindications

Cefotaxime should not be used in patients with a known or suspected hypersensitivity to cefotaxime or cephalosporins.

4.4 Warnings And Precautions

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 treatment, appropriate measures should be taken.

Anaphylactic reactions

Cefotaxime should be used with caution in persons with a history of allergies or asthma.

Preliminary enquiry about hypersensitivity to penicillin and other β-lactam antibiotics is necessary before prescribing cephalosporins since cross allergy occurs in 5-10% of cases. Use of cephalosporins should be undertaken with extreme caution in penicillin-sensitive subjects

Hypersensitivity reactions (anaphylaxis) occurring with the two types of antibiotics can be serious and occasionally fatal. If a hypersensitivity reaction occurs, treatment must be stopped.

The use of cefotaxime is strictly contraindicated in subjects with a history of immediate-type hypersensitivity to cephalosporins.

Serious bullous reactions

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

Clostridium difficile associated disease (e.g., pseudomembranous colitis)

Diarrhoea, particularly if severe and/or persistent, occurring during treatment or in the initial weeks following treatment, may be symptomatic of Clostridium difficile associated disease (CDAD). CDAD may range in severity from mild to life threatening, the most severe form of which is pseudomembranous colitis.

The diagnosis of this rare but potentially fatal condition can be confirmed by endoscopy and/or histology. It is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of cefotaxime.

If a diagnosis of pseudomembranous colitis is suspected, cefotaxime should be stopped immediately and appropriate specific antibiotic therapy should be started without delay.

Clostridium difficile associated disease can be favoured by faecal stasis. Medicinal products that inhibit peristalsis should not be given.

Hematological reactions

Leucopenia, neutropenia and more rarely, agranulocytosis, may develop during treatment with cefotaxime, particularly if given over long periods. For treatment courses lasting longer than 7-10

days, the blood white cell count should be monitored and treatment stopped in the event of neutropenia.

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

Patients with renal insufficiency

The dosage should be modified according to the creatinine clearance calculated.

Caution should be exercised if cefotaxime is administered together with aminoglycosides or other nephrotoxic drugs. Renal function must be monitored in these patients, the elderly and those with pre-existing renal impairment.

Neurotoxicity

High doses of beta lactam antibiotics including cefotaxime, particularly in patients with renal insufficiency, may result in encephalopathy (e.g., impairment of consciousness, abnormal movements and convulsions). Patients should be advised to contact their doctor immediately prior to continuing treatment if such reactions occur.

Precautions for administration

During post-marketing surveillance, potentially life-threatening arrhythmia has been reported in a very few patients who received rapid intravenous administration of cefotaxime through a central venous catheter. The recommended time for injection or infusion should be followed.

Effects on Laboratory Tests

As with other cephalosporins, a positive Coombs test has been found in some patients treated with cefotaxime. This phenomenon can interfere with the cross-matching of blood.

Urinary glucose testing with non-specific reducing agents may yield false positive results. This phenomenon is not seen when a glucose-oxidase specific method is used.

Sodium intake

The sodium content of this product (48.2 mg/g) should be taken into account when prescribing to patients requiring sodium restriction.

4.5 Interactions with Other Medicaments Cefotaxime / Other Antibiotics

As far as possible, Cefotaxime should not be combined with substances having a bacteriostatic action (e.g., tetracycline, erythromycin, chloramphenicol or sulfonamides), since antagonistic effect has been observed regarding the anti-bacterial effect in vitro. A synergistic effect can result with the combination with aminoglycosides.

An increased risk of oto- and nephrotoxicity has been reported when cefotaxime has been used concomitantly with cephalosporins or aminoglycosides. Dose adjustment may be necessary, and the kidney function must be watched.

Cefotaxime / Probenecid

The simultaneous administration of Probenecid leads to higher, more prolonged plasma concentrations of Cefotaxime by interfering with renal tubular transfer thereby delaying excretion.

Cefotaxime / Potentially Nephrotoxic Drugs and Loop Diuretics

In combination with potentially nephrotoxic drugs (such as, for example, aminoglycoside antibiotics, polymyxin B and colistin) and with potent diuretics, (e.g., furosemide) the kidney function should be monitored, since the nephrotoxicity of the substances quoted may be accentuated.

Influence on Laboratory Diagnostic Tests

False positives may occur in the Coombs-Test in rare cases during treatment with cefotaxime.

In glucose determinations in urine and blood, false positive as well as false negative results may alsobe obtained, depending on the method; these may be avoided by the use of enzymatic methods.

4.6 Pregnancy and Lactation

Pregnancy

The safety of cefotaxime has not been established in human pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. There are howeverno adequate and well controlled studies in pregnant women.

Cefotaxime passes through the human placenta. Therefore, Cefotaxime should only be used during pregnancy if the anticipated benefit outweighs any potential risks.

Lactation

Cefotaxime is excreted in human milk in low concentrations. Use during lactation can lead in infants to an effect on the physiological intestinal flora with diarrhoea, colonisation by yeast-like fungi and may also lead to sensitisation of the infant. Therefore a decision must be made whether to discontinue breast-feeding or to discontinue therapy, taking into account the benefit of breast- feeding to the child and the benefit of therapy to the mother.

4.7 Effects on ability to drive and use machines

There is no evidence that cefotaxime impairs the ability to drive or operate machinery.

4.8 Undesirable effects

System organclass	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Very rare (<1/10,000)**	**Not known (cannot be estimated from available data)**
Infections and infestation						Superinfection
Blood and the lymphatic system			Leucopoenia, Eosinophilia, Thrombocytopenia			Neutropenia, agranulocytosis, haemolytic anaemia

disorders						
Immune system disorders			Jarisch-Herxheimerreaction			Anaphylactic reactions, angioedema, bronchospasm, anaphylactic shock
Nervous system disorders			Convulsions			Headache, dizziness, encephalopathy (e.g. impairment of consciousness, abnormal movements)
Cardiac disorders						Arrhythmia following rapid bolus infusion through central venous catheter
Gastro-intestinal disorders			Diarrhoea			Nausea, vomiting, abdominal pain, pseudomembranous colitis
Hepato-biliary disorders			Increase in liver enzymes (ALAT, ASAT, LDH, gamma GT and or alkaline phosphatase) and/or bilirubin			Hepatitis (sometimes withjaundice)
Skin and subcutaneous tissue disorders			Rash, pruritis, urticaria			Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis
Renal and urinary disorders			Decrease in renal function/increase of creatinine (particularly when co-prescribed with aminoglycosides)			Interstitial nephritis

General disorders and administration site conditions	Pain at the injection site		Fever Inflammatory reactions at the injection site including phlebitis, thrombophlebitis			Systemic reactions to lidocaine (if reconstituted with lidocaine)

Jarisch-Herxheimer reaction

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 in breathing, joint discomfort

Hepatobiliary disorders

Increase in liver enzymes (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase) and/or bilirubin have been observed. These laboratory abnormalities may rarely exceed twice the upper limit of the normal range and elicit a pattern of liver injury, usually cholestatic and most often asymptomatic.

4.9 Overdosage

Symptoms of intoxication

Cefotaxime has a wide margin of safety. Cases of acute intoxication with cefotaxime have not been published. Symptoms of overdose may largely correspond to the profile of side effects. In cases of overdosage (particularly in renal insufficiency) there is a risk of reversible encephalopathy.

Therapy of intoxication

There is no specific antidote for overdose. Serum levels of cefotaxime can be reduced by haemodialysis or peritoneal dialysis.

Therapy of hypersensitivity reactions

Anaphylactic shock requires immediate countermeasures. Upon first signs of hypersensitivity reactions (e.g. cutaneous reactions such as skin rashes or urticaria, headache, nausea, restlessness) the administration of Cefotaxime should be discontinued. In cases of severe hypersensitivity reactions or anaphylactic reactions, emergency treatment should be initiated, such as administration of epinephrine and / or glucocorticoids.

According to the clinical severity additional therapeutic measures may be required (e.g. artificial breathing, application of histamine-receptor antagonists). In cases of circulatory collapse, resuscitation must be initiated according to the current guidelines.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system (see details below).

Paper based reporting: TMDA yellow card

Online reporting: https://sqrt.tmda.go.tz/

*USSD reporting: send a simple short text message to report any suspected Adverse Drug Reaction by dialing *152*00# and follow the instructions*

5 Pharmacological properties

5.1 Pharmacodynamic properties

ATC Classification

Pharmacotherapeutic group: Beta-lactam antibiotics, cephalosporins. ATC Code: J01D D01

Mode of action

Cefotaxime exerts its action by binding to one or more of the penicillin-binding proteins (PBPs) whichin turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thereby inhibiting cell wall synthesis.

Mechanisms of resistance

Resistance to Cefotaxime may be due to one or several of the following mechanisms:

- production of extended-spectrum beta-lactamases (ESBLs)
- induction and/or constitutive expression of AmpC beta- lactamases
- reduced outer membrane permeability
- efflux pump mechanisms.
- Modification of target enzymes (altered PBPs)

More than one of these mechanisms may co-exist in a single bacterium.

Breakpoints: According to the EUCAST (European Committee on Antimicrobial Susceptibility Testing) Clinical MIC breakpoints (v 2.0, dated 25-05-2009) the following breakpoints have been identified forcefotaxime:

	Susceptible (<)/Resistant (>)
Enterobacteriaceae[2]	½
Pseudomonas	-
Acinetobacter	-
Staphylococcus[3]	Note3
Enterococcus	-
Streptococcus A, B, C, G	Note4
Streptococcus pneumoniae	0.5/ 2
Other streptococci	0.5/ 0.5
Haemophilus influenzae	0.12/ 0.12
Moraxella Catarrhalis	1/ 2
Neisseria gonorrhoeae	0.12/ 0.12
Neisseria Meningitidis	0.12/ 0.12
Gram-positive, anaerobes	-
Gram-negative, anaerobes	-

Non-species related breakpoints1 S≤/ R>	1/ 2
1. Non-species related breakpoints have been determined mainly on the basis of Pk/Pd data and are independent of MIC distributions of specific species. They are for use only for species not mentioned in the table or footnotes. 2. The cephalosporin breakpoints for Enterobacteriaceae will detect reduced susceptibility mediated by most clinically important beta-lactamases in Enterobacteriaceae. Occasional ESBL-producing strains will be reported susceptible. For purposes of infection control, epidemiology and surveillance, laboratories may wish to use specific tests to screen for and confirm ESBL-production. 3. Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility. 4. The susceptibility of streptococcus groups A, B, C nd G can be inferred from their susceptibility to benzylpenicillin. -- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug	

Susceptibility

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable particularly when treating severe infections. This information gives only an approximate guidance on the probabilities whether micro-organisms will be susceptible to cefotaxime or not.

Species
<u>Susceptible</u>
Gram-positive aerobes
Staphylococcus aureus (Methicillin-susceptible) *
Group A Streptococci (including *Streptococcus pyogenes*) *
Group B Streptococci
β-hemolytic Streptococci (Group C, F, G)
Streptococcus pneumoniae *$
Viridans Group Streptococci
Gram-negative aerobes
Citrobacter spp. *
Escherichia coli *
Haemophilus influenzae *
Haemophilus parainfluenzae *
Klebsiella spp. *
Moraxella catarrhalis *

Neisseria gonorrhoeae *
Neisseria meningitides *
Proteus spp. *
Providencia spp. *
Yersinia enterocolitica
Anaerobes
Clostridium spp. (not *Clostridium difficile)*
Peptostreptococcus spp.
Propionibacterium spp.
Others
Borrelia spp.
Resistant
Gram-positive aerobes
Enterococcus spp.
Enterococcus faecalis
Enterococcus faecium
Listeria spp.
Staphylococcus aureus (MRSA)
Staphylococcus epidermidis (MRSE)
Gram-negative aerobes
Acinetobacter spp.
Citrobacter spp.
Enterobacter spp.
Morganella morganii
Pseudomonas spp.
Serratia spp.

Xanthomonas maltophilia
Anaerobes
Bacteroides spp.
Clostridium difficile
Others
Clamydiae
Mycoplasma spp.
Legionella pneumophilia

*Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications.

$ Frequency of resistance ranges in EU is >10% (extreme values); Streptococcus pneumoniae show a variable degree of resistance - 12.7%.

Methicillin-(oxacillin) resistant staphylococci (MRSA) are resistant to all currently available β-lactam antibiotics including cefotaxime.

Penicillin-resistant Streptococcus pneumoniae show a variable degree of crossresistance to cephalosporins such as cefotaxime.

5.2 Pharmacokinetics

properties Absorption

Cefotaxime is for parenteral application. Mean peak concentrations 5 minutes after intravenous injection are about 81-102 mg/l following a 1 g dose cefotaxime and about 167-214 mg/l 8 minutes after a 2 g dose. Intramuscular injection produces mean peak plasma concentrations of 20 mg/l within 30 minutes following a 1 g dose.

Distribution

Cefotaxime gives good penetration into different compartments. Therapeutic drug levels exceeding the minimum inhibitory levels for common pathogens can rapidly be achieved. Cerebrospinal fluid concentrations are low when the meninges are not inflamed but cefotaxime usually passes the blood-brain barrier in levels above the MIC of the sensitive pathogens when the meninges are inflamed (3-30 µg/ml). Cefotaxime concentrations (0.2-5.4 µg/ml), inhibitory for most Gram- negative bacteria, are attained in purulent sputum, bronchial secretions and pleural fluid after doses of 1 or 2 g. Concentrations likely to be effective against most sensitive organisms are similarly attained in female reproductive organs, otitis media effusions, prostatic tissue, interstitial fluid, peritoneal fluid and gall bladder wall, after therapeutic doses. High concentrations of cefotaxime and O-desacetyl-cefotaxime are attained in bile. Cefotaxime passes the placenta and attains high concentrations in foetal fluid and tisues (up to 6 mg/kg). Small amounts of cefotaxime diffuses into the breast milk.

Protein binding for cefotaxime is approximately 25-40%. The apparent distribution volume for cefotaxime is 21-37 l after 1g intravenous infusion over 30 minutes.

Biotransformation

Cefotaxime is partly metabolized in human beings. Approximately 15-25% of a parenteral dose is metabolized to the O-desacetylcefotaxime metabolite, which also has antibiotic properties.

Elimination

The main route of excretion of cefotaxime and O-desacetylcefotaxime is the kidney. Only a small amount (2%) of cefotaxime is excreted in the bile. In the urine collected within 6 hours 40-60% ofthe administered dose of cefotaxime is recovered as unchanged cefotaxime and 20% is found as O- desacetlycefotaxime. After administration of radioactive labeled cefotaxime more than 80& can be recovered in the urine, 50-60% of this fraction is unchanged cefotaxime and the rest contains metabolites.

The total clearance of cefotaxime is 240-390 ml/min and the renal clearance is 130- 150 ml/min. The serum half-lives of cefotaxime and O-desacetylcafotaxime are normally about 50-80 and 90 minutes respectively. In the elderly, the serum half-life of cefotaxime is 120-150 min. In patients with impaired renal function (creatinine clearance 3-10ml/min) the serum half-life of cefotaxime can be increased to 2.5-3.6 hours. In neonates, the pharmacokinetics are influenced by gestation andchronological age, the half- life being prolonged in premature and low birth weight neonates of the same age.

6. Pharmaceutical particulars

6.1 List of excipients

Not applicable.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Keep out of reach of children.

Store below 30°C. Protected from light.

6.5 Nature and contents of container

10 ml colorless glass vial

Pack of one vial with water for injection.

6.6 Special precautions for disposal and other handling

Following reconstitution: Cefotaxime sodium is compatible with the following diluents:Water for Injections

Sodium Chloride 0.9%
Dextrose 5 and 10%

Ringer's Solution

Ringer-Lactate

Solution

Lignocaine 1% (only freshly prepared solutions should be used)

Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C-8°C. However,from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not exceed 24 hours at 2°C-8°C.

After 24 hours any unused solution should be discarded.

7. MARKETING AUTHORISATION HOLDER

ALKEM LABORATORIES LTD.

H.O.: Alkem House, Senapati Bapat Marg,Lower Parel, Mumbai – 400013, India.

8. Marketing authorization number(s)

TAN 20 HM 0096

9. Date of first authorization/renewal of the authorization

July 09, 2020

10. Date of revision of the text

October 09, 2023