

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cefotaxime Sodium for Injection 1g

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each Vial contains:

Cefotaxime Sodium BP.....1 g

3. PHARMACEUTICAL FORM

Powder for solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. Cefotaxime is indicated in the treatment of serious infections, either before the infecting organism has been identified or when caused by bacteria of established sensitivity, including osteomyelitis, septicaemia, bacterial endocarditis, meningitis, and peritonitis. and other serious bacterial infections suitable for parenteral antibiotic therapy.

2. Cefotaxime may be used for pre-operative prophylaxis in patients undergoing surgical procedures, that may be classified as contaminated or potentially so.

4.2 Posology and Method of Administration:

Cefotaxime may be administered intravenously by bolus injection or by infusion, or by intramuscular injection. The dosage, route and frequency of administration should be determined by the severity of infection, the sensitivity of causative organisms and condition of the patient. Therapy may be initiated before the results of sensitivity tests are known.

Adults:

The recommended dosage for mild to moderate infections is 1g 12 hourly. However, dosage may be varied according to the severity of the infection, sensitivity of causative organisms and condition of the patient. Therapy may be initiated before the results of sensitivity tests are known.

In severe infections dosage may be increased up to 12g daily given in three or four divided doses. For infections caused by sensitive *Pseudomonas* species daily doses of greater than 6g will usually be required.

Children:

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

Neonates: The recommended dosage is 50mg/kg/day in two to four divided doses. In severe infections 150-200mg/kg/day, in divided doses, have been given.

Dosage in renal impairment: Because of extra-renal elimination, it is only necessary to reduce the dosage of cefotaxime in severe renal failure (GFR <5ml/min = serum creatinine approximately 751 micromol/litre). After an initial loading dose of 1g, daily dose should be halved without change in the frequency of dosing, i.e. 1g twelve hourly

becomes 0.5g twelve hourly, 1g eight hourly becomes 0.5g eight hourly, 2g eight hourly becomes 1g eight hourly etc. As in all other patients, dosage may require further adjustment according to the course of the infection and the general condition of the patient.

Dosage in hepatic impairment: No dosage adjustment is required.

Intravenous and Intramuscular Administration: Reconstitute cefotaxime with Water for Injections PhEur as directed in Section 6.6 (Instructions for use/handling). Shake well until dissolved and then withdraw the entire contents of the vial into the syringe.

Intravenous administration (Injection or Infusion): Cefotaxime may be administered by intravenous infusion using the fluids stated in Section 6.6 (Instructions for use/handling). The prepared infusion may be administered over 20-60 minutes.

For intermittent I.V. injections, the solution must be injected over a period of 3 to 5 minutes. 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.

Cefotaxime and aminoglycosides should not be mixed in the same syringe or perfusion fluid.

4.3 Contraindication:

Hypersensitivity to cephalosporins.

In patients with a history of hypersensitivity to Cefotaxime and/or to any component of Cefotaxime 500mg or 1g Powder for solution for injection or infusion, a penicillin or to any other type of beta-lactam drug.

Allergic cross reactions can exist between penicillins and cephalosporins (see section 44.).

For pharmaceutical forms containing lidocaine:

- known history of hypersensitivity to lidocaine or other local anaesthetics of the amide type
- non-paced heart block
- severe heart failure
- administration by the intravenous route
- infants aged less than 30 months of age.

4.4 Special Warning and Precautions for Use:

As with other antibiotics, the use of cefotaxime, especially if prolonged, may result in overgrowth of non susceptible organisms, such as *Enterococcus spp*, *candida*, *Pseudomonas aeruginosa*. Repeated evaluation of the condition of the patient is essential. If superinfection occurs during treatment with cefotaxime, appropriate measures should be taken and specific anti-microbial therapy should be instituted if considered clinically necessary.

Anaphylactic reactions: 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. The use of cefotaxime is strictly contra-indicated in subjects with a previous history of immediate-type hypersensitivity to cephalosporins. Since cross allergy exists between penicillins and cephalosporins, use of the latter should be undertaken with extreme caution in penicillin sensitive subjects. Serious, including fatal hypersensitivity reactions have been reported in patients receiving cefotaxime (see sections 4.3 and 4.8). If a hypersensitivity reaction occurs, treatment must be stopped.

Serious bullous reactions: Cases of serious bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with cefotaxime (see section 4.8). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Patients with renal insufficiency: The dosage should be modified according to the creatinine clearance calculated (see section 4.2). Patients with severe renal dysfunction should be placed on the dosage schedule recommended under "Posology and Method of Administration".

Caution should be exercised if cefotaxime is administered together with aminoglycosides, probenecid or other nephrotoxic drugs (see section 4.5). Renal function must be monitored in these patients, the elderly, and those with pre-existing renal impairment.

Haematological reactions: Leukopenia, 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 cases of eosinophilia and thrombocytopenia, rapidly reversible on stopping treatment, have been reported. Cases of haemolytic anaemia have also been reported (see section 4.8).

Sodium intake: The sodium content of cefotaxime (2.09mmol/g) should be taken into account when prescribing to patients requiring sodium restriction.

Clostridium difficile associated disease (e.g. pseudomembranous colitis): Cefotaxime may predispose patients to pseudomembranous colitis. Although any antibiotic may predispose to pseudomembranous colitis, the risk is higher with broad spectrum drugs, such as cephalosporins. This side effect, which may occur more frequently in patients receiving higher doses for prolonged periods, should be considered as potentially serious.

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 pseudo-membranous colitis.

The diagnosis of this rare but possibly 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 antibody 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.

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) (see section 4.8).

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 lifethreatening 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 (see section 4.2).

See section 4.3 for contraindications for formulations containing lidocaine.

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-oxydase specific method is used.

4.5 Interaction with other medicinal products and other forms of interaction:

Aminoglycoside antibiotics and diuretics: As with other cephalosporins, cefotaxime may potentiate the nephrotoxic effects of nephrotoxic drugs such as aminoglycosides or potent diuretics (e.g. furosemide). Renal function must be monitored (see section 4.4).

Uricosurics: Probenecid interferes with renal tubular transfer of cefotaxime, thereby increasing cefotaxime exposure about 2-fold and reducing renal clearance to about half at therapeutic doses. Due to the large therapeutic index of cefotaxime, no dosage adjustment is needed in patients with normal renal function. Dosage adjustment may be needed in patients with renal impairment (see sections 4.4 and 4.2).

Interference with Laboratory Tests:

A false positive Coombs test may be seen during treatment with cephalosporins. This phenomenon may occur during treatment with cefotaxime and can interfere with blood crossmatching.

A false positive reaction to urinary glucose may occur with copper reduction methods (Benedict's, Fehling's or Clinitest) but not with the use of specific glucose oxidase methods.

There is a potential for mezlocillin and azlocillin to reduce the clearance of cefotaxime.

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, however, no adequate and well controlled studies in pregnant women.

Cefotaxime crosses the placental barrier. Therefore, cefotaxime should not be used during pregnancy unless the anticipated benefit outweighs any potential risks.

Lactation: Cefotaxime passes into human breast milk in small amounts and is usually compatible with breast feeding, but careful monitoring of the infant is recommended.

Effects on the physiological intestinal flora of the breast-fed infant leading to diarrhoea, colonisation by yeast-like fungi, and sensitisation of the infant cannot be excluded.

Therefore, a decision must be made whether to discontinue breast-feeding or to discontinue therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 Effect on ability to drive and use machine

Cefotaxime has been associated with dizziness, which may affect the ability to drive or operate machinery.

There is no evidence that cefotaxime directly impairs the ability to drive or to operate machines. High doses of cefotaxime, particularly in patients with renal insufficiency, may cause encephalopathy (e.g. impairment of consciousness, abnormal movements

and convulsions) (see section 4.8). Patients should be advised not to drive or operate machinery if any such symptoms occur.

4.8 Undesirable effects

System organ class	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 infestations						Superinfection (see section 4.4)
Blood and the lymphatic system disorders			Leukopenia Eosinophilia Thrombocytopenia			Neutropenia Granulocytopenia Agranulocytosis (see section 4.4) Haemolytic anaemia
Immune system disorders			Jarisch-Herxheimer reaction			Anaphylactic reactions Angioedema Bronchospasm Anaphylactic shock
Nervous system disorders			Convulsions (see section 4.4)			Headache Dizziness Encephalopathy (e.g. impairment of consciousness, abnormal movements) (see section 4.4)
Cardiac disorders						Arrhythmia following rapid bolus infusion through central venous catheter
Gastrointestinal disorders			Diarrhoea			Nausea Vomiting Abdominal pain Pseudomembranous colitis (see section 4.4)
Hepato-biliary disorders			Increase in liver enzymes (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase) and/or bilirubin			Hepatitis* (sometimes with jaundice)

Skin and subcutaneous disorders			Rash Pruritus Urticaria Drug fever			Erythema multiforme Stevens-Johnson syndrome Toxic epidermal necrolysis (see section 4.4)
Renal and Urinary disorders			Decrease in renal function/increase of creatinine (particularly when co-prescribed with aminoglycosides)			Interstitial nephritis Candidiasis
General disorders and administration site conditions	For IM formulations: Pain at the injection site		Fever Inflammatory reactions at the injection site, including phlebitis/thrombophlebitis			For IM formulations (since the solvent contains lidocaine): Systemic reactions to 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 week's treatment of borreliosis: skin rash, itching, fever, leucopenia, increase in liver enzymes, difficulty of 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.

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

4.9 Overdose:

Symptoms of overdose may largely correspond to the profile of side effects.

There is a risk of reversible encephalopathy in cases of administration of high doses of β -lactam antibiotics including cefotaxime.

In case of overdose, cefotaxime must be discontinued, and supportive treatment initiated, which includes measures to accelerate elimination, and symptomatic treatment of adverse reactions (e.g. convulsions).

No specific antidote exists. Serum levels of cefotaxime may be reduced by peritoneal dialysis or haemodialysis.

5. Pharmacological properties

5.1 Pharmacodynamic Properties:

General Properties

ATC Classification

Pharmacotherapeutic group: Beta-lactam antibiotics, cephalosporins.

ATC Code: J01D A10

Mode of action

Cefotaxime is a third generation broad spectrum bactericidal cephalosporin antibiotic. The bactericidal properties are due to the inhibitory effect of cefotaxime on bacterial cell wall synthesis.

Mechanisms of resistance

Resistance to Cefotaxime may be due to production of extended-spectrum beta-lactamases that can efficiently hydrolyse the drug, to the induction and/or constitutive expression of AmpC enzymes, to impermeability or to efflux pump mechanisms. More than one of these possible mechanisms may co-exist in a single bacterium.

Breakpoints:

Current MIC breakpoints used to interpret cefotaxime susceptibility data are shown below.

European Committee on Antimicrobial Susceptibility Testing (EUCAST) Clinical MIC Breakpoints (V1.1, 31/03/2006)

	Susceptible ($\leq$) / Resistant ($\geq$)
<i>Enterobacteriaceae</i> ²	1/2
<i>Pseudomonas</i>	--
<i>Acinetobacter</i>	--
<i>Staphylococcus</i> ³	Note ³
<i>Enterococcus</i>	--
<i>Streptococcus A, B, C, G</i>	0.5/0.5 ⁴
<i>Streptococcus pneumonia</i>	0.5/2 ⁴
<i>Haemophilus influenza</i> <i>Moraxella Catarrhalis</i>	0.12/0.12 ⁴
<i>Neisseria gonorrhea</i>	0.12/0.12 ⁴
<i>Neisseria Meningitidis</i>	0.12/0.12 ⁴
<i>Gram-negative, anaerobes</i>	--
Non-species related breakpoints ¹ S $\leq$ />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 that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or IE in the table).

2. The cephalosporin breakpoints for *Enterobacteriaceae* will detect resistance mediated by most ESBLs and other clinically important beta-lactamases in *Enterobacteriaceae*. However, some ESBL-producing strains may appear susceptible

or intermediate with these breakpoints. Laboratories may want to use a test which specifically screens for the presence of ESBL.

3. Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility (except ceftazidime which should not be used for staphylococcal infections).

4. Strains with MIC values above the S/I breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.

IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.

RD = rationale document listing data used by EUCAST for determining breakpoints.

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	Frequency of resistance ranges in EU (if > 10%) (extreme values)
<u>Susceptible</u>	
Gram-positive aerobes	
<i>Staphylococcus aureus</i> (Methicillin-susceptible) *	
Group A Streptococci (including <i>Streptococcus pyogenes</i>) *	
Group B Streptococci	
β-hemolytic Streptococci (Group C, F, G)	
<i>Streptococcus pneumoniae</i> *	12.7%
Viridans Group Streptococci	
Gram-negative aerobes	
<i>Citrobacter</i> spp. *	
<i>Escherichia coli</i> *	
<i>Haemophilus influenzae</i> *	
<i>Haemophilus parainfluenzae</i> *	
<i>Klebsiella</i> spp. *	
<i>Moraxella catarrhalis</i> *	
<i>Neisseria gonorrhoeae</i> *	
<i>Neisseria meningitidis</i> *	
<i>Proteus</i> spp. *	

<i>Providencia</i> spp. *	
<i>Yersinia enterocolitica</i>	
Anaerobes	
<i>Clostridium</i> spp. (not <i>Clostridium difficile</i>)	
<i>Peptostreptococcus</i> spp.	
<i>Propionibacterium</i> spp.	
Others	
<i>Borrelia</i> spp.	
<u>Resistant</u>	
Gram-positive aerobes	
<i>Enterococcus</i> spp.	
<i>Enterococcus faecalis</i>	
<i>Enterococcus faecium</i>	
<i>Listeria</i> spp.	
<i>Staphylococcus aureus</i> (MRSA)	
<i>Staphylococcus epidermidis</i> (MRSE)	
Gram-negative aerobes	
<i>Acinetobacter</i> spp.	
<i>Citrobacter</i> spp.	
<i>Enterobacter</i> spp.	
<i>Morganella morganii</i>	
<i>Pseudomonas</i> spp.	
<i>Serratia</i> spp.	
<i>Xanthomonas maltophilia</i>	
Anaerobes	
<i>Bacteroides</i> spp.	
<i>Clostridium difficile</i>	
<u>Others</u>	
<i>Chlamydiae</i>	
<i>Mycoplasma</i> spp.	
<i>Legionella pneumophila</i>	

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

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 cross-resistance to cephalosporins such as cefotaxime.

5.2 Pharmacokinetic properties

After a 1000mg intravenous bolus, mean peak plasma concentrations of cefotaxime usually range between 81 and 102 microgram/ml. Doses of 500mg and 2000mg

produce plasma concentrations of 38 and 200 microgram/ml, respectively. There is no accumulation following administration of 1000mg intravenously or 500mg intramuscularly for 10 or 14 days.

The apparent volume of distribution at steady-state of cefotaxime is 21.6 litres/1.73m² after 1g intravenous 30 minute infusion.

Concentrations of cefotaxime (usually determined by non-selective assay) have been studied in a wide range of human body tissues and fluids. Cerebrospinal fluid concentrations are low when the meninges are not inflamed, but are between 3 and 30 microgram/ml in children with meningitis. Cefotaxime usually passes the blood-brain barrier in levels above the minimum inhibitory concentration of common sensitive pathogens when the meninges are inflamed. Concentrations (0.2-5.4 microgram/ml), inhibitory for most Gram-negative bacteria, are attained in purulent sputum, bronchial secretions and pleural fluid after doses of 1 or 2g. Concentrations likely to be effective against most sensitive organisms are similarly attained in female reproductive organs, otitis media effusions, prostatic tissue, interstitial fluid, renal tissue, peritoneal fluid and gall bladder wall, after usual therapeutic doses. High concentrations of cefotaxime and desacetyl-cefotaxime are attained in bile.

Cefotaxime is partially metabolised prior to excretion. The principal metabolite is the microbiologically active product, desacetyl-cefotaxime. Most of a dose of cefotaxime is excreted in the urine - about 60% as unchanged drug and a further 24% as desacetyl-cefotaxime. Plasma clearance is reported to be between 260 and 390ml/minute and renal clearance 145 to 217 ml/minute.

After intravenous administration of cefotaxime to healthy adults, the elimination half-life of the parent compound is 0.9 to 1.14 hours and that of the desacetyl metabolite, about 1.3 hours.

In neonates the pharmacokinetics are influenced by gestational and chronological age, the half-life being prolonged in premature and low birth weight neonates of the same age.

In severe renal dysfunction the elimination half-life of cefotaxime itself is increased minimally to about 2.5 hours, whereas that of desacetyl-cefotaxime is increased to about 10 hours. Total urinary recovery of cefotaxime and its principal metabolite decreases with reduction in renal function.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber that are additional to those included in other sections.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities:

Cefotaxime sodium should not be mixed with alkaline solutions such as sodium bicarbonate injection or solutions containing aminophylline.

Cefotaxime should not be admixed with aminoglycosides. If they are used concurrently they should be administered in separate sites.

Cefotaxime should not be mixed with other medicinal products except those listed in section 6.6.

6.3 Shelf Life

24 Months

6.4 Special precautions for storage

Store below 25° C/30° C. Protect from direct light.

6.5 Nature and content of container

One colourless vial packed in a carton.

6.6 Special precautions for disposal and other handling

Not Applicable

7. MARKETING AUTHORIZATION HOLDER

CENTURION HEALTHCARE PVT LTD

At Survey No: 494-495, Khambhat Petlad Road

At Post Bamanva 388 580, Gujarat, India

8. MARKETING AUTHORIZATION NUMBER

FDA/GD.243-030048

9. DATE OF FIRST AUTHORIZATION OR RENEWAL

07/03/2024

10. DATE OF REVSION OF THE TEXT

17/07/2025