SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Cefotaxime for Injection USP 500 mg

2. Qualitative and quantitative composition

Each vial contains

Sterile Cefotaxime Sodium USP

Eq. to Cefotaxime ..... 500 mg

Batch Size: 100000 vials

Composition of FPP and their amount on per unit basis:

Sr. No.	Ingredients	Quantity/ Unit	Std. Quantity/ Batch in kg	Required quantity in Kg	Overages	Function	Reference/ Monograph
1.	Sterile Cefotaxime Sodium USP Eq. to Cefotaxime	500 mg	56.273	*	*	Antibacterial	USP

Note: * denotes blank and will be mentioned at the time of issuance.

Calculation for the batch

For Example:

(i) If Assay is 91.6% (eq.to Cefotaxime) and LOD is 3.0% of Cefotaxime Sodium then

$$\text{Target fill weight of Cefotaxime Sodium (Per vial in mg)} = \frac{\text{Label Claim} \times 100 \times 100}{\text{Assay (ODB)} \times (100 - \text{water content})}$$

$$\frac{500 \times 100 \times 100}{91.6 \times (100-3.0)}$$

$$= 562.73 \text{ mg / vial}$$

$$\text{Required qty. of Cefotaxime Sodium} = \frac{\text{No. of vials} \times \text{Target fill weight}}{1000 \times 1000}$$

$$= \frac{100000 \times 562.73}{1000 \times 1000} = 112.547 \text{ kg}$$

Note: The above calculated quantity of Cefotaxime Sodium is based on minimum assay (91.6%) & maximum LOD (3.0%)

3. Pharmaceutical form

Vials containing powder for solution for injection or infusion

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
peritonitis
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 micromole/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. 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 Contraindications

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.
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 warnings 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. 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. 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. 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 or other nephrotoxic drugs. 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.

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) 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-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

Uricosurics:

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

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 cross-matching.

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.

Breast Feeding

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 Effects on ability to drive and use machines

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). 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
Blood and the lymphatic system disorders			Leukopenia Eosinophilia Thrombocytopenia			Neutropenia Granulocytopenia Agranulocytosis Haemolytic anaemia
Immune system disorders			Jarisch-Herxheimer reaction			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
Gastrointestinal disorders			Diarrhoea			Nausea Vomiting Abdominal pain Pseudomembranous colitis

Hepato-biliary disorders			Increase in liver enzymes (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatise) and/or bilirubin			Hepatitis* (sometimes with jaundice)
Skin and subcutaneous disorders			Rash Pruritus Urticaria Drug fever			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 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

* post marketing experience

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.

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

5.1 Pharmacological properties

5.2 Pharmacodynamic properties

ATC classification:

Antibacterials for systemic use. Third-generation 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.

Mechanism 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 (≤)/Resistant (≥)
Enterobacteriaceae[2]	1/2
Pseudomonas	--
Acinetobacter	--
Staphylococcus[3]	Note[3]
Enterococcus	--
Streptococcus A, B, C, G	0.5/0.5[4]

Streptococcus pneumoniae	0.5/2[4]
Haemophilus influenzae *Moraxella Catarrhalis*	0.12/0.12[4]
Neisseria gonorrhoea	0.12/0.12[4]
Neisseria Meningitidis	0.12/0.12[4]
Gram-negative, anaerobes	--

Non-species related breakpoints[1] 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 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 Cefotaxime 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)
Susceptible	
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 *	12.7%
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.

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.

5.3 Pharmacokinetic properties

After a 1000 mg 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/1.73m^2 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.

5.4 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.

6.3 Shelf life

Unopened: 2 years.

For the reconstituted solution, chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C. From a microbiological point of view, once opened, 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 would normally not be longer than 24 hours at 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Unopened: Store below 30°C.Do not allow to freeze

After reconstitution: store at 2-8°C.

6.5 Nature and contents of container

7.5 ml clear glass vial USP Type-III sealed with grey bromo butyl rubber stopper and 20 mm dark blue colour flip-off seal.

6.6 Special precautions for disposal and other handling

No special precaution recommended.

7. Marketing authorization holder

THEON PHARMACEUTICALS LTD
VILLAGE SAINI MAJRA, TESHSIL NALAGARH, DISTT. SOLAN (H.P)-174101

8. Marketing authorization number(s)

05745/07452/REN/2020

9. Date of first authorization/renewal of the authorisation

Mar 8, 2021

10. Date of revision of the text

Not Applicable