SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE MEDICINAL PRODUCT:

Cefotaxime Sodium - ORITAXIM

2. QUALITATIVE AND QUANTITATIVE COMPOSITIONS:

Each vial contains:

Cefotaxime Sodium U.S.P. Equivalent to Cefotaxime 500 mg or 1000mg

3. PHARMACEUTICAL FORM:

Dry Powder For Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication:

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. It is generally administered in serious and life threatening infections.

Septicaemias

Respiratory tract infections: Acute and chronic bronchitis, bacterial pneumonia, infected bronchiectasis, lung abscess and post-operative chest infections.

Urinary tract infections: Acute and chronic pylonephritis, 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 it is penicillin-resistant or if penicillin is unsuitable.

Other bacterial infections: Meningitis and other sensitive infections suitable for parenteral antibiotic therapy.

Prophylaxis: The administration of Cefotaxime prophylactically may reduce the incidence of certain post-operative infections, internally and parenterally in patients undergoing surgical procedures that are classified as contaminated or potentially contaminated or in clean operations where infection should have serious effects.

4.2 POSOLOGY & METHOD OF ADMINISTRATION:

Cefotaxime may be administered intravenously or intramuscularly. Dosage, route and frequency of administration should be determined by severity of infection, sensitivity of causative organisms and condition of the patients. Therapy may be started before the result of sensitivity tests are known.

Adults: The usual dose in adults for mild to moderate infections is 1g 12 hourly, depending upon the severity of the infection. However, dosage may be varied according to the severity of the infection sensitivity of causative organisms and condition of the patient. For infections caused by sensitive Pseudomonas species daily doses of more than 6 g are usually required.

Guidelines for dosage: Mild to moderate or uncomplicated infections such as UTI 1g every 12 hours. Moderate to serious infections 1g every 8 hours. Life threatening infections 2g every 8 hours. In exceptional circumstances of life threatening infections caused by an organism less sensitive to cefotaxime, e.g. Pseudomonas, up to 12 g per day (in divided dosage) may occasionally be of advantage. Gonorrhoea 1g single dose.

Children : The usual dosage is 100 - 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.

Neonates : The recommended dosage is 50 mg/Kg/day in 2 to 4 divided doses. In severe infections, 150-200 mg/Kg/day in 2 to 4 divided doses have been given.

Prophylaxis : Protection is best assured by achieving adequate local tissue concentrations at the time when 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.

Dosage in renal impairment: Because of extra-renal elimination, it is only necessary to reduce the dosage of cefotaxime in severe renal failure (GFR < 5 ml/min). After an initial loading dose of 1g the 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 & 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. 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. 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 5minutes. 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:

Cefotaxime is contraindicated in patients who are hypersentive 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 & SPECIAL PRECAUTIONS FOR USE:

A false positive Coomb's test may be seen during treatment with cephalosporins. This phenomena may occur during treatment with cefotaxime.

A false positive reaction to glucose may occur with reducing substances but not with the use of specific glucose oxidase methods.

As with all cephalosporins, pseudomembranous colitis may rarely occur during treatment. If this occurs, the drug should be discontinued.

Renal function should be checked when cefotaxime is co-administered with aminoglycosides. Cefotaxime should not be used during pregnancy particularly during the first trimester. As with all cephalosporins, pseudomembranous colitis may rarely occur during treatment. If this occurs, the drug should be discontinued.

Anaphylactic reactions: Preliminary enquiry about hypersensitivity to penicillin and otherβ-Lactam antibiotics is necessary before prescribing cephalosporins since cross allergyoccurs in 5–10% of cases. The use of cefotaxime is strictly contra-indicated in subjects witha previous history of immediate-type hypersensitivity to cephalosporins. Since cross allergyexists between penicillins and cephalosporins.

Serious bullous reactions: Cases of serious bullous skin reactions like Stevens-Johnsonsyndrome or toxic epidermal necrolysis have been reported with cefotaxime (see section4.8). Patients should be advised to contact their doctor immediately prior to continuingtreatment if skin and/or mucosal reactions occur.

Haematological reactions: Leukopenia, neutropenia, and more rarely, agranulocytosis maydevelop during treatment with cefotaxime, particularly if given over long periods. Fortreatment courses lasting longer than 7-10 days, the blood white cell count should bemonitored and treatment stopped in the event of neutropenia.

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

Neurotoxicity: High doses of beta-lactam antibiotics, including cefotaxime, particularly inpatients with renal insufficiency, may result in encephalopathy (e.g. impairment ofconsciousness, abnormal movements and convulsions)

4.5 DRUG INTERACTION

Aminoglycosides: There is in vitro evidence of synergy between Oritaxim 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 addition of an aminoglycoside antibiotic may be indicated. Concomitant administration of high dosage Oritaxim and aminoglycoside is not recommended as these combinations are suspected to adversely alter renal function.

Diuretics: Co-administration of high dose Oritaxim and diuretics like frusemide may cause renotoxicity since these combination is suspected to adversely affect renal function.

Uricosurics: Probenecid interferes with renal tubular transfer of cefotaxime, there by 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.

4.6 PREGNANCY AND LACTATION:

Although studies in animals have not shown an adverse effect on the developing foetus, the safety of Oritaxim in human pregnancy has not been established. Consequently, Oritaxim should not be administered during pregnancy especially during the first trimester, without carefully weighing the expected benefits against the possible risks. Oritaxim is excreted in milk. Therefore, Oritaxim should not be administered to nursing mothers.

4.7 EFFECT ON ABILITY TO DRIVE OR USE MACHINES:

Cefotaxime has been associated with dizziness, which may affect the ability to drive oroperate machinery.There is no evidence that cefotaxime directly impairs the ability to drive or to operatemachines. High doses of cefotaxime, particularly in patients with renal insufficiency, maycause encephalopathy (e.g. impairment of consciousness, abnormal movements andconvulsions) (see section 4.8). Patients should be advised not to drive or operate machineryif any such symptoms occur.

4.8 UNDESIRABLE EFFECTS:

Adverse reactions to Cefotaxime have occurred relatively infrequently and have generally been mild and transient. Effects reported include diarrhea, candidiasis, rashes, fever, eosinophilia, leukopenia and transient rises in liver transaminase and alkaline phosphatase.

Transient pain may be experienced at the site of injection. This is more likely to occur with higher doses.

As with all cephalosporins, pseudomembranous colitis may occur during treatment. In each cases the drug should be stopped and specific treatment instituted.

Administration of high doses of cephalosporins, particularly in patients with renal insufficiency may result in encephalopathy.

As with other β-lactam antibiotics, granulocytopenia and more rarely aggranulocytosis may occur particularly with longer periods of therapy. A few cases of eosinophilia and neutropenia have been observed, which are reversible when treatment is ceased. Rare cases of hemolytic anemia have been observed.

Hypersensitivity reactions have been reported, these include skin rashes, drug fever and very rarely anaphylaxis.

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 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 (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

4.9 OVERDOSE:

In the case of overdosage, particularly in renal insufficiency there is a risk of reversible encephalopathy. Serum levels of cefotaxime may be reduced by peritoneal dialysis or haemodialysis. In case of overdose, cefotaxime must be discontinued, and supportive treatment initiated,which includes measures to accelerate elimination, and symptomatic treatment of adversereactions (e.g. convulsions).

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic Properties:

Bactericidal activity of cefotaxime sodium results from inhibition of cell wall synthesis. Cefotaxime sodium has in vitro activity against a wide range of gram-positive and gram-negative organisms.

Cefotaxime sodium has a high degree of stability in the presence of beta-lactamases, both penicillinases and cephalosporinases of gram-negative and gram-positive bacteria. Cefotaxime sodium has been shown to be a potent inhibitor of □-lactomases produced by certain gram-negative bacteria. Cefotaxime sodium is usually active against the following micro-organisms both in vitro and in clinical infections.

Aerobes, Gram-positive : Staphylococcus aureus, including penicillinase and non-penicillinase producing strains, staphylococcus epidermidis, Enterococci species, streptococcus pyogenes, Streptococcus agalactiae, Streptococcus pneumoniae.

Aerobes, Gram-negative : Citrobacter species, Enterobacter species, Escherichia coli, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella species, Neisseria gonorrhoeae, Neisseria meningitidis, Proteus mirabilis, Proteus vulgaris, proteus inconstans.

Anaerobes : Bacteroides species, including some strain of □-fragilis, clostridium species, Peptococcus species, Peptostreptococcus species and Fusobacterium species.

Cefotaxime sodium and aminoglycosides have been shown to be synergistic in vitro against some strains of Pseudomonas aeruginosa.

Mechanism of Action:

Cefotaxime like all other cephalosporins inhibits peptidoglycan (a mucopolysaccharide) synthesis. It inhibits peptidoglycan synthesis by inactivating the enzyme transpeptidase. Peptidoglycan is a heteropolymeric component of cell wall that provides rigid mechanical stability by virtue of its highly cross linked lattice structure. Through inhibition of peptidoglycan synthesis and other unknown mechanisms which may be leading to activation of bacterial cell wall autolytic enzymes-autolysins or murein hydrolases cefotaxime causes bacterial lysis.

5.2 PHARMACOKINETIC EFFECTS:

Cefotaxime is rapidly absorbed after IM injection and mean peak plasma concentrations of about 12 to 20µg/mL have been reported 30 minutes after 0.5 and 1g of Cefotaxime respectively.

Approximately 20 – 36% of an intravenously administered dose of 14C – cefotaxime is excreted by the kidney as unchanged cefotaxime and 15-25% as the desacetyl derivative, the major metabolite. The desacetyl metabolite has been shown to contribute to the bactericidal activity.

Cefotaxime usually passes the blood-brain barrier in levels above the MIC of common sensitive pathogens when the meninges are inflammed. 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 inflammed by gestational and chronological age, the half-life being prolonged in premature and low birth weight neonates of the same age.

5.3 ANIMAL TOXICOLOGICAL DATA:

A summary of numerans acute, subacute, chronic and reproductive studies conducted in rats and rabbits indicates that cefotaxime is a safe drug and does not influence fertility or fetal and postnatal development.

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.

6.3 Shelf life:

2 years.

6.4 Special precautions for storage

Store below 30ºC, Protect from light.

6.5 Nature and contents of container

10ml flint USP type III glass vials

6.6 Special precautions for disposal and other handling

Keep all medicines out of reach of children

To dissolve the content, use sterile water for injection as under:

1)2ml for I.M. use

2) 10ml for I.V. use.

Reconstituted solution should be stored below 20°C and used within 24 hours.

Shake Well. I.V administration should be slow and over a 3 to 5 minutes period

7. MARKETING AUTHORISATION HOLDER

Cadila Pharmaceuticals Limited

1389, Trasad Road, Dholka – 382 225,

District: Ahmedabad, Gujarat,

INDIA

8. MARKETING AUTHORISATION NUMBER(S)

Oritaxim 500: CADI/IND/003

Oritaxim 1000: CADI/IND/009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Oritaxim 500: 13/04/2021

Oritaxim 1000: 03 Oct 2019

10. DATE OF REVISION OF THE TEXT

July 2023