CEFOTAXIME SODIUM
1Gr INJECTION

Cefotaxime Sodium For Injection 1000mg

1. TRADE NAME OF THE MEDICINAL PRODUCT
Cefotaxime Sodium For Injection 1000mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
1g vial
Contains Cefotaxime sodium Ph. Eur equivalent to 1g cefotaxime base. Each gram of Cefotaxime contains approximately 48mg (2.09mmol) of sodium.

3. PHARMACEUTICAL FORM
Vials containing powder for injection or infusion.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Properties: is a broad-spectrum bactericidal cephalosporin antibiotic. is exceptionally active in vitro against Gram-negative organisms sensitive to first or second generation cephalosporins. It is similar to other cephalosporins in activity against Gram-positive organisms.

Indications: Cefotaxime is indicated in the treatment of severe infections of the respiratory tract, kidneys and urinary tract, of the skin and soft tissues, bones and joints, genital organs including gonorrhoea, abdominal infections, sepsis, endocarditis, meningitis.

Protection:best achieved by achieving adequate local tissue concentrations at the time contamination is likely to occur. Cefotaxime should therefore be administered immediately prior to surgery and if necessary continued in the immediate post-operative period.

Administration should usually be stopped within 24 hours since continuing use of any antibiotic in majority of surgical procedures does not reduce the incidence of subsequent infection.

Bacteriology:
The following organisms have shown in vitro sensitivity to Cefotaxime.

- Gram-positive: Staphylococci, including coagulase-positive, coagulase-negative and penicillinase-producing strains
- Beta-haemolytic and other streptococci such as Streptococcus milleri (viridans) (many strains of enterococci, e.g. Streptococcus faecalis, are relatively resistant.
- Streptococcus (Biphticoccus) pneumoniae.
- Clostridium spp.
- Gram-negative:
- Escherichia coli.
- Haemophilus influenzae including ampicillin resistant strains.
- Klebsiella spp.
- Proteus spp. (both indole positive and indole negative). Enterobacter spp.
- Neterobacter (including ß-lactamase producing strains of N. gonorrhoea).
- Providencia spp.
- Serratia spp.

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

There is in vitro evidence of synergy between Cefotaxime and aminoglycoside antibiotics, as gentamicin against some species of Gram-negative bacteria including some strains of Pseudomonas. In vitro antagonism has been noted. In severe infections caused by Pseudomonas spp. the addition of an aminoglycoside antibiotic may be indicated.

4.2 Posology and method of administration
DOSEAGE:
Cefotaxime is administered intravenously, by bolus injection, by infusion. The dosage and frequency of administration should be determined by the severity of the 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 3 or 4 divided doses.

For children, the usual dosage range is 100-150mg/kg/day in 2 to 4 divided doses. However, in very severe infections doses of up to 200mg/kg/day may be required.

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

Dosage in Gonorrhoea: A single injection of 1g is administered intravenously. Dosage in Renal Impairment: Because of extra renal elimination, it is only necessary to reduce the dosage of Cefotaxime in severe renal failure (GFR < 50 ml/min) given as approximately 751 micromol). After an initial loading dose of 1g, daily dosage should be halved in change of the frequency of dosing, i.e. 1g/12 hourly becomes 0.5g 12 hourly, 1g 8 hourly becomes 0.5g 8 hourly, 2g 8 hourly becomes 1g 8 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.

ADMINISTRATION:
Intravenous Administration: Reconstitute Cefotaxime with Water for Injection Ph.Eur as given in the Dilution Table. Shake well until dissolved and then withdraw the entire contents of the vial into the syringe and use immediately.

Dilution Table:

<table>
<thead>
<tr>
<th>Vial size</th>
<th>Diluent to be added</th>
</tr>
</thead>
<tbody>
<tr>
<td>500mg</td>
<td>2ml</td>
</tr>
<tr>
<td>1g</td>
<td>4ml</td>
</tr>
<tr>
<td>2g</td>
<td>10ml</td>
</tr>
</tbody>
</table>

Infusion:
Cefotaxime may be administered by intravenous infusion. 1-2g are dissolved in 40-100ml of Water for Injection Ph.Eur or in the infusion fluids listed under ‘Pharmaceutical Particles’. The prepared infusion may be administered over 20-60 minutes. To produce an infusion using vials with an infusion connector, remove the safety cap and directly connect the infusion bag. The needle in the closure will automatically pierce the vial stopper. Pressing the infusion bag will transfer solution into the vial. Reconstitute by shaking the vial and finally, transfer the reconstituted solution back to the infusion bag ready for use.

4.3 Contra-indications
Known or suspected hypersensitivity to cephalosporins.

4.4 Special warnings and special precautions for use

Preliminary enquiry about hypersensitivity to penicillin and other ß-Lactam antibiotics is necessary before prescribing cephalosporins since cross allergy occurs in 5-10% of cases.

Hypersensitivity reactions (anaphylaxis) occurring with the two types of antibiotics can be serious and occasionally fatal, and therefore their concurrent use is contraindicated.

4.5 Interaction with other medicaments and other forms of interaction
Cephalosporin antibiotics at high dosage should be given with caution to patients receiving aminoglycoside antibiotics or potent diuretics such as furosemide as these combinations are suspected to adversely affect renal function. However, at the recommended doses, enhancement of nephrotoxicity is unlikely to be a problem with Cefotaxime.

Probenecid interferes with renal tubular transfer of Cefotaxime delaying its excretion and increasing the plasma concentration.

4.6 Pregnancy and lactation
Pregnancy: It is known that Cefotaxime crosses the placental barrier. Although studies in animals have not shown an adverse effect on the developing foetus, the safety of Cefotaxime in human pregnancy has not been established. Consequently, Cefotaxime should not be administered during pregnancy, especially during the first trimester, without carefully weighing the expected benefit against possible risks.

Lactation: Cefotaxime is excreted in the milk.

4.7 Effects on ability to drive and use machines
There is no evidence that Cefotaxime directly impairs the ability to drive or to operate machines.
4.8 Undesirable effects

Adverse reactions to Cefotaxime have occurred relatively infrequently and have generally been mild and transient. Effects reported include candidiasis, nausea, vomiting, abdominal pain, diarrhoea (diarrhoea may sometimes be a symptom of pseudomembranous colitis ([see warnings])), transient rises in liver transaminases, alkaline phosphatase and/or bilirubin.

As with other cephalosporins, changes in renal function have been rarely observed with high doses of Cefotaxime, particularly when co-prescribed with aminoglycosides. Rare cases of interstitial nephritis have been reported in patients treated with Cefotaxime. Administration of high doses of cephalosporins, particularly in patients with renal insufficiency, may result in encephalopathy (e.g. impairment of consciousness, abnormal movements and convulsions). Hypersensitivity reactions have been reported. These include skin rashes, pruritus and less frequently urticaria, drug fever and very rarely anaphylaxis (e.g. angioedema and bronchospasm possibly culminating in shock).

As with other beta-lactam antibiotics, granulocytopenia and more rarely agranulocytosis may develop during treatment with Cefotaxime, particularly if given over long periods. A few cases of eosinophilia and neutropenia have been observed, reversible when treatment is ceased. Some cases of rapidly reversible eosinophilia and thrombocytopenia on stopping treatment, have been reported. Rare cases of haemolytic anaemia have been reported. For cases of treatment lasting longer than 10 days, blood count should therefore be monitored. Transient pain may be experienced at the site of injection. This is more likely to occur with higher doses. Occasionally, phlebitis has been reported in patients receiving intravenous Cefotaxime. However, this has rarely been a cause for discontinuation of treatment.

A very small number of cases of arthralgias have occurred following rapid bolus infusion through a central venous catheter. The following symptoms have occurred after several weeks of treatment for bacteraemia (Laime’s Disease): skin rash, itching, fever, leucopenia, increases in liver enzymes, difficulty of breathing, joint discomfort. To some extent these manifestations are consistent with the symptoms of the underlying disease, for which the patient is being treated.

4.9 Overdose

Serum levels of Cefotaxime may be reduced by peritoneal dialysis or haemodialysis. In the case of overdosage, particularly in renal insufficiency there is a risk of reversible encephalopathy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Cefotaxime is a broad spectrum bactericidal cephalosporin antibiotic. Cefotaxime is exceptionally active in vitro against Gram-negative organisms sensitive or resistant to first or second generation cephalosporins. It is similar to other cephalosporins in activity against Gram-positive bacteria.

5.2 Pharmacokinetic properties

After a 1000mg intravenous bolus, mean peak plasma concentrations of cefotaxime usually range between 81 and 102µg/ml. Doses of 500mg and 2000mg produce plasma concentrations of 38 and 200µg/ml, respectively. There is no accumulation following administration of 1000mg intravenously.

The apparent volume of distribution at steady-state of cefotaxime is 21.8L/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 30µg/ml in children with meningitis. Cefotaxime usually passes the blood-brain barrier in levels above the MIC of common sensitive pathogens when the meninges are inflamed. Concentrations (0.2-5.4µg/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 350ml/minute and renal clearance 145 to 217ml/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

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipient(s) None.

6.2 Incompatibilities None stated.

6.3 Shelf-life

Finished product: 24 months. Reconstituted solution: 24 hours.

6.4 Special precautions for storage

Finished Product: Store below 25°C. Protect from light. Reconstituted Solution: Whilst it is preferable to use only freshly prepared solutions for intravenous injection, Cefotaxime is compatible with several commonly used intravenous infusion fluids and will retain satisfactory potency for up to 24 hours refrigerated (2-8°C) in the following:

- Water for Injections Ph. Eur.
- Sodium Chloride Injection BP
- 5% Dextrose Injection BP
- Dextrose and Sodium Chloride Injection BP (Ringer-lactate injection).

After 24 hours any unused solution should be discarded. Cefotaxime is also compatible with 1% lignocaine, however freshly prepared solutions should be used.

Cefotaxime is also compatible with metronidazole infusion (500mg/100ml) and both will maintain potency when refrigerated (2-8°C) for up to 24 hours. Some increase in colour of prepared solutions may occur on storage. However, provided the recommended storage conditions are observed, this does not indicate change in potency or safety.

6.5 Nature and contents of container

Cefotaxime is supplied in tubular or moulded glass vials Ph. Eur, closed with a grey elastomer stopper and sealed with either an aluminium cap fitted with a detachable flip top, or an infusion connector closure. The bottles are boxed individually and in packs of 10.

6.6 Instructions for use/handling Not applicable.

7. Manufacturer: Lupin Ltd., India