1 Name of the Medicinal Product

1.1 Name of the Medicinal Product

TOX INJECTION

Cefotaxime for Injection USP 1gm

1.2. Strength

Each vial contains:

Cefotaxime sodium (sterile) USP

Eq. to Cefotaxime 1000 mg

1.3. Pharmaceutical Dosage Form

Injectable Preparation (Sterile Preparation)

2. Qualitative And Quantitative Composition

Qualitative Declaration

The TOX INJECTION contains (Cefotaxime for Injection USP 1gm)

Quantitative Declaration

Composition:

Each Vial contains		
Cefotaxime sodium (sterile)	USP	
Eq. to cefotaxime		1000mg

3. Pharmaceutical Form

Powder for solution for injection or infusion.

4. Clinical Particulars

4.1 Therapeutic 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 species.)

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

Posology

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 of a sensitive micro-organism: 1g every 12 hours corresponding to a total daily dosage of 2g intramuscularly or intravenously.

Infection in the presence 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.

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.

Elderly

No dosage adjustment is required, provided that renal and hepatic functions 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 may be 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 $\leq$ 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 solution or 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 over 3-5 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 Special Warning and Precautions for Use

Special care is indicated in patients who have had an anaphylactic response to penicillin. Preliminary enquiry about hypersensitivity to penicillin and other lactam antibiotics is necessary before prescribing cephalosporins since cross allergy occurs in 5-10% of cases. In case of allergic reaction, the treatment should be stopped immediately.

• Patients with severe renal dysfunction may need dosage adjustment

• Cefotaxime should be used with caution in patients with allergic asthma.

• As with other broad-spectrum antibiotics, prolonged used may result in the overgrowth of non-susceptible organisms, which may require interruption of treatment. If super-infection occurs during treatment, specific anti-microbial therapy should be instituted if considered clinically necessary.

• Pseudomembranous colitis has been reported with the use of broad-spectrum antibiotics. Therefore, it is important to consider its diagnosis in patients who develop severe diarrhea during or after antibiotic use. The presence of C. difficile toxin should be investigated and treatment with cefotaxime stopped in cases of suspected colitis. The diagnosis can be confirmed by toxin detection and antibiotic therapy (e.g. oral vancomycin or metronidazole) should be initiated if considered clinically necessary. The administration of products which cause foecal stasis should be avoided.

• Since haematological abnormalities may develop during treatment with cefotaxime, blood count should be monitored if treatment lasts for longer than 7 days. In case of neutropenia (< 1400 neutrophils/mm3), treatments should be interrupted.

• Do not mix aminoglycosides and cefotaxime in the same syringe of liquids for perfusion.

• Fast infusion in a central vein can cause arrhythmia.

• The sodium content of cefotaxime (2.09mmol/g) should be taken into account when prescribing to patients requiring sodium retention.

• Cefotaxime constituted with lidocaine must never be used:

- by the intravenous route.
- in infants under 30 months.
- in subjects with a previous history of hypersensitivity to this product.
- in patients who have an unpaced heart block.
- in patients with severe heart failure.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

With other medicaments:

Concomitant administration of probenecid leads to an increase and prolongation of serum concentrations of cefotaxime by inhibition of renal elimination of cefotaxime.

The efficacy of oral contraceptives may be decreased during concomitant use of cefotaxime. Therefore during therapy with Cefotaxime additional contraceptive measured should be used.

Concurrent treatment with high doses of cephalosporins and nephrotoxic drugs such as aminoglycosides or potent diuretics (e.g. furosemide) may adversely affect renal function. The monitoring of the renal function is strictly recommended.

Cefotaxime should not be combined with bacteriostatic antibiotics (e.g. tetracyclines, erythromycin and chloramphenicol) since an antagonistic effect is possible.

Other forms of interaction:

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.

A false-positive reaction to glucose may occur with reducing substances (Benedict's or Fehling's solution, or with Clinitest tablets) but not with the use of specific enzyme-based tests (glucose oxidase methods).

4.6 Fertility, pregnancy and lactation

There are no adequate data to assess possible harmfulness of cefotaxime during pregnancy. To date, animal experiments show no indication for adverse effects. Caution should be exercised when prescribing to pregnant women.

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, to Saccharomyces colinisation and may also lead to desensitization. A decision should be made whether to discontinue nursing or discontinue treatment taking into account the importance of cefotaxime to the nursing woman.

4.7 Effects on Ability to Drive and Use Machines

There have been no reports of the effects of Cefotaxime on the ability to drive.

4.8 Undesirable Effects

Infections and infestations

Prolonged use may result in overgrowth of non-susceptible organisms

Blood and lymphatic system disorders

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, but these were reversible when treatment was ceased. Rare cases of haemolytic anaemia have been reported. Rare cases of thrombocytopenia have been recorded, but these were rapidly reversible on withdrawal of treatment. It is therefore recommended that blood count should be monitored if treatment lasts for longer than 7 days.

Nervous system disorders

Administration of high doses of antibiotic belonging to this group (particularly in patients with renal insufficiency) may result in encephalopathy, which may result in dizziness, convulsions and fatigue.

Cardiac disorders

A very small number of cases of arrhythmia have occurred following rapid bolus infusion through a central venous catheter.

Gastrointestinal disorders

Commonly, patients receiving cefotaxime experience gastrointestinal disturbance such as candidasis, nausea, vomiting, abdominal pain, diarrhea. If severe and persistent diarrhea occurs, pseudomenbranous colitis should be considered. In cases or suspicion of pseudomenranous colitis, treatment with cefotaxime should be discontinued and appropriate therapy should be initiated.

Hepato-biliary disorders

Moderate and transient increase in bilirubin, liver transaminase and other enzymes has been observed rarely (ALT, AST, LDH, GGT, alkaline phosphatase).

Skin and cutaneous tissue disorders

Hypersensitivity reactions have been reported, these include cutaneous reactions such as skin rashes, pruritus, urticaria

• Drug fever

• Erythema multiforme exsudativum,

• Stevens-Johnson syndrome

• Toxic epidermal necrolysis

• Anaphylactic shock

In patients with allergic reactions, hypersensitivity reactions after administration of Cefotaxime are more likely to occur.

During therapy of infections with spirochetes, a Herxheimer-like reaction may occur. This may result in fever, shivering, headache and joint pain.

Renal and urinary disorders

• There may be a temporary increase in creatinine and urea in the serum.

• There have been very rare reports of reversible interstitial nephritis.

General disorder and administration site conditions

Common

Transient and local pain may be experienced at the site of injection. This is more likely to occur with higher doses. Phlebitis has been reported in patients receiving intravenous cefotaxime. However, this has rarely been a cause for discontinuation of treatment.

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

4.9 Overdose

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.

5 Pharmacological Properties

5.1 Pharmacodynamic properties

ATC Code: J01DD10

Pharmacotherapeutic group: Beta-lactam antibiotics, cephalosporins

General properties:

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.

5.2 Pharmacokinetic 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-desacetyl cefotaxime metabolite, which also has antibiotic properties.

Elimination

The main route of excretion of cefotaxime and O-desacetyl cefotaxime is the kidney. Only a small amount (2%) of cefotaxime is excreted in the bile. In the urine collected within 6 hours 40-60% of the 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-desacetylcefotaxime 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 and chronological age, the half-life being prolonged in premature and low birth weight neonates of the same age.

5.3 Preclinical Safety Data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat dose toxicity, genotoxicity, and toxicity to reproduction.

Cefotaxime passes through the placenta. After intravenous administration of 1 g cefotaxime during the birth values of 14 μg/ml were measures in the umbilical cord serum in the first 90 minutes after application, which dropped to approximately 2.5 μg/ml by the end of the second hour after application. In the amniotic fluid, the highest concentration of 6.9 μg/ml was measured after 3-4 hours. This value exceeds the MIC for most gram-negative bacteria.

6. Pharmaceutical Particulars

6.1 List of Excipients

Water for Injection BP (For reconstitution)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6

6.3 Shelf Life

Vial before opening: 3 years.

Vial after first opening: The product should be used immediately.

After reconstitution: The product should be used immediately.

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 would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special Precautions for Storage

Unopened: Store below 25ºC, Protect from light and moisture and do not freeze.

6.5 Nature and Contents of Container

Type II Clear glass vial, with a bromobutyl stopper and a flip off aluminum and polypropylene cap.

6.6 Special Precautions for Disposal and Other Handling

Cefotaxime is supplied as a off white to pale yellow crystalline which when dissolved in Water for Injections. forms a straw-coloured solution suitable for IV or IM injection. Variations in the intensity of colour of the freshly prepared solution do not indicate a change in potency or safety.

Whilst it is preferable to use only freshly prepared solutions for both intravenous and intramuscular injection, Cefotaxime is compatible with several commonly used intravenous infusion fluids:

Cefotaxime is also compatible with metronidazole infusion (500mg/100ml). 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.

This medicinal product is for single use only; Discard any contents remaining in the vial immediately after use.

The reconstituted solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.

7. Registrant/Sole Agent

EMBASSY PHARMACEUTICAL & CHEMICALS LTD.

41, Ademola Street, South West Ikoyi,

Lagos, Nigeria, Tel.: 01-2900791

8. Manufacturer

LABORATE PHARMACEUTICALS INDIA LIMITED

31, Rajban Road, Nariwala, Paonta sahib (H.P.)

HO: E-11, Indl. Area, Panipat – 132 103 (INDIA)

laborate@laborate.com

9. Date of Revision of Text

To be given after approval of product

10. Dosimetry (If applicable)

Not applicable

11. Instructions for Preparation of Radiopharmaceuticals (If applicable)

Not applicable