**SUMMARY OF PRODUCT CHARACTERISTICS**

**1. Name of the medicinal product:**
Cefotax vial

**2. Qualitative and quantitative composition:**
CEFOTAX 250 mg Vial:
Each Vial contains:
Cefotaxime sodium ..... 262 mg
Equivalent to Cefotaxime..... 250 mg
Each Ampoule contains:
Water for injection..... 2 ml
CEFOTAX 500 mg Vial:
Each Vial contains:
Cefotaxime sodium ..... 524 mg
Equivalent to Cefotaxime..... 500 mg
Each Ampoule contains:
Water for injection..... 2 ml
CEFOTAX 1 g Vial:
Each Vial contains:
Cefotaxime sodium ..... 1048 mg
Equivalent to Cefotaxime..... 1000 mg
Each Ampoule contains:
Water for injection..... 5 ml
CEFOTAX 2 g Vial:
Each Vial contains:
Cefotaxime sodium ..... 2096.6 mg
Equivalent to Cefotaxime..... 2000 mg
Each Ampoule contains:
Water for injection..... 10 ml

**3. Pharmaceutical form:**
It is white or slightly yellow powder, hygroscopic. Freely soluble in water and sparingly soluble in methanol.

**4. Clinical particulars:**

**4.1 Therapeutic indications:**

**CEFOTAX** 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, septicemia, bacterial endocarditis, meningitis, peritonitis and other serious bacterial infections suitable for parenteral antibiotic therapy.

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

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**4.2 Posology and method of administration:**

**CEFOTAX** 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 12 g daily given in three or four divided doses. For infections caused by sensitive Pseudomonas species daily doses of greater than 6 g will usually be required.

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

**Neonates**: The recommended dosage is 50 mg/kg/day in two to four divided doses. In severe infections 150-200 mg/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 CEFOTAX in severe renal failure (GFR <5ml/min = serum creatinine approximately 751 micromol/litre). After an initial loading dose of 1 g, daily dose should be halved without change in the frequency of dosing, i.e. 1 g 12 hourly becomes 0.5 g 12 hourly, 1 g 8 hourly becomes 0.5 g 8 hourly, 2 g 8 hourly becomes 1 g 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.

**Dosage in Hepatic Impairment:** No dosage adjustment is required.

**Intravenous and Intramuscular Administration:** Reconstitute CEFOTAX 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):** CEFOTAX may be administered by intravenous infusion using the fluids stated in (Special precautions for disposal). 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 **CEFOTAX**, penicillin or to any other type of beta-lactam drug.

Allergic cross reactions can exist between penicillins and cephalosporins.

**4.4 Special warnings and precautions for use:**

As with other antibiotics, the use of **CEFOTAX**, 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 **CEFOTAX**, 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 **CEFOTAX** is strictly contraindicated 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 "Dosage and Administration".

Caution should be exercised if **CEFOTAX** is administered together with aminoglycosides, probenecid or other nephrotoxic drugs.

Renal function must be monitored in these patients, the elderly, and those with pre-existing renal impairment.

**Hematological Reactions:** Leukopenia, neutropenia, and more rarely, agranulocytosis may develop during treatment with **CEFOTAX**, 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 hemolytic anemia have also been reported.

Sodium Intake: The sodium content of cefotaxime 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.

Diarrhea, 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 pseudomembranous 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 diarrhea during or subsequent to the administration of **CEFOTAX**.
If a diagnosis of pseudomembranous colitis is suspected, **CEFOTAX** should be stopped immediately and appropriate specific antibody therapy should be started without delay.
Clostridium difficile associated disease can be favored by fecal 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-oxidase specific method is used.
**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 **Special precautions for disposal.**

**4.5 Interaction with other medicinal products:**
**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 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.

**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.

Cefotaxime crosses the placental barrier. Therefore, CEFOTAX 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 diarrhea, colonization by yeast-like fungi, and sensitization 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 to 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:**

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:**

Not known: Superinfection.

Blood and the Lymphatic System disorders:

Uncommon: Leukopenia, eosinophilia, thrombocytopenia.

Not known: Neutropenia, granulocytopenia, agranulocytosis, hemolytic anemia.

**Immune System disorders:**

Uncommon: Jarisch- Herxheimer reaction.

Not known: Anaphylactic reactions, angioedema, bronchospasm, anaphylactic shock.

**Nervous System disorders:**

Uncommon: Convulsions.

Not known: Headache, dizziness, encephalopathy, (e.g. impairment of consciousness, abnormal movements).

**Cardiac disorders:**

Not known: Arrhythmia following rapid bolus infusion through central venous catheter.

**Gastrointestinal disorders:**

Uncommon: Diarrhea.

Not known: Nausea, vomiting, abdominal pain, pseudomembranous colitis.

**Hepatobiliary disorders:**

Uncommon: Increase in liver enzymes (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase) and/or bilirubin.

Not known: Hepatitis* (sometimes with jaundice).

**Skin and Subcutaneous disorders:**

Uncommon: Rash, pruritus, urticaria, drug fever.

Not known: Erythema multiforme, Stevens- Johnson syndrome, toxic epidermal necrolysis.

**Renal and Urinary disorders:**

Uncommon: Decrease in renal function/Increase of creatinine (particularly when co-prescribed with aminoglycosides).

Not known: Interstitial nephritis, candidiasis.

**General disorders and Administration site condition:**
Very common: For IM Formulations: Pain at the injection site.
Uncommon: Fever Inflammatory reactions at the injection site, including phlebitis/thrombophlebitis.
* 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, CEFOTAX 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 hemodialysis.

**5. Pharmacological properties:**
**5.1 Pharmacodynamic properties:**
General Properties.
**Pharmacotherapeutic group:** Beta-lactam antibiotics, cephalosporins.
**Mechanism 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.
**Susceptible Species:**
**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*.
Viridans Group Streptococci.
Gram-negative aerobes:
Citrobacter spp.*.
Escherichia coli*.
Hemophilus influenzae*.
Hemophilus 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.

**5.2 Pharmacokinetic properties:**

After a 1000mg intravenous bolus, mean peak plasma concentrations of cefotaxime usually range between 81 and 102 microgram/ml. Doses of 500 mg and 2 g produce plasma concentrations of 38 and 200 microgram/ml, respectively. There is no accumulation following administration of 1 g 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 1 g 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 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, 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 metabolized 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 decreases with reduction in renal function.

**6. Pharmaceutical particulars:**

**6.1 List of excipients:**

None.

**6.2 Incompatibilities:**

None.

**6.3 Shelf life:**

2 years.

**6.4 Special precautions for storage:**

**CEFOTAX 250 mg Vial:** Store at a temperature not exceeding 30°C and used directly after reconstitution.
**CEFOTAX 500 mg Vial:** Store at a temperature not exceeding 30°C and after reconstitution store for 24 hours at (2-8)°C.
**CEFOTAX 1 g Vial:** Store at a temperature not exceeding 30°C and after reconstitution store for 24 hours at (2-8)°C.
**CEFOTAX 2 g Vial:** Store at a temperature not exceeding 30°C and after reconstitution store for 24 hours at (2-8)°C.

**6.5 Nature and contents of container:**

**CEFOTAX 250 mg Vial:** Carton box containing 1, 50 colorless transparent type I glass vials each containing 262 mg powder with bromobutyl elastic rubber stopper and AL flip off cap and 1, 50 colorless transparent glass (type I) ampoules containing 2ml water for injection and an inner leaflet

**CEFOTAX 500 mg Vial:** Carton box containing 1, 50 transparent colorless glass (Type I) vials each containing powder of 524 mg with bromobutyl rubber stopper, sealed with aluminium and covered with HDPE plastic flip off tear cap & 1, 50 transparent glass (Type I) ampoules containing 2 ml water for injection and an inner leaflet .
**CEFOTAX 1 g Vial:** Carton box containing 1, 50 colorless glass (type I) vials (its capacity is 20 ml) with bromobutyl rubber stopper sealed with AL flip off cap each containing 1048 mg powder & 1, 50 low density polyethylene ampoules with immediate label containing 5 ml water for injection (capacity = 6 ml) and an inner leaflet.
**CEFOTAX 2 g Vial:** Carton box containing 1, 50 colourless glass (type I) sterile vials with rubber stopper & AL flip off cap & 1, 50 ampoules (10 ml water for injection) and insert leaflet.

**6.6 Special precautions for disposal and other handling:**
When dissolved in Water for Injections PhEur, **Cefotax** forms a straw-coloured solution suitable for intravenous and intramuscular injection. Variations in the intensity of colour of the freshly prepared solutions do not indicate a change in potency or safety.
**Dilution table (Intramuscular and Intravenous Administration):**

| **Vial size** | **Diluent to be added** | **Approx. available volume** | **Approx. displacement volume** |
|---|---|---|---|
| **250, 500 mg** | 2 ml | 2.3 ml | 0.3 ml |
| **1 g** | 4 ml | 4.6 ml | 0.6 ml |
| **2 g** | 10 ml | 11.4 ml | 1.4 ml |

*** Water for injection**

**Reconstituted Solution:** 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 and will retain satisfactory potency when stored at temperature 2 – 8 °C for 24 hours refrigerated in the following:
Water for Injections,
0.9% Sodium Chloride Intravenous Infusion,
5% Dextrose Intravenous Infusion,
Ringer-lactate solution Intravenous Infusion.
Intravenous Infusion:

1-2g cefotaxime are dissolved in 40-100ml of infusion fluid.
After 24 hours at room temperature any unused solution should be discarded.
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 color of prepared solutions may occur on storage. However, provided the recommended storage conditions are observed, this does not indicate change in potency or safety.

**7. Marketing authorisation holder:**
EIPICO

**8. Date of revision of the text:**
MARCH 2020