SECTION 2: SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

Cefotaxime

1 g powder for solution for injection or infusion

Cefotaxime (as Cefotaxime Sodium)

1. NAME OF THE MEDICINAL PRODUCT

CEFOTAXIME 1 g powder for solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1 g Cefotaxime as Cefotaxime sodium

Excipient with known effect:

Cefotaxime contains approximately 48mg (2.09 mmol) of sodium per gram of Cefotaxime.

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion.

Cefotaxime is a white to pale yellow powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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:

- Lower respiratory tract infections, including pneumonia
- Urinary tract infections
- Genital infections caused by gonococci, particularly when penicillin has failed or is unsuitable
- Gynecologic infections, including pelvic inflammatory disease, endometritis and pelvic cellulitis. Cefotaxime, like other cephalosporins, has no activity against *Chlamydia trachomatis*. Therefore, when cephalosporins are used in the treatment of patients with pelvic inflammatory disease and *C. trachomatis* is one of the suspected pathogens, appropriate anti-chlamydial coverage should be added
- Skin and skin structure infections
- Intra-abdominal infections including peritonitis

- Bone and/or joint infections including osteomyelitis
- Central nervous system infections, e.g., meningitis and ventriculitis
- Lyme-borreliosis (especially stages II and III)
- Septicemia
- Endocarditis in case of gram-negative microorganism in combination with another suitable antibiotic

Cefotaxime may be used for peri-operative prophylaxis in surgical procedures such as colorectal, gastrointestinal, prostatic, urogenital and gynecological surgery in patients who have a definite risk of post-operative infections. Cefotaxime should be used in combination with another antibiotic that can provide anaerobic cover in the treatment of intra-abdominal infections. Cefotaxime should be used in combination with an aminoglycoside in the treatment of infections caused by *Pseudomonas*.

Consideration should be given to official guidelines on the appropriate use of antibacterial agents.

4.2. Posology and method of administration

Posology

Cefotaxime may be administered intravenously (IV) by bolus injection or by infusion, or by intramuscular (IM) 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 and children over 12 years

The usual dose in adults and adolescents is 2 to 6 g daily. The daily dosage should be divided in 2 single doses each 12 hour. However, dosage may be varied according to the severity of the infection, sensitivity of causative organism and condition of the patient.

Common infections in presence (or suspicion) of a sensitive pathogen: 1 g every 12 hours corresponding to a total daily dosage of 2 g.

Infections in presence (or suspicion) of several sensitive or moderately sensitive pathogens: 1 - 2 g every 12 hours corresponding to a total daily dosage of 2 - 4 g.

Severe infection by non-sensitive pathogens or for infections that cannot be localised: 2 - 3 g as a single dose every 6 to 8 hours up to a maximum daily dosage of 12 g.

Perioperative Prophylaxis

For peri-operative infection prophylaxis the administration of a single dose of 1 to 2 g

Cefotaxime 30 to 60 minutes prior to the operation is recommended. Another antibiotic to cover anaerobic organisms is necessary. A repeat dose is required if the duration of the operation exceeds 90 minutes.

Cesarean Section Patients

The first dose of 1 g is administered intravenously as soon as the umbilical cord is clamped. The second and third doses should be given as 1 g intravenously or intramuscularly at 6 and 12 hours after the first dose.

Infants and children up to 12

Infants and Children (1 month to 12 years)

The usual dosage for infants and children <50 kg 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.

In infants and children >50 kg the usual dose in adults should be given, without exceeding the maximum daily dose of 12 g.

Term newborn infants (0 to 27 days):

The recommended dosage is 50mg/kg/day in 2 to 4 divided doses (every 12 – 6 hours). In severe infections it may be necessary to increase the daily dose to 150-200 mg/kg/day under consideration of differences in maturity of the kidneys and renal function.

Please see also "Special Dose Recommendations / Bacterial meningitis" below.

Preterm newborn infants: It is not necessary to differentiate between premature and normal-gestational age infants.

Elderly: No dosage adjustment is required, provided that the renal and hepatic functions are normal.

Special Dose Recommendations

Lyme borrelisosis: A daily dose of 6 g Cefotaxime (14 to 21 days duration). The daily dose was generally administered divided into 3 individual administrations at 8 hour intervals respectively (2 g Cefotaxime 3 times daily).

Infections caused by Neisseria gonorrhoeae: For the treatment of gonorrhoea in adults, a single injection of 0.5 g – 1 g Cefotaxime is administered (intramuscularly or intravenously).

Bacterial meningitis:

In adults daily doses of 6 to 12 g divided into equal doses every 6 to 8 hours are recommended.

Infants and children (from 1 month up to 12 years of age): 150 to 200 mg/kg/day divided into equal doses every 6 to 8 hours.

Term newborn infants:

Term newborn infants 0 to 7 days: 50 mg/kg every 12 hours.

Term newborn infants 8 to 27 days: 50 mg/kg every 8 hours.

Intra-abdominal infections: Cefotaxime should be used in combination with an antibiotic that is active against anaerobes in the treatment of intra-abdominal infections (see section 5.1).

Dosage in renal impairment

Because of extra-renal elimination, it is only necessary to reduce the dosage of cefotaxime in severe renal failure (kidney glomerular filtration rate (GFR) ≤5ml/min = serum creatinine approximately 751 µmol/L). 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.

Duration of therapy

The duration of the treatment depends on the course of the disease. As a general rule Cefotaxime is administered for a further 3 to 4 days after improvement/regression of the symptoms.

Method of administration

Intramuscular (IM) Administration

Reconstitute cefotaxime with sterile water for injections as directed in Section 6.6. Shake well until dissolved and then withdraw the entire contents of the vial into the syringe. As with all IM preparations, Cefotaxime powder for solution for injection or infusion should be injected well within the body of a relatively large muscle such as the upper outer quadrant of the buttock (i.e., gluteus maximus); aspiration is necessary to avoid inadvertent injection into a blood vessel. Individual IM doses of 2 g may be given if the dose is divided and is administered in different intramuscular sites.

Intravenous (IV) administration (Injection or Infusion)

The IV route is preferable for patients with bacteremia, bacterial septicemia, peritonitis, meningitis, or other severe or life-threatening infections, or for patients who may be poor risks because of lowered resistance resulting from such debilitating conditions as malnutrition, trauma, surgery, diabetes, heart failure, or malignancy, particularly if shock is present or impending.

For intermittent IV injections, the solution containing 1 g or 2 g in 10 ml of sterile water for

injection 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 may be administered by IV infusion using the fluids stated in Section 6.6. The prepared solution may be administered over 20-60 minutes.

4.3. Contraindications

Hypersensitivity to cefotaxime or to other cephalosporins.
Previous, immediate and/or severe hypersensitivity reaction to penicillin or any beta-lactam antibiotics. Allergic cross reactions can exist between penicillins and cephalosporins (see section 4.4).
For pharmaceutical forms containing lidocaine:

- known history of hypersensitivity to lidocaine or other local anesthetics 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, *Pseudomona*s *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 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 (see sections 4.3 and 4.8). 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 (see section 4.8). 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". (see section 4.2). Caution should be exercised if cefotaxime is administered together with aminoglycosides, probenecid or other nephrotoxic drugs (see section 4.5). 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 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 hemolytic anemia have also been reported (see section 4.8).

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.

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 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 diarrhea 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 favored 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) (see section 4.8).
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 (see section 4.2).
See section 4.3 for contraindications for formulations containing lidocaine.
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.
Probenecid: 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 (see sections 4.2).
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. Fertility, 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 only be used during pregnancy if 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 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.

Fertility

Reproductive studies have shown no evidence of adverse effects on male or female fertility.

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. High doses of cefotaxime, particularly in patients with renal insufficiency, may cause encephalopathy (e.g. impairment of consciousness, abnormal movements and convulsions) (see section 4.8). Patients should be advised not to drive or operate machinery if any such symptoms occur.

4.8. Undesirable effects

a. *Summary of the safety profile*

Cefotaxime is tolerated well when it is used in recommended dosages and dosing regimens. The most common adverse reactions have been local reactions following IM or IV injection. Other adverse reactions have been encountered infrequently.

b. *Tabulated list of adverse reactions*

For estimation of development frequency of side effects the following criteria are used: very

common (≥1/10), common (from ≥1/100 to <1/10), uncommon (from ≥1/1000 to <1/100), rare (from ≥1/10 000 to <1/1000), very rare (from <1/10 000 including individual case safety report), and "the frequency is not known" (according to the available data, it is not possible to estimate the frequency).

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known *
Infections and infestations						Superinfection, e.g. oral or vaginal candidiasis
Blood and the lymphatic system disorders			Leukopenia Eosinophilia Thrombocytopenia			Neutropenia Granulocytopenia Agranulocytosis Hemolytic anemia
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			Diarrhea			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			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
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

* postmarketing 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.

c. *Reporting of suspected adverse reactions.* Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

To report any side effect(s):

- _____:

- _____

Fax: _____

Call ____ at _____, Exts: _____.

Toll free phone: _____

E-mail____@_____

Website: _____

Please contact the relevant competent authority.

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. Plasma levels of cefotaxime may be reduced by peritoneal dialysis or hemodialysis.

5. PHARMACODYNAMIC PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use, third-generation cephalosporins.

ATCcode: [J01D A10].

Mechanism of Action

Cefotaxime inhibits bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death.

Mechanism of resistance

Resistance to Cefotaxime may be due to production of extended-spectrum beta-lactamases that can efficiently hydrolyze the drug, to the induction and/or constitutive expression of AmpC enzymes, to reduced outer membrane permeability or to efflux pump mechanisms. More than one of these possible mechanisms may co-exist in a single bacterium.

Susceptibility test interpretive criteria for Cefotaxime

Current MIC breakpoints used to interpret cefotaxime susceptibility data are shown below:

European Committee on Antimicrobial Susceptibility Testing (EUCAST) Clinical MIC Breakpoints (v. 9.0, valid from 2019-01-01)

Pathogens	Susceptible	Resistant
Enterobacteriaceae[2]	≤1 mg/l	>2mg/l
Staphylococcus[1]	-[1]	-[1]
Streptococcus A, B, C, G[2]	-[2]	-[2]
Streptococcus pneumoniae	≤0.5mg/l	>2mg/l
Haemophilus influenzae	≤0.12mg/l	>0.12mg/l
Moraxella catarrhalis	≤1mg/l	>2mg/l

Neisseria gonorrhoea	≤0.12mg/l	>0.12mg/l
Neisseria meningitidis	≤0.12mg/l	>0.12mg/l
Non-species related breakpoints[3*]	≤1mg/l	>2mg/l

[1] Susceptibility of staphylococci to cephalosporins is inferred from the cefoxitin susceptibility. Methicillin-(Cefoxitin-)resistant Staphylococci are assessed as resistant, independent from the test results.

[2] The susceptibility of streptococcus groups A, B, C an d G to cephalosporins is inferred from the benzylpenicillin susceptibility.

[3] Breakpoints apply to a daily intravenous dose of 3 x 1 g and a high dose of at least 3 x 2 g.

* Generally based on serum pharmacokinetics

Prevalence of acquired resistance

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.

Susceptible
Gram-positive bacteria:
Staphylococcus aureus (methicillin-susceptible isolates only)[1]
Staphylococcus epidermidis
Streptococcus pneumoniae[1] (incl. penicillin-resistant strains)
Streptococcus pyogenes (Group A beta-hemolytic streptococci)
Streptococcus spp. (Viridans group streptococci)
Gram-negative bacteria:
Aeromonas hydrophyla
Borrelia burgdorferi
Citrobacter spp.[2]
Enterobacter spp.[2]
Escherichia coli.[2]
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella spp. (including *Klebsiella pneumoniae*)2
Morganella morganii2
Moraxella ctarrhalis

Neisseria gonorrhoeae (including beta-lactamase-positive and negative strains)
Neisseria meningitidis
Proteus mirabilis[2]
Proteus vulgaris[2]
Providencia rettgeri[2]
Providencia stuartii[2]
Serratia marcescens[2]
Yersinia enterocolitica
[1] Methicillin-(oxacillin) resistant staphylococci (MRSA) are resistant to all currently available β-lactam antibiotics including cefotaxime. [2] Most extended spectrum beta-lactamase (ESBL)-producing and carbapenemase-producing isolates are resistant to cefotaxime.
Anaerobic bacteria:
Bacteroides spp., including some isolates of *Bacteroides fragilis*
Clostridium spp. (most isolates of *Clostridium difficile* are resistant)
Fusobacterium spp. (including *Fusobacterium nucleatum*)
Peptococcus spp. *Peptostreptococcus* spp.
Resistant
Gram-positive aerobes
Enterococcus spp.
Enterococcus faecalis
Enterococcus faecium
Listeria monocytogenes
Staphylococcus aureus (MRSA)
Staphylococcus epidermidis (MRSE)
Gram-negative aerobes
Acinetobacter spp.
Legionella pneumophila
Pseudomonas aeruginosa
Stenotrophomonas maltophilia
Anaerobes
Clostridium difficile

Others
Clamydiae spp.
Chlamydophila spp.
Mycoplasma spp.

5.2 Pharmacokinetic properties

Absorption

Cefotaxime is for parenteral application. After a 1000 mg intravenous bolus, mean peak plasma concentrations of cefotaxime usually range between 81 and 102 microgram/ml. Doses of 500 mg and 2000 mg produce plasma concentrations of 38 and 200 mg/l, respectively. Intramuscular injection produces mean peak plasma concentrations of about 20 mg/l within 30 minutes following a 1 g dose. There is no accumulation following administration of 1000mg intravenously or 500mg intramuscularly for 10 or 14 days.

Distribution

The apparent volume of distribution at steady-state of cefotaxime is 21.6 litres/1.73m^2 after 1 g intravenous 30 min infusion. Protein binding for cefotaxime is approximately 25 - 40 %.

Cefotaxime has 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 are between 3 and 30 µg/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 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, renal tissue, peritoneal fluid and gall bladder wall, after usual therapeutic doses. High concentrations of cefotaxime and desacetyl-cefotaxime are attained in bile.

Cefotaxime passes the placenta and attains high concentrations in foetal fluid and tissues (up to 6 mg/kg). Small amounts of cefotaxime diffuse into the breast milk (concentrations in the human breast milk: 0.4 mg/l after administration of 2 g).

Biotransformation

Cefotaxime is metabolised in humans to a considerable extent. Approximately 15 - 25 % of a parenteral dose are metabolised to the O-desacetyl-cefotaxime metabolite, which also has antibiotic properties. In addition to O-desacetyl-cefotaxime, there are two inactive lactones. O-

desacetyl-cefotaxime forms a lactone as a short-lived intermediate, that can not be detected in urine or plasma, because it undergoes rapid conversion to stereoisomers of the open ring (beta-lactam ring) lactone. These are also excreted in the urine.

Elimination

The main route of excretion of cefotaxime and O-desacetyl-cefotaxime is through the kidneys. Only a small amount (about 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-desacetyl-cefotaxime. After IV administration of radioactive labelled cefotaxime more than 80% can be recovered in the urine; 50 - 60 % of this fraction is unchanged cefotaxime and the rest contains three 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-desacetyl-cefotaxime are normally about 50 - 80 and 90 minutes, respectively. In elderly, the serum half-life of cefotaxime is 120 - 150 min. In patients with severely impaired renal function (creatinine clearance 3 - 10 ml/min) the serum half-life of cefotaxime can be increased to 2.5-10 hours. There is no accumulation of cefotaxime following administration of 1 g intravenously or 500 mg intramuscularly for 10 or 14 days. In term newborn infants the pharmacokinetics are influenced by gestation and chronological age, the half-life being prolonged in preterm and low birth weight term newborn infants of the same age.

5.3. Preclinical safety data

There are no pre-clinical data of relevance to the prescriber that are additional to those included in other sections.

5. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

None.

6.2. Incompatibilities

Cefotaxime sodium should not be mixed with alkaline solutions having a pH-value of more than 7.5, e. g. sodium bicarbonate

Cefotaxime should not be mixed with aminoglycosides in the same syringe or solution for infusion.. 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 section 6.6.

6.3. Shelf life

Unopened vials: 3 years.

For the reconstituted solution, chemical and physical in-use stability has been demonstrated for at least 6 hours at or below 30°C or 24 hours at 2-8°C.

6.4. Special precautions for storage

Unopened: Do not store above 30°C, keep the vials in the outer carton.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Cefotaxime 1 g powder for solution for IV and IM injection.

10 ml glass vial with rubber stopper and aluminium or flip-off cap, containing a sterile powder, equivalent to 1 g Cefotaxime.

The vials are boxed individually and in packs of 5, 10, 1-50 or 50 vials.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Dilution Table: Intravenous Administration

Vial size	Diluent* to be added	Approx available volume	Approx displacement volume
1 g	10 ml	10.6 ml	0.6 ml

*Water for injection

Intravenous Infusion: For IV infusion, a solution of cefotaxime may be added to 40-100ml of one of the following infusion fluids:

- 0.9% sodium chloride solution
- 5% dextrose solution
- 5% dextrose + 0.45% sodium chloride solution
- Ringer-lactate solution for injection

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.

Dilution Table: Intramuscular Administration

Vial size	Diluent* to be added	Approx available volume	Approx displacement volume
1 g	4 ml	4.6 ml	0.6 ml

*Water for injection or 1% lidocaine

Cefotaxime is compatible with 1% lidocaine injection; however freshly prepared solutions should be used.

When dissolved in water for injections, cefotaxime may 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.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder

"KRASPHARMA" OJSC

Russia, 660042, 60 let Oktyabrya st. 2, Krasnoyarsk

Tel.: +7 (391) 261-25-90. Fax: +7 (391) 261-17-44

8. Marketing authorization number(s)

Cefotaxime 1 g Powder for solution for injection or infusion _____

9. Date of first Authorisation/ renewal of the authorisation

_____.

10. Date of revision of the text

_____.