SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cefotaxime, 2 g, powder for solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains cefotaxime sodium equivalent to 2 g cefotaxime.

Excipient(s) with known effect

1 g of powder contains 48 mg of sodium (2,09 mmol) - see section 4.4.

3 PHARMACEUTICAL FORM

Powder for solution for injection/infusion.

A white or slightly yellow powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cefotaxime is indicated in the treatment of the following severe infections when known or thought very likely to be caused by bacteria that are susceptible to cefotaxime (see section 4.4 and 5.1):

- Bacterial pneumonia

- Complicated infections of the urinary tract including pyelonephritis
- Severe skin and soft tissue infections
- Genital infections, including gonorrhoea
- Intra-abdominal infections (such as peritonitis)
- Bacterial meningitis
- Endocarditis
- Borreliosis

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Perioperative prophylaxis. For surgical operations with increased risk of infections with anaerobic pathogens, e.g. colorectal surgery, a combination with an appropriate drug with activity against anaerobes is recommended.

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

4.2 Posology and method of administration

Cefotaxime may be administered by intravenous bolus injection or intravenous infusion or by intramuscular injection after reconstitution of the solution.

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 microbiological tests are known.

Adults and adolescents over 12 years

Adults and adolescents usually receive 2 to 6 g cefotaxime daily. The daily dose should be divided in two single doses every 12 hours.

- Common infections in presence (or suspicion) of sensitive bacteria: 1 g every 12 hours.
- Infections in presence (or suspicion) of several sensitive or moderately sensitive bacteria: 1 – 2 g every 12 hours.
- Severe infections or for infections that cannot be localised: 2 – 3 g as a single dose every 6 to 8 hours (maximum daily dose: 12 g).

A combination of cefotaxime and other antibiotics is indicated in severe infections.

Term newborn (0-28 days), infants and children up to 12 years of age

Depending on the severity of the infection: 50 – 100 – 150 mg / kg / day, 12 – 6 hourly.

In life-threatening situations the daily dose may be raised to 200 mg/kg/day under careful attention of the renal function, especially in the newborn period 0 – 7 days due to not fully matured kidney function.

Premature infants

The recommended dosage is 50 mg / kg / day divided into 2 to 4 doses (every 12 to 6 hours). This maximum dose should not be exceeded due to the not yet fully matured kidneys.

Elderly

No dosage adjustment is required, provided that the function of the kidneys and the liver is normal.

Other special recommendations

Gonorrhoea

For gonorrhoea, a single injection (intramuscularly or intravenously) of 500 mg – 1 g cefotaxime. For complicated infections, consideration should be given to available official guidelines. Syphilis should be excluded before initiating treatment.

Bacterial meningitis

Adults: Daily dose of 9 – 12 g cefotaxime divided into equal doses every 6 – 8 hours (3 g 3 – 4 times daily).

Children: 150 – 200 mg / kg / day divided into equal doses every 6 – 8 hours.

Newborns: 0 – 7 days: 50 mg / kg every 12 hours, 7 – 28 days: 50 mg / kg every 8 hours.

Perioperative prophylaxis

1 – 2 g as single dose as close to start of surgery as possible. In those cases where the operation time exceeds 90 minute an additional dose of prophylactic antibiotic should be given.

Intra-abdominal infections

Intra-abdominal infections should be treated with cefotaxime in combination with other antibiotics with coverage for anaerobic bacteria.

Dosage in renal function impairment:

In adult patients with a creatinine clearance of $\leq$ 5 mL / min, the initial dose equal to the recommended usual dose but the maintenance dose should be reduced by half

without change in the frequency of dosing. Blood tests to determine the required dose may be carried out.

Dosage in dialysis or peritoneal dialysis

In patients on haemodialysis and peritoneal dialysis an intravenous injection of 500 mg – 2 g, given at the end of each dialysis session and repeated every 24 hours, is sufficient to treat most infections efficaciously.

Duration of therapy

The duration of therapy with cefotaxime depends on the clinical condition of the patient and varies according to the bacteriological progress. 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).

Method of administration

Intravenous infusion

In order to avoid any risk of infection, the reconstitution of the solution for infusion should be done in close aseptic conditions. Do not postpone the infusion after the reconstitution of the solution.

For *short intravenous infusion:* Following reconstitution, the solution should be administered over 20 minutes.

For *long lasting intravenous infusion:* Following reconstitution, the solution should be administered over 50 – 60 minutes.

Intravenous injection

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.

Intramuscular injection

The intramuscular method of administration is restricted to exceptional clinical situations (e.g. gonorrhoea). It is not indicated in severe infections and should undergo a risk-benefit assessment. It is recommended that no more than 4 ml are injected unilaterally. If the daily dose exceeds 2 g cefotaxime or if cefotaxime is injected more frequently than twice per day, the intravenous route is recommended. In case of severe infections, intramuscular injection is not recommended.

The solution should be administered by deep intramuscular injection. Solutions with lidocaine must not be administered intravenously. Cefotaxime reconstituted with

lidocaine should not be administrated to children in the first year of age. The product information of the chosen lidocain containing medicinal product must be regarded.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

Cefotaxime and aminoglycosides should not be mixed in the same syringe or perfusion fluid.

4.3 Contraindications

- Hypersensitivity to the active substance, to other cephalosporins or any of the excipients listed in section 6.1.
- Previous, immediate and/or severe hypersensitivity reaction to penicillin or any beta-lactam antibiotic.

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. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

- Anaphylactic reactions

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.

The use of cefotaxime is strictly contra-indicated 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.

- Severe skin reactions

Severe cutaneous adverse reactions (SCARs) including acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported post-marketing in association with cefotaxime treatment.

At the time of prescription patients should be advised of the signs and symptoms for skin reactions.

If signs and symptoms suggestive of these reactions appear, cefotaxime should be withdrawn immediately. If the patient has developed AGEP, SJS, TEN or DRESS with the use of cefotaxime, treatment with cefotaxime must not be restarted and should be permanently discontinued.

In children, the presentation of a rash can be mistaken for the underlying infection or an alternative infectious process, and physicians should consider the possibility of a reaction to cefotaxime in children that develop symptoms of rash and fever during therapy with cefotaxime.

Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

- *Clostridium difficile* associated disease (e.g. pseudomembranous colitis)

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 antibiotic therapy should be started without delay. *Clostridium difficile* associated disease can be favoured by faecal stasis. Medicinal products that inhibit peristalsis should not be given.

- Haematological reactions

Leucopenia, neutropenia and, more rarely, bone marrow failure, pancytopenia or agranulocytosis may develop during treatment with cefotaxime (see Section 4.8.). 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 haemolytic anemia have also been reported. (see section 4.8).

- Patients with renal insufficiency

For patients with impaired renal function, the dosage should be modified according to the creatinine clearance calculated (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 preexisting renal impairment.

- 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.

- The use of cefotaxime for treatment of endocarditis should be restricted to patients known to have penicillin allergy (not type 1). Cefotaxime should be used in combination with other appropriate antibacterial agents, considering its limited antibacterial spectrum.

- 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.

- Sodium intake

This medicinal product contains 48 mg (2.09 mmol) sodium per 1 of powder, equivalent to 2.4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Cefotaxime is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

This medicinal product is administered only after reconstitution - see section 6.6.

The sodium content of the diluent should be taken into account when calculating the total sodium content of the prepared dilution of the product. For detailed information on the sodium content of the solution used to dilute the product, please refer to the product characteristics of the diluent used.

4.5 Interaction with other medicinal products and other forms of interaction

Uricosurics: Probenecid interferes with the 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 4.4 and 4.2).

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 in these patients (see section 4.4).

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

Interference with Laboratory Tests: As with other cephalosporins, a positive Coombs' test has been seen 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 (e.g. Fehling's solution) but not with the use of specific glucose oxidase methods.

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 not be used during pregnancy unless the anticipated benefit outweighs any potential risks.

Breastfeeding

Cefotaxime passes into human breast milk.

Effects on the physiological intestinal flora of the breast-fed infant leading to diarrhoea, colonisation by yeast-like fungi, and sensitisation 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 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).

In the case of side effects such as dizziness the patient's ability to concentrate and to react properly may be impaired. In such cases patients should refrain from driving cars and using machines.

4.8 Undesirable effects

System organ class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (<1/10,000)	Not kno be estim availabl
Infections and infestations						Superin section
Blood and the lymphatic system disorders			Leukopenia Eosinophilia Thrombocytopenia			Bone m failure Pancyto Neutrop Agranul (see sec Haemol anaemia

Immune system disorders			Jarisch-Herxheimer reaction			Anaphy reaction Angioed Broncho Anaphy
Nervous system disorders			Convulsions (see section 4.4)			Headacl Dizzine Encepha (e.g. im of conso abnorma moveme (see sec
Cardiac disorders						Arrhyth followir bolus in through venous Palpitat
Gastrointestinal disorders			Diarrhea			Nausea Vomitin Abdomi Pseudor colitis (s 4.4) Candidi
Hepato-bilary disorders			Increase in liver enzymes (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase) and/or bilirubin			Hepatiti (someti jaundice
Skin and subcutaneous tissue disorders			Rash Pruritus Urticaria			Erythem multifor Stevens- syndron Toxic ep necrolys (see sec Acute g exanthe pustulos Drug re eosinop systemi (DRESS section

Renal and urinary disorders			Decrease in renal function/increase of creatinine (particularly when coprescribed with aminoglycosides)			Acute re (see sec Interstit nephriti
General disorders and administration site conditions	*For IM formulations:* Pain at the injection site		Fever Inflammatory reactions at the injection site, including phlebitis/ thrombophlebitis, Malaise, Fatigue			*For IM formula the solv contains lidocain* Systemi to lidoc

* postmarketing experience

Jarisch-Herxheimer reaction

For the treatment of borreliosis (Lyme's Disease), 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.

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. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme, Website: (www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 ß-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. Serum levels of cefotaxime can be reduced by haemodialysis or peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Third-generation cephalosporin, ATC code: J01DD01

Mechanism of action

The bactericidal activity of cefotaxime results from the inhibition of bacterial cell wall synthesis (during the period of growth) caused by an inhibition of penicillin-binding proteins (PBPs) like transpeptidases.

Mechanism of resistance

A resistance to cefotaxime may be caused by following mechanisms:

- Inactivation by beta-lactamases. Cefotaxime can be hydrolysed by certain betalactamases, especially by extended-spectrum beta-lactamases (ESBLs) which can be found in strains of *Escherichia coli* or *Klebsiella pneumoniae*, or by chromosomal encoded inducible or constitutive beta-lactamases of the AmpC type which can be detected in *Enterobacter cloacae*. Therefore infections caused by pathogens with inducible, chromosomal encoded AmpC-beta-lactamases should not be treated with cefotaxime even in case of proven *in-vitro*susceptibility because of the risk of the selection of mutants with constitutive, derepressed AmpC- beta-lactamases-expression.
- Reduced affinity of PBPs to cefotaxime. The acquired resistance of Pneumococci and other Streptococci is caused by modifications of already existing PBPs as a consequence of a mutation process. In contrast to this concerning the methicillin-(oxacillin-) resistant *Staphylococcus*, the creation of an additional PBP with reduced affinity to cefotaxime is responsible for resistance.
- Inadequate penetration of cefotaxime through the outer cell membrane of gramnegative bacteria so that the inhibition of the PBPs is insufficient.
- The presence of transport mechanism (efflux pumps) being able to actively transport cefotaxime out of the cell. A complete cross resistance of cefotaxime occurs with ceftriaxone and partially with other penicillins and cephalosporins.

Breakpoints

	Susceptible	Resistant
Enterobacteriaceae	≤ 1 mg / L	> 2 mg / L
Staphylococcus spp. HE	Note[1]	Note[1]
Streptococcus (group A, B, C, G)	Note[2]	Note[2]
Streptococcus pneumoniae	≤ 0.5 mg / L	> 2 mg / L
Viridans group *streptococci*	≤ 0.5 mg / L	> 0.5 mg / L
Haemophilus influenzae	≤ 0.125 mg / L	> 0.125 mg / L
Moraxella catarrhalis	≤ 1 mg / L	> 2 mg / L
Neisseria gonorrhoea	≤ 0.125 mg / L	> 0.125 mg / L
Neisseria meningitidis[3]	≤ 0.125 mg / L	> 0.125 mg / L
Pasteurella multocida	≤ 0.03 mg / L	> 0.03 mg / L
Kingella kingae	≤ 0.125 mg / L	> 0.125 mg / L
PK-PD (Non-species related) breakpoints	≤ 1 mg / L	> 2 mg / L

The following minimal inhibitory concentrations were defined for sensitive and resistant germs:

EUCAST (European Committee on Antimicrobial Susceptibility Testing) breakpoints (2019-01-01):

HE = high exposition / high dose only for *S. aureus* (high dose of at least 3 x 2 g iv)

1 Susceptibility of staphylococci to cephalosporins is inferred from the cefoxitin susceptibility except for cefixime, ceftazidime, ceftazidime-avibactam, ceftibuten and ceftolozane-tazobactam which do not have breakpoints and should not be used for staphylococcal infections.

2 The susceptibility of *streptococcus* groups A, B, C and G to cephalosporins is inferred from the benzylpenicillin susceptibility.

Non-susceptible isolates are rare or not yet reported. The identification and antimicrobial susceptibility test result on any such isolate must be confirmed and the isolate sent to a reference laboratory.

Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. If the efficacy of cefotaxime is questionable due to the local prevalence of resistance, expert opinion should be sought regarding the choice of therapy. In particular in the case of severe infections or failure of therapy, a microbiological diagnosis including a verification of the germ and its susceptibility should be aspired.

COMMONLY SUSCEPTIBLE SPECIES
Gram-positive aerobe *Staphylococcus aureus* (Methicillin-susceptible) *Streptococcus agalactiae* *Streptococcus pneumoniae* (incl. penicillin-resistant strains) *Streptococcus pyogenes*
Gram-negative aerobes *Borrelia burgdorferi* *Haemophilus influenzae* *Moraxella catarrhalis* *Neisseria gonorrhoea* *Neisseria meningitides* *Proteus mirabilis* [%]
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Gram-positive aerobes *Staphylococcus aureus* *Staphylococcus epidermidis* [+] *Staphylococcus haemolyticus* [+] *Staphylococcus hominis* [+]
Gram-negative aerobes *Citrobacter freundii* *Enterobacter aerogenes* *Enterobacter cloacae* *Escherichia coli* [%] *Klebsiella oxytoca*[%] *Klebsiella pneumoniae*[# %] *Morganella morganii* *Proteus vulgaris* *Serratia marcescens*
Anaerobes *Bacteroides fragilis*

INHERENTLY RESISTANT SPECIES
Gram-positive aerobes *Enterococcus* spp. *Listeria monocytogenes* *Staphylococcus aureus* (methicillin-resistant)
Gram-negative aerobes *Acinetobacter* spp.
Pseudomonas aeruginosa *Stenotrophomonas maltophilia*
Anaerobes *Clostridium difficile*
Others *Chlamydia* spp. *Chlamydophila* spp. *Legionella pneumophila* *Mycoplasma* spp. *Treponema pallidum*

+ In at least one region the resistance rate is > 50 %.

 # In Intensive Care Units the resistance rate is < 10 %.

% Extended Spectrum Beta-Lactamase (ESBL) producing strains are always resistant.

5.2 Pharmacokinetic properties

Absorption

Cefotaxime is for parenteral application. Mean peak concentrations 5 minutes after intravenous administration are about 81 – 102 mg / L following a 1 g dose of 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 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 cefotaxime usually passes the bloodbrain 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 gramnegative bacteria, are attained in purulent sputum, bronchial secretions and pleural fluid after doses of 1or 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 achieved 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.

Protein binding for cefotaxime is approximately 25 – 40%.

The apparent distribution volume for cefotaxime is 21-37 l after 1 g intravenous infusion over 30 minutes.

Biotransformation

Cefotaxime is partly metabolised in humans. Approximately 15-25 % of a parenteral dose are

metabolised to the O-desacetyl-cefotaxime metabolite, which also has antibiotic properties.

Elimination

The main route of excretion of cefotaxime and O-desacetyl-cefotaxime is through the kidneys. 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 Odesacetylcefotaxime. After 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 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 halflife of cefotaxime can be increased to 2.5 – 3.6 hours.

There is no accumulation following administration of 1000 mg intravenously or 500 mg intramuscularly for 10 or 14 days.

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, repeated 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 measured in the umbilical cord serum in the first 90 minutes after

administration, 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

None

6.2 Incompatibilities

Aminoglycosides are incompatible with cephalosporins in parenteral mixtures.

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

6.3 Shelf life

Unopened vials: 2 years.

After reconstitution:

The reconstituted product is chemically and physically stable:

- at a temperature of 2°C to 8°C for 24 hours for solutions prepared for intramuscular injection, intravenous injection and intravenous infusion;

- at a temperature below 25°C:

- for 6 hours for solutions prepared for intramuscular injection and intravenous injection,
- for 12 hours for solutions prepared for intravenous infusion.

See section 6.6 for preparation of solutions.

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.

The reconstituted product does not require protection from light.

The solution after reconstitution may be colorless to yellow.

6.4 Special precautions for storage

Unopened: This medicinal product does not require any special temperature storage conditions.

Keep the vials in the outer carton in order to protect from light.

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

6.5 Nature and contents of container

Cefotaxime is supplied in type III colourless glass vials, closed with a rubber stopper and aluminium caps or aluminium caps and plastic flip-off.

Each vial contains 2 g of cefotaxime.

Pack sizes: 10 vials.

6.6 Special precautions for disposal

The expiry date should be checked before administration. Do not use the product after the expiry date given on the pack.

After the solvent is added to the vial contents, the vial should be shaken until the powder dissolves; the solution should be clear after 1–2 minutes. The solution of the reconstituted product should be inspected visually for clearness and particulate matter prior to administration. If it is cloudy or it contains particulate matter, the solution is not suitable for use. The solution has a clear to yellow colour.

For instructions on administration, see section 4.2.

Preparation of solution for injection and infusion

Antibiotic content per vial	**Solvent volume**		
	Intramuscular injection	**Intravenous injection**	**Intravenous infusion**
1 g	4 ml	10 ml	40–100 ml
2 g	-	10 ml	40–100 ml

Intramuscular injection

The contents of 1 g vial should be dissolved in 4 ml of water for injection, 0.9% sodium chloride solution or 1% lidocaine solution. The product must not be administered intravenously with lidocaine solution.

Intravenous injection (from 3 to 5 minutes)

The contents of a vial should be dissolved in 10 ml of water for injection, 0.9% sodium chloride solution or 5% glucose solution.

Intravenous infusion (from 20 to 60 minutes)

In order to prepare solutions of cefotaxime for intravenous infusion, the powder is dissolved in water for injection (in the same way as for intravenous injections). The solution thus obtained should be further diluted with one of the following solutions:

0.9% sodium chloride solution,

5% glucose solution,

5% glucose solution with 0.9% sodium chloride solution 1:1,

5% glucose solution with 0.9% sodium chloride solution 2:1,

Ringer’s solution,

lactated Ringer’s solution.

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

7 MARKETING AUTHORISATION HOLDER

hameln pharma ltd
Nexus, Gloucester Business Park
Gloucester, GL3 4AG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 01502/0145

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/02/2025

10 DATE OF REVISION OF THE TEXT

24/04/2025