SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cefotaxime 1g Powder for Solution for Injection or Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains Cefotaxime sodium equivalent to 1g cefotaxime.

Also contains 48 mg (2.09 mmol) of sodium per vial.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

White or slightly creamy powder.

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 (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
- Intraabdominal 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, 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 microbiological tests are known.

Adults and adolescents over 12 years

The usual dose in adults and adolescents is 2 to 6g cefotaxime daily. The daily dose should be divided in two single doses every 12 hours.

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

A combination of cefotaxime and other antibiotics in 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 of 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 renal and hepatic function are 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 doses of 9 - 12 g cefotaxime divided into equal doses every 6 – 8 hours (3g 3 – 4 times daily).

Children: 150 - 200 mg/kg/day divided in equal doses every 6 to 8 hours.

New-borns: 0 – 7 days 50 mg/kg every 12 hours; 7 – 28 days: 50mg/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 infection 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 is similar to the recommended usual dose should be halved 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 500mg - 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 accoriding 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).

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 intravenous injections the solution must be injected over a period of 3-5 minutes. During post-marketing surveilance, 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 2g cefotaxime or if cefotaxime is injected more frequently than twice per day, the intravenous route is recommended.

Incase 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.
- Previous, immediate and/or severe hypersensitivity reaction to penicillin or any betalactam antibiotic.

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.

4.4 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.

-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.

- 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 contraindicated in subjects with a previous history of immediate-type hypersensitivity to cephalosporins.

Since cross allergy extists between penicillins and

cephalosporins, use of the latter should be undertaken with extreme caution in penicillin sensitive subjects.

- 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.

- 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, particulary 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 48.07 mg (2.09 mmol) sodium per vial, equivalent to 4.8% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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) since an antagonistic effect is possible.

Interference with 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.
A false-positive reaction to glucose may occur with reducing substances (Fehling’s solution) but not with the use of specific enzyme-based tests (glucose oxidase methods).

4.6 Fertility, pregnancy and lactation

Pregnancy

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 crosses the placental barrier. Therefore, cefotaxime should not be used during pregnancy unless the anticipated benefit outweighs any potential risks.

Breastfeeding

Cefotaxime is excreted in human milk in low concentrations. Use during lactation can have effects on the physiological intestinal flora of the breast-fed infant leading to diarrhoea, to colinisation by yeast-like fungi and sensitization. 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 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

Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, ≤1/100), rare (≥1/10000, ≤1/1000), very rare (≤1/10000), not known (cannot be estimated from the available data).

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 (</10,000)***	***Not known (cannot be estimated from available data)****
Infections and infestations						Superinfection (see section 4.4)
Blood and the lymphatic system disorders			Leukopenia Eosinophilia Thrombocytopenia			Bone marrow failure Pancytopenia Neutropenia Agranulocytosis (see section 4.4) Haemolytic anaemia
Immune system disorders			Jarisch-Herxheimer reaction			Anaphylactic reactions Angioedema Bronchospasm Anaphylactic shock

Nervous system disorders			Convulsions (see section			Headache Dizziness

			4.4)			Encephalopathy (e.g. impairment of consciousness, abnormal movements) (see section 4.4)
Cardiac disorders						Arrhythmia following rapid bolus infusion through central venous catheter Palpitations
Gastrointestinal disorders			Diarrhea			Nausea, Vomiting Abdominal pain Pseudomembranous colitis (see section 4.4)
Hepato-bilary disorders			Increase in liver enzymes (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase) and/or bilirubin			Hepatitis* (sometimes with jaundice)
Skin and subcutaneous tissue disorders			Rash Pruritus Urticaria			Erythema multiforme Stevens-Johnson syndrome Toxic epidermal necrolysis (see section 4.4) Acute generalized Exanthematous pustulosis (AGEP) Drug reaction with eosinophilia and system symptoms (DRESS) (see section 4.4)
Renal and urinary disorders			Decrease in renal function/ increase of creatinine (particularly when co-prescribed with aminoglycosides)			Acute renal failure (see section 4.4) Interstititial nephritis

General disorders and administration site conditions	*For IM formulations:* Pain at		Fever Inflammatory reactions at			*For IM formulations (since the solvent contains*

	the injection **site**		the injection site, including phlebitis/ thrombophlebitis Malaise, Fatigue			*lidocaine):* Systemic reaction to lidocaine

*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 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 via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcardor 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 exist. 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 penicillinbinding 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:

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

EUCAST (European Committee on Antimicrobial Susceptibility Testing) break points (2019-01-01):Pathogen	Susceptible	Resistant
Enterobacteriaceae	≤ 1 mg/l	> 2 mg/l
Staphylococcus spp.	Note1	Note1
Streptococcus (group A, B, C,G)	Note2	Note2
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 gonorrhoeae	≤ 0.12 mg/l	> 0.12 mg/l
Neisseria meningitidis	≤ 0.12 mg/l***	> 0.12 mg/l
Not species-specific breakpoints****	≤ 1 mg/l	> 2 mg/l

	Susceptible	Resistant
Enterobacteriaceae	< 1 mg/L	>2 mg/L
Staphylococcus sppHE	Note1	Note1
Streptococcus (group A, B, C, G	Note2	Note2

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	>2mg/L
Neisseria gonorrhoeae	≤0.125 mg/L	>0.125 mg/L
Neisseria Meningitidis3	≤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	≤1mg/L	>2mg/L

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.

[3] 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
Borrellia burgdorferi
Haemophilus influenzae
Moraxella catarrhalis
Neisseria gonorrhoeae
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* *sppChlamydoph* *ila* 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 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 micrograms/ml). Cefotaxime concentrations (0.2-5.4 micrograms/ml), inhibitory for most Gram-negativebacteria, 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-desacetylcefotaxime metabolite, which also has antibiotic properties.

Elimination

The main route of excretion of cefotaxime and O-desacetylcefotaxime 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-desacetylcafotaxime 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.

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, 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 micrograms/ml were measures in the umbilical cord serum in the first 90 minutes after application, which dropped to approximately 2.5 micrograms/ml by the end of the second hour after application. In the amniotic fluid, the highest concentration of 6.9 micrograms/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

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: 2 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 8ºC, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Unopened: Do not store above 25ºC. Keep the vial 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

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

Packs of 10 or 50 vials.

6.6 Special precautions for disposal

Cefotaxime is supplied as a white to slightly creamy powder, which when dissolved in Water for Injections Ph. Eur. 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:

- Water for Injections Ph. Eur.

- Sodium Chloride Injection BP.
- 5% Dextrose Injection BP.
- Dextrose and Sodium Chloride Injection BP.
- Compound Sodium Lactate Injection BP (Ringer-lactate Injection).

Any unused solution should be discarded.

Cefotaxime is also compatible with 1% lignocaine, however freshly prepared solutions should be used.

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

Reig Jofre UK Limited

Follaton House, Plymouth Road, Totnes, Devon, TQ9 5NE,

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8 MARKETING AUTHORISATION NUMBER(S)

PL 44095/0030

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

02/12/2025