SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cefotaxime 1 g powder for solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1.0 g vial contains 1.048 g cefotaxime sodium, equivalent to 1.0 g cefotaxime.

Excipients(s):
Each gram of Cefotaxime contains 48 mg (2.09 mmol) of sodium (48 mg per vial).

3 PHARMACEUTICAL FORM

Powder for solution for injection or infusion.

Appearance: White to 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 due to bacteria that are susceptible to Cefotaxime (see section 5.1):

- Bacterial pneumonia,,
- Complicated urinary tract infection including pyelonephritis,
- Bacterial meningitis,
- Intraabdominal infections (such as peritonitis),
- Severe skin and soft tissue infections,
- Genital infections caused by gonococci,
- Preoperative prophylaxis in colorectal surgery

Consideration should be given to official local guidance on the appropriate use of antibiotics when using Cefotaxime.

4.2 Posology and method of administration

Cefotaxime may be administered by intravenous bolus injection, by intravenous infusion, or by intramuscular injection, after reconstitution of the solution according to the directions given below. Dosage, route and frequency of administration should be based on the severity of the infection, susceptibility of the causative organism and the patient's condition. Therapy may be started before the results of sensitivity tests are known.
Cefotaxime and aminoglycosides should not be mixed in the same syringe or perfusion fluid.

Dose recommendations:

Adults and adolescents (12 to 16-18 years)
The usual dose is 1 g cefotaxime every 12 hours. However, dosage may be varied according to the severity of the infection, sensitivity of causative organisms and condition of the patient.
In severe cases, the daily dose can be increased up to 12 g. Daily doses up to 6 g can be divided into at least two individual administrations at 12 hour intervals. Higher daily doses must be divided into at least 3 to 4 individual administrations at 8 or 6-hour intervals respectively.
The following table may serve as a guide to dosages:

Type of infection	Single dose cefotaxime	Dose interval	Daily dose cefotaxime
Typical infections, in which a sensitive bacterium is proven or suspected	1 g	12 h	2 g
Infections, in which various bacteria with high to medium sensitivity are demonstrated or suspected	2 g	12 h	4 g
Severe infections	2-3g	8 h 6 h	6-9 g 8-12 g

Infants, toddlers (28 days to 23 months) and children (2 to 11 years)
The usual dose is 50 to 150 mg cefotaxime according to the severity of the infection per kilogram of body weight per day in 2 to 4 divided doses (every 12 - 6 hours).
In very severe infections up to 200 mg/kg/day divided into 2-4 doses may be required. For children >50 kg the adult dosage should be used, without exceeding the maximum daily dosage of 12 g.

Neonates (0-27 days)
The recommended dosage is 50 mg cefotaxime per kilogram of body weight per day in 2 to 4 divided doses (every 12-6 hours). In case of life-threatening

situations it may be necessary to increase the daily dose. For severe infections 150-200 mg/kg/day, in divided doses have been given. The following table may serve as a guide to dosages:

Age	Daily dose of cefotaxime
0-7 days	50 mg/kg every 12 hours i.v.
8 days – 1 month	50 mg/kg every 8 hours i.v.

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

Other recommendations:
Gonorrhoea:
For gonorrhoea, a single injection Cefotaxime 0.5 g – 1 g is administered (intramuscularly or intravenously). For complicated infections consideration should be given to available official guidelines. Syphilis should be excluded before initiating the treatment.

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

Bacterial meningitis:
Adults and adolescents over 12 years:
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 divided into equal doses every 6 to 8 hours.

Neonates:
In neonates 0-7 days old 50 mg/kg cefotaxime may be administered every 12 hours and in infants 8 -28 days old every 8 hours.

Duration of therapy:
The duration of therapy with Cefotaxime depends on the clinical condition of the patient and varies according to the cause 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).

Impaired renal function:
In adult patients with a creatinine clearance of $\leq$ 5 ml/min, the initial dose is equal to the recommended usual dose but the maintenance dose should be reduced by half without change in the frequency of dosing.

Dialysis or peritoneal dialysis:
In patients on haemodialysis and peritoneal dialysis an i.v. injection of 0.5-2 g, administered at the end of each dialysis session and repeated every 24 hours, is sufficient to treat most infections effectively.

Method of administration:
Cefotaxime is administered by intravenous injection, intravenous infusion or intramuscular injection (see section 4.4). The product is made into solution according to the instructions in the section 6.6

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

Intravenous infusion:
For *short intravenous infusion*: Following reconstitution the solution should be administered as a 20 minute intravenous infusion.

For *long lasting intravenous infusion:* Following reconstitution, the solution should be administered as a 50-60 minutes intravenous infusion.

Intravenous administration (injection or infusion):
For intermittent I.V. injections, the solution must be injected over a period of 3 to 5 minutes.

Intramuscular injection:
The solution should be administered by deep intramuscular injection.

The following table shows the volume of dissolution for each vial size.

	Mode of administration			
Vial size	Short intravenous infusion	Long-lasting intravenous infusion	Intravenous injection	Intramuscular injection
0.5 g	-	-	2 ml	2 ml
1 g	40-50 ml	-	4 ml	4 ml
2 g	40-50 ml	100 ml	10 ml	-

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

4.3 Contraindications

Hypersensitivity to cefotaxime or other cephalosporins.
History of an acute and/or severe hypersensitivity to penicillin or any other type of beta-lactam antibiotic.

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 reactions 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.

In patients with previously documented history of hypersensitivity to penicillins or other β-lactam antibiotics, special care is required. Cross-sensitivity may occur with cephalosporin antibiotics, including cefotaxime. In this situation the possibility of anaphylactic reactions, which may be serious, or even fatal, should be borne in mind.

Cefotaxime should be used with caution in patients with allergic diathesis and asthma.

- 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)

Diarrhoea, 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.
As with all cephalosporins, pseudomembranous colitis may rarely occur during or after treatment with cefotaxime. In patients developing fever, diarrhoea and abdominal cramps, the possibility of this diagnosis must be seriously considered. If this occurs, the drug should be stopped immediately and investigation by sigmoidoscopy and stool culture conducted, followed by appropriate therapy as necessary.
Clostridium difficile associated disease can be favoured by faecal stasis. Medicinal products that inhibit peristalsis should not be given.

- Haematological 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 haemolytic anaemia have also been reported (see section 4.8).

- Patients with renal insufficiency

The dose of cefotaxime must be adjusted in patients with severe impaired renal function, according to the creatinine clearance calculated, to avoid accumulation of cefotaxime in the body (see 4.2; Posology and Method of Administration).

Caution should be exercised if cefotaxime is administered together with aminoglycosides 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.

- 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).

In case of severe infections, intramuscular injection is not recommended. It is recommended that no more than 4 ml is injected unilaterally. If the daily dose exceeds 2 g cefotaxime, or if cefotaxime is injected more frequently than twice per day, the i.v. route is recommended.

- Effects on Laboratory Tests

As with other cephalosporins a positive Coombs' test has been found in some patients treated with cefotaxime. This phenomenon can interfere with the cross-matching of blood.
Urinary glucose testing with non-specific reducing agents may yield false-positive results. This phenomenon is not seen when a glucose-oxidase specific method is used.

- Cefotaxime constituted with lidocaine should 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 unpaced heart block

- in patients with severe heart failure

- The product information of the chosen lidocaine-containing medicinal product must be regarded.

- Sodium intake

The sodium content of Cefotaxime 1g (48mg (2.09mmol) per gram, approximately 48mg per vial) should be taken into account if intended for use in patients on sodium-restricted diets (see section 2).

4.5 Interaction with other medicinal products and other forms of interaction

Aminoglycosides, 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 (see section 4.4).

Probenecid:
Probenecid interferes with the renal tubular transfer of cephalosporins, including cefotaxime, thereby delaying their excretion and increasing their plasma concentration.

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

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

Other forms of interactions:
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 (Benedict's or Fehling's solution, or with Clinitest tablets) but not with the use of specific enzyme-based tests (glucose oxidase methods).

4.6 Fertility, Pregnancy and lactation

Pregnancy
The safety of cefotaxime in human pregnancy has not been established.
Limited data are available on the use of cefotaxime during pregnancy and lactation.

Cefotaxime is known to cross the placental barrier, however animal studies have not shown a foetotoxic effect. Caution should therefore be exercised especially in the first trimester, by balancing the potential benefits of treatment against any possible hazard.

Lactation
Cefotaxime is excreted in 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). Patients should be advised not to drive or operate machinery if any such symptoms occur.

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 (≥1/10,0000 to <1/1,000)	Very rare (<1/10,000)	Not known (cannot be estimated from available data)*
Infections and infestations						Superinfection (see section 4.4) Candidiasis
Blood and lymphatic system disorders			Leukopenia Eosinophilia Thrombocytopenia			Neutropenia Granulocytopenia Agranulocytosis (see section 4.4) Haemolytic anaemia
Immune system disorders			Jarisch-Herxheimerreaction			Anaphylactic reactions Angioedema Bronchospasm Anaphylactic shock

System organ class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,0000 to <1/1,000)	Very rare (<1/10,000)	Not known (cannot be estimated from available data)*
Nervous system disorders			Convulsions (see section 4.4)			Headache Dizziness Encephalopathy (e.g. impairment of consciousness, abnormal movements) (see section 4.4)
Cardiac disorders						Arrhythmia following rapid bolus infusion through central venous catheter
Gastro-intestinal disorders			Diarrhoea			Nausea Vomiting Abdominal pain Pseudomembranous colitis (see section 4.4)
Hepatobiliary disorders			Increase in liver enzymes (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatise) and/or bilirubin			Hepatitis* (sometimes with jaundice)
Skin and subcutaneous tissue disorders			Rash Prurits Urticaria			Erythema multiforme Stevens-Johnson syndrome Toxic epidermal necrolysis (see section 4.4)
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 (sincethe solvent containslidocaine):* Systematic reactions to lidocaine

* Postmarketing experience

Information about selected adverse reactions:

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 oneor more of the following symptoms has been reported after several weeks' treatment of borreliosis: skin rash, itching, fever, leucopenia, increase in liver enzymes, difficulty 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 andelicit 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 balanceof the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: 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 overdose or administration of high doses of β-lactam antibiotics including cefotaxime, especially when there is renal insufficiency.

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. Peritoneal dialysis or haemodialysis can be used to reduce the serum levels of cefotaxime.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other Beta-Lactam Antibacterials
ATC Code: J01D D01

Cefotaxime is a parenteral beta lactam-antibiotic of the group of cephalosporins.

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.

Pharmacokinetics and pharmacodynamics relationship
The extent of the bactericidal activity depends on the period of time when the serum level exceeds the minimal inhibitory concentration (MIC) of the pathogen.

Mechanism of resistance
A resistance to cefotaxime may be caused by following mechanisms:

- inactivation by beta-lactamases. Cefotaxime can be hydrolysed by certain beta-lactamases, 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 against 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 against cefotaxime is responsible for resistance.
- inadequate penetration of cefotaxime through the outer cell membrane of gram-negative 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 (2009-05-25):

Pathogen	Susceptible	Resistant
Enterobacteriaceae	1 mg/l	> 2 mg/l
Staphylococcus spp.	--*	--*
Streptococcus (group A, B, C, g)	--**	--**
Other Streptococci	0.5 mg/l	0.5 ml/l
Streptococcus pneumoniae	0.5 mg/l	> 2 mg/l
Haemophilus influenzae	0.12 mg/l	> 0.12 mg/l
Moraxella catarrhalis	1 mg/l	> 2 mg/l
Neisseria gonorrhoeae	0.12 mg/l	> 0.12 mg/l
Neisseria meningitides	0.12 mg/l	> 0.12 mg/l
Not species-specific breakpoints***	1 mg/l	> 2 mg/l

*For *Staphylococcus* the test results of oxacillin is used. Oxacillin-resistant Staphylococcus is assessed as resistant against cefotaxime.
** The susceptibility of streptococcus groups A, B, C and g can be inferred from their susceptibility to benzylpenicillin.
*** generally based on serum pharmacokinetics

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 aerobes
Staphylococcus aureus (methicillin-susceptible)
Streptococcus agalactiae
Streptococcus pneumoniae (incl. penicillin-resistant)
Streptococcus pyogenes

Gram-negative aerobes
Escherichia coli[%]
Haemophilus influenzae
Klebsiella oxytoca[%]
Klebsiella pneumoniae[#%]
Moraxella catarrhalis
Morganella morganii
Neisseria gonorrhoeae
Neisseria meningitidis
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
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 baumannii
Pseudomonas aeruginosa
Stenotrophomonas maltophilia
Anaerobes
Clostridium difficile
Others
Chlamydia spp.
Chlamydophila spp.
Legionella pneumophila
Mycoplasma spp.
Treponema pallidum

Literature data, reference books and therapy guidelines support susceptibility.
+ 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.
In the community area the resistance rate is <10%.

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 blood-brain barrier in levels above the MIC of the sensitive pathogens when the meninges are inflamed (3-30 μg/ml). Cefotaxime concentrations (0.2-5.4 μg/ml), inhibitory for most gram-negative bacteria, are attained in purulent sputum, bronchial secretions and pleural fluid after doses of 1 or 2 g. Concentrations likely to be effective against most sensitive organisms are similarly attained in female reproductive organs, otitis media effusions, prostatic tissue, interstitial fluid, peritoneal fluid and gall bladder wall, after therapeutic doses. High concentrations of Cefotaxime and O-desacetyl-cefotaxime are 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 O-desacetyl cefotaxime. 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 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 reveals no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or 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

Cefotaxime should not be mixed with other antibiotics in the same syringe or solution for infusion. This applies in particular for aminoglycosides. If both cefotaxime and aminoglycosides shall be administered these medicinal products should be administered separately at different sites. Cefotaxime should not be dissolved in solutions having a pH-value of more than 7.5, e.g. sodium bicarbonate. This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened : 24 months. Reconstitution: Chemical and physical in-use stability has been demonstrated for 3 days at 2-8°C. From a microbiological point of view, the

product should be used immediately. If not used immediately, in-use storage times and conditions before use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

For the unopened product, do not store above 25°C. Keep the vial in the outer carton in order to protect from light. When reconstituted store at 2-8°C.

6.5 Nature and contents of container

Colourless glass Type III vial closed with rubber stopper and aluminium cap.
The vials are packed as; 1, 5, 10, 25 or 50 vials.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Reconstitution:
From the calculated dose, determine the appropriate number of vials to be used. Add the recommended volume of reconstitution solution and shake well until the contents of the vial have dissolved completely.

Route of Administration	Reconstitution solution	Diluent required			Displacement volume		
		500mg	1g	2g	500mg	1g	2g
Intravenous or intramuscular injection	Water for Injections Ph.Eur.	2ml	4ml	10ml	0.45ml	0.9ml	1.8ml
Intravenous infusion	Water for Injections Ph.Eur. Sodium Chloride Injection BP 5% Dextrose Injection BP Dextrose and Sodium Chloride Injection BP Sodium lactate Injection BP	40-100ml for 1-2g of Cefotaxime					

Prepared injections should be used immediately (see 6.3; Shelf-life).
Prepared infusion to be administered over 20-60 minutes.
Cefotaxime is for single patient use only, discard any unused solution.

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

Reconstitute with:

Water for Injections Ph.Eur.
Sodium Chloride Injection BP
5% Dextrose Injection BP
Dextrose and Sodium Chloride Injection BP
Sodium lactate Injection BP
Metronidazole Infusion (500mg/100ml)
1% lidocaine/lignocaine (freshly prepared) - See 4.4; Special Warnings and Precautions for Use.

The compatibility of cefotaxime in other infusion fluids should be checked before use.

The reconstituted solution should be clear, do not use the solution if particles are present.

7 MARKETING AUTHORISATION HOLDER

Cox Pharmaceutical Ltd.
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London, N3 2JU,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 42671/0005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

15/12/2022