1.6.1 Prescribing information (Summary of products characteristics)

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

1. NAME OF THE MEDICIANAL PRODUCT

Karefotax Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains: Cefotaxime sodium 1g

For excipients see section 6.1

3. PHARMACEUTICAL FORM

Powder for solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cefotaxime sodium is indicated for the treatment of the following severe infections when known or thought very likely to be due to organisms that are susceptible to Cefotaxime.

- Infections of the lower respiratory tract
- Infections of the kidneys and urinary tract
- Infections of the skin and soft tissue
- Genital infections caused by gonococci, particularly when penicillin has failed or is unsuitable
- Intra-abdominal infections (including Peritonitis)
- Lyme-borreliosis (especially stages II and III)
- Acute Meningitis in case of gram-negative microorganisms in combination with another suitable antibiotic
- Sepsis in case of gram-negative microorganism in combination with another suitable antibiotic
- Endocarditis in case of gram-negative microorganism in combination with another suitable antibiotic

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

Protection is best insured by achieving adequate local tissue concentrations at the time contamination is likely to occur.

Administration should usually be stopped within 24 hours since continuing use of any antibiotic in the majority of surgical procedures does not reduce the incidence of subsequent infection.

4.2 Posology and method of administration

Cefotaxime sodium may be administered intravenously, by bolus injection or infusion, or intramuscularly. The dosage, route and frequency of administration should be determined by the severity of infection, the sensitivity of causative organisms and condition of the patient. Therapy may be initiated before the results of sensitivity tests are known.

The clinician should consult published protocols for information on dosage regimens in specific conditions such as gonorrhoea, Pseudomonas infections and CNS infections.

Dosage and type of administration depend on the severity of the infection, the sensitivity of the bacterium and the condition of the patient.

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

Adults and children over 12 years in general receive 1 g Cefotaxime every 12 hours. 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 hourly 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 sensitivity is demonstrated and bacterium is proven or suspected	1g	12h	2g
Infections, in which various bacteria with high to medium sensitivity are demonstrated or suspected	2g	12h	4g
Unclear bacterial illness which cannot be localised and where the patient is critically ill	2 – 3g	8h up to 6 h up to 6 h	6 g up to 8 g up to 12 g

For the treatment of gonorrhoea in adults, 1 vial of Cefotaxime Sodium for Injection 500mg administered as a single administration.

In most cases due to less sensitive infective bacteria, an increase may be necessary, i.e. 1 g Cefotaxime. Examination for syphilis needs to be carried out before commencing therapy.

Perioperative Prophylaxis

For peri-operative infection prophylaxis the administration of a single dose of 1 to 2 g Cefotaxime 30 to 60 minutes prior to the operation is recommended. Another antibiotic to cover anaerobic organisms is necessary. A repeat dose is required if the duration of the operation exceeds 90 minutes.

Special Dose Recommendations

Lyme borrelisosis: A daily dose of 6 g Cefotaxime (14 to 21 days duration). The daily dose was generally administered divided into 3 parts (2 g Cefotaxime 3 times daily).

Infants and children up to 12 years receive 50 to 100 mg Cefotaxime according to the severity of the infection (up to 150 mg) per kilogram of body weight per day, divided into equal doses, administered at 12 (up to 6) hour intervals. In individual cases – particularly in life threatening situations – it may be necessary to increase the daily dose to 200 mg Cefotaxime per kilogram of body weight.

In neonates and infants doses of 50 mg Cefotaxime per kilogram of body weight per day should not be exceeded in view of not fully matured kidney clearance.

In case of life-threatening situations it may be necessary to increase the daily dose.

In those situations the following table is recommended.

Age	**Daily dosage of Cefotaxime**
0 – 7 days	50 mg/kg every 12 hours IV
7 days – 1 month	50 mg/kg every 8 hours IV
> 1 month	75 mg/kg every 8 hours IV

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

Dosage in the Case of Impaired Renal Function

With patients with a creatinine clearance of 20ml/minute or less, the maintenance dose is reduced to half the normal dose. With patients with a creatinine clearance of 5 ml/minute or less, a reduction of the maintenance dose to 1 g Cefotaxime (divided into 2 individual administrations at 12 hour intervals), seems to be appropriate. The stated recommendations are based on experiences with adults.

Since Cefotaxime is to a large extent eliminated by haemodialysis, an additional dose should be administered to patients who are dialysed, after the dialysis procedure.

Elderly Patients

No dosage adjustments are needed in patients with normal function.

Other Advice

Electrolyte content of the injections solutions: Since Cefotaxime is available as the sodium salt, the sodium content per dose should be taken into account within the framework of the overall therapy and with special balance checks.

Basis for calculation: 1 g Cefotaxime (equivalent to 1.04 g Cefotaxime sodium) should be calculated as 48 mg sodium equivalent to 2.1 mmol sodium.

Posology and Method of Administration

Intravenous Injection

For IV, Cefotaxime Sodium for Injection 500mg is dissolved in at least 2 ml water for injections, Cefotaxime Sodium for Injection 1 g in at least 4 ml and subsequently injected directly into the vein over 3 to 5 minutes or after clamping of the infusion tube into the distal end of the tube.

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.

Infusion

For brief infusion 2g of Cefotaxime Sodium for Injection is dissolved in 100 ml of isotonic sodium chloride or glucose solution and subsequently IV infused over 50 to 60 minutes. Another compatible infusion solution can also be used for the solution.

Intramuscular Injection

For intramuscular injection. Cefotaxime Sodium for Injection 500mg is dissolved in 2 ml and Cefotaxime Sodium for Injection 1 g in 4 ml water for injections respectively. Afterwards the injection should take place deep into the gluteal muscle. Pain with the IM injection can be avoided by dissolving Cefotaxime Sodium for Injection 500mg in 2ml or Cefotaxime Sodium for Injection 1 g in 4 ml 1% lidocaine solution. An intravascular injection is to be avoided in this case, since with intravascular administration lidocaine may lead to unrest, tachycardia, disturbances of cardiac conduction as well as vomiting and cramp. Cefotaxime reconstituted with lidocaine should not be administered to infants under 30 months.

It is recommended that no more than 4 ml be injected unilaterally. If the daily dose exceeds 2 g Cefotaxime or if Cefotaxime is injected more frequently than twice per day, the IV route is recommended.

Combination Therapy

Combination therapy of Cefotaxime with aminoglycosides is indicated without availability of an antibiogram in the case of severe, life-threatening infections. Kidney function must be watched in such combination usage. Cefotaxime and aminoglycosides should not be mixed in the same syringe or infusion fluid.

In cases of infections with *Pseudomonas aeruginosa* combination with other antibiotics effective against *Pseudomonas* can also be indicated.

For infection prophylaxis (peri-operative prophylaxis in surgical procedures such as colorectal, gastro-intestinal, prostatic, urogenital, obstetric and gynaecological surgery) in patients with weakened defence mechanisms, combination can also be indicated with other suitable antibiotics.

4.3 Contraindications

Known or suspected hypersensitivity to Cefotaxime or other cephalosporins. Allergic cross-reactions can exist between penicillins and cephalosporins (see section 4.4).

Cefotaxime constituted with Lidocaine Injection BP must never be used:

- By the intravenous route

- In infants under 30 months of age
- In subjects with a previous history of hypersensitivity to Lidocaine or other local anaesthetics of the amide type
- In patients who have a non-paced 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 patients condition is essential. If superinfection occurs during treatment, appropriate measures should be taken.

Anaphylactic reactions

Cefotaxime should be used with caution in persons with a history of allergies or asthma.

Preliminary enquiry about hypersensitivity to penicillin and other β-lactam antibiotics is necessary before prescribing cephalosporins since cross allergy occurs in 5-10% of cases.
Use of cephalosporins should be undertaken with extreme caution in penicillin-sensitive subjects

Hypersensitivity reactions (anaphylaxis) occurring with the two types of antibiotics can be serious and occasionally fatal (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 history of immediate-type hypersensitivity to Cephalosporins.

Serious bullous reactions

Cases of serious bullous skin reactions such as 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 pseudomembranous colitis.

The diagnosis of this rare but potentially fatal condition can be confirmed by endoscopy and/or histology. It is important to consider this diagnosis in patients who present with diarrhoea 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, 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 case 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 dosage should be modified according to the creatinine clearance calculated.

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).

See section 4.3 for contraindications for formulations reconstituted with 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-oxidase specific method is used.

Sodium intake

The sodium content of this product (48.2 mg/g) should be taken into account when prescribing to patients requiring sodium restriction.

4.5 Interaction with other medicinal products and other forms of interaction

Cefotaxime / Other Antibiotics

As far as possible, Cefotaxime should not be combined with substances having a bacteriostatic action (e.g. tetracycline, erythromycin, chloramphenicol or sulfonamides), since antagonistic effect has been observed regarding the anti-bacterial effect in vitro. A synergistic effect can result with the combination with aminoglycosides.

An increased risk of oto- and nephrotoxicity has been reported when cefotaxime has been used concomitantly with cephalosporins or aminoglycosides. Dose adjustment may be necessary, and the kidney function must be watched (see 4.2 Posology).

Cefotaxime / Probenecid

The simultaneous administration of Probenecid leads to higher, more prolonged plasma concentrations of Cefotaxime by interfering with renal tubular transfer thereby delaying excretion.

Cefotaxime / Potentially Nephrotoxic Drugs and Loop Diuretics.

In combination with potentially nephrotoxic drugs (such as, for example, aminoglycoside antibiotics, polymyxin B and colistin) and with potent diuretics, (e.g. furosemide) the kidney function should be monitored (see section 4.4), since the nephrotoxicity of the substances quoted may be accentuated.

Influence on Laboratory Diagnostic Tests

False positives may occur in the Coombs-Test in rare cases during treatment with cefotaxime.

In glucose determinations in urine and blood, false positive as well as false negative results may also be obtained, depending on the method; these may be avoided by the use of enzymatic 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 passes through the human placenta. Therefore, Cefotaxime should only be used during pregnancy if the anticipated benefit outweighs any potential risks.

Lactation

Cefotaxime is excreted in human milk in low concentrations. Use during lactation can lead in infants to an effect on the physiological intestinal flora with diarrhoea, colonisation by yeast-like fungi and may also lead to sensitisation of the infant. Therefore a decision must be made whether to discontinue breast-feeding or to discontinue therapy, taking into account the benefit of breast-feeding to the child and the benefit of therapy to the mother.

4.7 Effects on ability to drive and use machines

There is no evidence that cefotaxime impairs the ability to drive or operate machinery.

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 effect

Adverse reactions to Cefotaxime sodium have occurred relatively infrequently and have generally been mild and transient.

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 known (cannot be estimated from available data)*
Infections and						Superinfection (see

infestation						section 4.4)
Blood and the lymphatic system disorders			Leucopoenia, Eosinophilia, Thrombocytopenia			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 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)
Hepato-biliary disorders			Increase in liver enzymes (ALAT, ASAT, LDH, gamma GT and or alkaline phosphatase) and/or bilirubin			Hepatitis* (sometimes with jaundice)
Skin and			Rash, pruritis,			Erythema multiforme,

subcutaneous tissue disorders			urticaria			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	Pain at the injection site		Fever Inflammatory reactions at the injection site including phlebitis, thrombophlebitis			Systemic reactions to lidocaine (if reconstituted with lidocaine)

* post-marketing experience

Jarisch-Herxheimer reaction

For the treatment of borreliosis, a Jarisch-Herxheimer reaction may develop during the first days of treatment. The occurrence of one or more of the following symptoms has been reported after several weeks of treatment of borreliosis: skin rash, itching, fever, leucopenia, increase in liver enzymes, difficulty in 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/yellowcard

4.9 Overdose

Symptoms of Overdose

Intoxication in the strictest sense, is not known in man. Symptoms of overdose may largely correspond to the profile of side effects. With certain risk patterns and with the administration of very high doses, there is a risk of reversible encephalopathy, central nervous system excitation conditions, myoclonia and cramp, as have been described for other beta lactams. The risk of the appearance of these undesirable effects is increased in patients with severely restricted kidney function, epilepsy and meningitis.

Emergency Measures

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.

Drug initiated cramps can be treated with diazepam or phenobarbital, but not with phenytoin. With anaphylactic reactions the usual emergency measures must be commenced, preferably with the first indications.

No specific antidote exists. Plasma levels of cefotaxime can be reduced by haemodialysis or peritoneal dialysis.

5.0 PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Beta-lactam antibiotics, cephalosporins

ATC CODE: J01D D01

Mode of action

Cefotaxime exerts its action by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thereby inhibiting cell wall synthesis.

Mechanisms of resistance

Resistance to Cefotaxime may be due to one or several of the following mechanisms:

• Production of extended-spectrum beta-lactamases (ESBLs)

• Induction and/or constitutive expression of AmpC beta- lactamases

• Reduced outer membrane permeability

• Efflux pump mechanisms.

• Modification of target enzymes (altered PBPs)

More than one of these mechanisms may co-exist in a single bacterium.

PK/PD relationship

Efficacy mainly depends on time above the minimal inhibitory concentration of cefotaxime for the pathogen(s) to be treated (T/MIC).

Current MIC breakpoints used to interpret Cefotaxime susceptibility data are shown below.

European Committee on Antimicrobial Susceptibility Testing (EUCAST) Clinical MIC B

European Committee on Antimicrobial Susceptibility Testing (EUCAST) Clinical MIC Breakpoints (V1.1, 31/03/2006)

	Susceptible (<)/ Resistant (>)
Enterobacteriaceae[2]	1/2
Pseudomonas	--
Acinetobacter	--
Staphylococcus[3]	Note[3]
Enterococcus	--
Streptococcus A, B, C, G	0.5/0.5[4]
Streptococcus pneumoniae	0.5/2[4]
Haemophilus influenzae *Moraxella Catarrhalis*	0.12/0.12[4]
Neisseria gonorrhoea	0.12/0.12[4]
Neisseria Meningitidis	0.12/0.12[4]
Gram-negative, anaerobes	--
Non-species related breakpoints[1] S≤ />R	1/2

1. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or IE in the table).

2. The cephalosporin breakpoints for Enterobacteriaceae will detect resistance mediated by most ESBLs and other clinically important beta-lactamases in Enterobacteriaceae. However, some ESBL-producing strains may appear susceptible or intermediate with these breakpoints. Laboratories may want to use a test which specifically screens for the presence of ESBL.

3. Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility (except ceftazidime which should not be used for staphylococcal infections).

4. Strains with MIC values above the S/I breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.

IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.

RD = rationale document listing data used by EUCAST for determining breakpoints.

Commonly susceptible species

Gram-positive aerobes
Staphylococcus aureus (Methicillin-susceptible)^*
Group A Streptococci (including *Streptococcus pyogenes*) *
Group B Streptococci
β-hemolytic Streptococci (Group C, F, G)
Viridans Group Streptococci
Gram-negative aerobes
*Haemophilus influenzae**
Haemophilus parainfluenzae *
*Moraxella catarrhalis**
Neisseria gonorrhoeae *
Neisseria meningitides *
Proteus spp.*
Providencia spp.*
Yersinia enterocolitica

Anaerobes
Clostridium spp. (not Clostridium difficile)
Peptostreptococcus spp.
Propionibacterium spp.
Others
Species for which acquired resistance may be a problem
Streptococcus pneumoniae
Citrobacter spp*
Enterobacter spp*
Klebsiella spp*
Escherichia coli*
Serratia spp
Morganella morganii
Streptococcus pneumoniae*
Inherently resistant organisms
Gram-positive aerobes
Enterococcus spp.
Enterococcus faecalis
Enterococcus faecium
Listeria spp.
Gram-negative aerobes
Acinetobacter spp.
Pseudomonas spp.
Stenotrophomonas maltophilia
Anaerobes
Bacteroides spp.

Clostridium difficile
Others
Clamydiae
Mycoplasma spp.
Legionella pneumophilia

*Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications.

^Methicillin-(oxacillin) resistant staphylococci (MRSA) are always resistant to cefotaxime.

Penicillin-resistant Streptococcus pneumoniae show a variable degree of resistance to cephalosporins such as cefotaxime.

5.2 Pharmacokinetic properties

After a 1000 mg intravenous bolus, mean peak plasma concentrations of Cefotaxime usually range between 81 and 102 microgram/ml. Doses of 500 mg and 2000 mg produce plasma concentrations of 38 and 200 microgram /ml, respectively. There is no accumulation following administration of 1000 mg intravenously or 500 mg intramuscularly for 10 or 14 days.

The apparent volume of distribution at steady-state of Cefotaxime is 21.6 litres/1.73 m^2 after 1 g intravenous 30 minute infusion.

Concentrations of Cefotaxime (usually determined by non-selective assay) have been studied in a wide range of human body tissues and fluids. Cerebrospinal fluid concentrations are low when the meninges are not inflamed, but are between 3 and 30 microgram/ml in children with meningitis. Cefotaxime usually passes the blood-brain barrier at levels above the MIC of common sensitive pathogens when the meninges are inflamed. Concentrations (0.2-5.4 microgram/ml), inhibitory for most Gram-negative bacteria, are attained in purulent sputum, bronchial secretions and pleural fluid after doses of 1 or 2 g. Concentrations likely to be effective against most sensitive organisms are similarly attained in female reproductive organs, otitis media effusions, prostatic tissue, interstitial fluid, renal tissue, peritoneal fluid and gall bladder wall, after usual therapeutic doses. High concentrations of cefotaxime and desacetyl-cefotaxime are attained in bile.

Cefotaxime is partially metabolised prior to excretion. The principal metabolite is the microbiologically active product, desacetyl-cefotaxime. Most of a dose of Cefotaxime is excreted in the urine about 60% as unchanged drug and a further 24% as desacetyl-cefotaxime. Plasma clearance is reported to be between 260 and 390 ml/minute and renal clearance 145 to 217 ml/minute.

After intravenous administration of Cefotaxime to healthy adults, the elimination half-life of the parent compound is 0.9 to 1.14 hours and that of the desacetyl metabolite, about 1.3 hours.

In neonates the pharmacokinetics are influenced by gestational and chronological age, the half-life being prolonged in premature and low birth weight neonates of the same age.

In severe renal dysfunction the elimination half-life of Cefotaxime itself is increased minimally to about 2.5 hours, whereas that of desacetyl-cefotaxime is increased to about 10 hours. Total urinary recovery of Cefotaxime and its principal metabolite decreases with reduction in renal function.

5.3 Preclinical safety data

There is no pre-clinical data of relevance to a prescriber which is additional to that already included in other sections of the SPC

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Not applicable

6.2 Incompatibilities

None known

6.3 Shelf-life

3 years

6.4 Special precautions for storage

Store in a cool dry place below 30° C out of direct sunlight

7. Manufacturer

REYOUNG PHARMACEUTICAL CO., LTD

No.1 Ruiyang Road, Yiyuan County, Shandong Province,

P.R. China