Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cefotaxime 500 mg Powder for Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains cefotaxime sodium equivalent to 500 mg cefotaxime.

3 PHARMACEUTICAL FORM

Powder for solution for injection.

White or slightly yellow powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the treatment of the following severe infections when known or thought very likely to be due to organisms that are susceptible to cefotaxime (see section 5.1)

- Infections of the lower respiratory tract
- Infections of the kidneys and other upper urinary tract infections
- 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) (cefotaxime should be used in combination with another antibiotic that can provide anaerobic cover in the treatment of intra-abdominal infections)
- Acute Meningitis

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 sodium may be administered intravenously by bolus injection or intramuscularly.

Cefotaxime 500 mg and 1000 mg are suitable for i.v. and i.m. injection.

The intramuscular method of administration is reserved to exceptional clinical situations and should undergo a risk-benefit assessment! It is recommended that no more than 4 ml is injected unilaterally. If the daily dose exceeds 2000 mg cefotaxime or if cefotaxime is injected more frequently than twice per day, the i.v. route is recommended. Intramuscular administration of cefotaxime reconstituted with lidocaine should not be administrated to children in the first year of age.

Dosage with individual and daily administration
Dosage and type of administration depends on the severity of the infection, the sensitivity of the bacterium and the condition of the patient.

For the dosages and routes of administration which are not possible with this strength, other strengths are available.

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

Adults and adolescents (12 to 16-18 years)
in general receive 1000 mg cefotaxime every 12 hours. In severe cases, the daily dose can be increased up to 12000 mg. Daily doses up to 6000 mg 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	1000 mg	12 h	2000 mg
Infections, in which various bacteria with high to medium sensitivity are demonstrated or suspected	2000 mg	12 h	4000 mg
Unclear bacterial illnesses which cannot be localised and where the patient is critically ill	2000-3000 mg	8 h 6 h	6000-9000 mg 8000-12000 mg

Infants, toddlers (28 days to 23 months) and children (2 to 11 years)
receive 50 mg to 100 mg cefotaxime according to the severity of the infection (up to 150 mg) per kilogram of body weight per day in 2 to 4 divided doses (every 12 - 6 hours). The following table may serve as a guide to dosages:

Type of infection	Dose interval	Daily dose cefotaxime
Typical infections, in which a sensitive bacterium is proven or suspected	6 - 12 h	50 mg/kg
Infections, in which various bacteria with high to medium sensitivity are demonstrated or suspected	6 - 12 h	100 mg/kg
Unclear bacterial illnesses which cannot be localised and where the patient is critically ill	6 - 8 h	150 mg/kg *

* 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 without exceeding the maximum daily dosage of 12000 mg.

Pre term new born infants and term new born infants (0-27 days)
receive in general doses of 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 mg/kg/day have been given. The following table may serve as a guide to dosages:

Type of infection	Age	Dose interval	Daily dose cefotaxime
Typical infections due to sensitive bacteria **or** in cases with high to medium sensitivity demonstrated or suspected	0 - 7 days 8 days – 1 month	6 - 12 h	50 mg/kg
Unclear bacterial illnesses which cannot be localised	0 - 7 days	6 - 12 h	100 mg/kg *

and where the patient is critically ill	8 days – 1 month		150 mg/kg *

* 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. This dosage should not be exceeded in view of not fully matured kidney clearance.

Gonorrhoea
Uncomplicated gonorrhoea: a single intramuscular injection of 500 mg to 1000 mg cefotaxime, although 1000 mg is recommended as preferable. In case of disseminated gonococcal infection, local official guidelines should be followed. The possibility of syphilis needs to be ruled out, before starting cefotaxime therapy.

Special dosage recommendations

Dosage in the case of impaired renal function
For adult patients with a creatinin clearance of 20 ml/minute or less, the maintenance dose is to be reduced to half the normal dose (see section 4.4).
For adult patients with a creatinin clearance of 5 ml/minute or less, after an initial loading dose of 1000 mg, daily dose should be halved without change in the frequency of dosing, i.e. 1000 mg in 12 hourly becomes 500 mg 12 hourly, 1000 mg 8 hourly becomes 500 mg 8 hourly, 2000 mg 8 hourly becomes 1000 mg 8 hourly etc. As in all other patients, dosage may require further adjustment according to the course of the infection and the general condition of the patient.

Haemodialysis
In patients on haemodialysis, 500 mg – 2000 mg is given by i.v. injection at the end of every dialysis. This dose is repeated every 24 hours.

Elderly
No dosage adjustments are needed in patients with normal renal function.

Method of administration
See also section 6.6. “Instructions for use and handling”.

Intravenous injection
For i.v. injection, Cefotaxime 500 mg powder for solution for injection is dissolved in at least 2 ml water for injection and Cefotaxime 1000 mg powder for solution for injection 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.

Intramuscular injection
For intramuscular injection, 500 mg Cefotaxime 500 mg powder for solution for injection and 1000 mg Cefotaxime 1000 mg powder for solution for injection is dissolved in 2 and 4 ml water for injection respectively. Afterwards the injection should take place deep into the gluteal muscle. Pain with the i.m. injection can be avoided by dissolving Cefotaxime 500 mg powder for solution for injection in 2 ml or Cefotaxime 1000 mg powder for solution for injection in 4 ml of 1% lidocaine solution. An intravascular injection is to be avoided in this case because of possible adverse effects. If Cefotaxime is intramuscularly administered after reconstitution with lidocaine, the SmPC of lidocaine should be checked for the necessary product information.

Combination therapy
A combination therapy of cefotaxime with aminoglycosides is indicated without availability of an antibiogram in the case of severe, life-threatening infections. The kidney function must be watched in using the combination with aminoglycosides.

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

The duration of the treatment depends on the course of the illness.

4.3 Contraindications

Hypersensitivity to cephalosporins.

In patients with a history of hypersensitivity to cefotaxime and/or to any component of this product, a penicillin or to any other type of beta-lactam drug.

Allergic cross reactions can exist between penicillins and cephalosporins (see section 4.4).

Contraindications to lidocaine must be excluded before intramuscular injection of cefotaxime when lidocaine solution is used as a solvent (see section 4.4.) See information in the Summary of Product Characteristics of lidocaine, especially contraindications.

4.4 Special warnings and precautions for use

As with other antibiotics, the use of cefotaxime, especially if prolonged, may result in overgrowth of non-susceptible organisms, such as *Enterococcus* spp, candida, *Pseudomonas aeruginos*a. Repeated evaluation of the patient's condition is essential. If super-infection occurs during treatment with cefotaxime, appropriate measures should be taken and specific anti-microbial therapy should be instituted if considered clinically necessary.

Anaphylactic reactions:

Serious, including fatal hypersensitivity reactions have been reported in patients receiving cefotaxime (see sections 4.3 “Contraindications” and 4.8 “Undesirable effects”). If a hypersensitivity reaction occurs, treatment must be stopped.

The use of cefotaxime is strictly contra-indicated in subjects with a previous history of immediate type hypersensitivity to cephalosporins.

Since cross allergy exists between penicillins and cephalosporins, cefotaxime should be given with extreme caution to patients who have had any other type of hypersensitivity reaction to a penicillin or any other beta-lactam drug. Before therapy with cefotaxime is instituted, careful inquiry should be made to determine whether the patient had any previous hypersensitivity reactions to cefotaxime, any other cephalosporin, or to any penicillin or other beta-lactam drug.

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

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

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

Antibiotic-associated diarrhoea, colitis and pseudomembranous colitis have all been reported with the use of cefotaxime. 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. The diagnosis of this rare but possibly fatal condition can be confirmed by endoscopy and/or histology.

These diagnoses should be considered in any patient who develops severe and/or bloody diarrhoea during or shortly after treatment.

The presence of *Clostridium difficile* should be investigated and if a diagnosis of pseudomembranous colitis is suspected, cefotaxime should be discontinued immediately. Appropriate treatment measures should be initiated and

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

Cefotaxime should be used with caution in individuals with a previous history of gastro-intestinal disease, particularly colitis.

As with other cephalosporins, prolonged use of cefotaxime may result in the overgrowth of non-susceptible organisms, such as enterococci and *Candida* spp.

Haematological reactions

Since haematological abnormalities such as leukopenia, neutropenia and, more rarely, agranulocytosis may develop during treatment with cefotaxime, particularly if given over long periods, blood count should be monitored if treatment lasts for longer than 7-10 days. In case of neutropenia (< 1400 neutrophils/mm^3), treatment should be interrupted.

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).

Fast infusion into a central vein can cause arrhythmia.

Renal insufficiency

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 pre-existing renal impairment.

If cefotaxime is intramuscularly administered after reconstitution with lidocaine, the SmPC of lidocaine should be checked for the necessary product information.
See section 4.3 for contraindications for formulations containing lidocaine.

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 “Undesirable effects”).

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. “Posology and method of administration”).

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 product contains sodium, which should be taken into account when prescribing to patients requiring sodium

restriction. Cefotaxime 500 mg powder for solution contains 524 mg cefotaxime sodium, which is equivalent to 1.1 mmol cefotaxime sodium and therefore to 1.1 mmol sodium (25.3 mg sodium).

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 an 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 have been reported when high doses of cephalosporins have been used concomitantly to aminoglycosides. A dose adjustment may be necessary, and the kidney function must be watched (see section 4.2 “Posology and method of administration”).

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).

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of cefotaxime has not been established in human pregnancy.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. There are, however, no adequate and well controlled studies in pregnant women.

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

Breast-feeding
Cefotaxime passes into human breast milk.
Effects on the physiological intestinal flora of the breast-fed infant leading to diarrhoea, to 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 women.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed.
There is no evidence that cefotaxime directly impairs the ability to drive or to operate machines.
In individual cases, in administration of high doses of cefotaxime and particularly in the patients with simultaneous kidney function impairment, encephalopathy may occur (e.g. impaired consciousness, abnormal movements and convulsions) and giddiness have been reported (see section 4.8). Patients should be advised not to drive or operate machinery if any such symptoms occur.

4.8 Undesirable effects

Adverse reactions to cefotaxime have occurred relatively infrequently and have generally been mild and transient and occur in about 5% of patients treated with cefotaxime.
The side effects, described below, are classified according to following frequencies:

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 the available data)*

Infections and infestations

Not known: Superinfection (see section 4.4)

Blood and lymphatic system disorders

Uncommon: Leukopenia, eosinophilia, thrombocytopenia

Rare Neutropenia, haemolytic anaemia, granulocytopenia.
Agranulocytosis may develop, particularly after prolonged therapy. These occurrences are reversible. If therapy lasts for more than 7 days blood picture checks should be instituted.

Immune system disorders

Uncommon: Jarisch-Herxheimer reaction

Rare Severe acute hypersensitivity reaction (anaphylaxia). An anaphylactic shock is life threatening and necessitates corresponding emergency measures.
Allergic skin-reactions (e.g. urticaria, exanthema), itching and drug-fevers.

Very rare, including isolated cases
Erythema multiforme (mild to severe forms i.e. Stevens-Johnson syndrome) and toxic-epidermal necrolysis.
In patients with an inclination to allergies an allergic reaction is more likely.

Not known Angioedema, bronchospasm.

Nervous system disorders

*Uncommon**:*** Convulsions have been reported, especially with high doses and in patients with renal function impairment (see section 4.4)

Not known: Headache, dizziness, encephalopathy (e.g. impairment of consciousness, abnormal movements) (see section 4.4)

Cardiac disorders

Very rare A very small number of cases of arrhythmias have occurred following rapid bolus infusion through a central venous catheter.

Gastrointestinal disorders

Common Gastrointestinal disturbances, like loss of appetite, nausea, sickness, stomach ache or diarrhoea, which are usually mild in nature and frequently fade away during or otherwise after termination of the therapy.

Rare Pseudomembranous colitis. See also section 4.4 “Special warnings and precautions for use”.

Not known: Vomiting

Renal and urinary disorders

Uncommon: Decrease in renal function/increased serum creatinine (particularly when co-prescribed with

aminoglycosides) and urea concentrations.

Very rare, including isolated cases
Acute interstitial nephritis

Hepato-biliary disorders

Uncommon Slight, transient increases in serum bilirubin and/or liver enzymes (ALAT, ASAT, Gamma GT, alkaline phosphatase, LDH)

Not known: Hepatitis* (sometimes with jaundice)

Skin and subcutaneous tissue disorders

Uncommon: Rash, pruritus, urticaria

Not known: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (see section 4.4)

General disorders and administration site conditions

Very common: For IM formulations: Transient pain may be experienced at the site of injection. This is more likely to occur with higher doses.

Common Occasionally, phlebitis has been reported in patients receiving intravenous cefotaxime. However, this has rarely been a cause for discontinuation of treatment.
Pain and hardening of the tissue (induration) occasionally arise at the injection site after intramuscular injection.

Uncommon: Fever

Not known: For IM formulations (since the solvent contains lidocaine): Systemic reactions to lidocaine.

* postmarketing experience

Description of selected adverse reactions

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' treatment of borreliosis: skin rash, itching, fever, leukopenia, 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.

Other advice
Liver and kidney function should be monitored in the event of prolonged use.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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 beta-lactam antibiotics including cefotaxime.

In the event of overdosing cefotaxime must be discontinued, and supportive treatment initiated which includes measures to accelerate elimination and symptomatic treatment of adverse reactions (e.g. convulsions).

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

a) symptoms of overdosing
Intoxication, sensu strictu, is not known in man. With certain risk patterns and with the administration of very high doses, central nervous system excitation conditions, myoclonia and cramp can occur, as have also been described for other betalactams. The risk of the appearance of these undesirable effects is increased in patients with severely restricted kidney function, epilepsy and meningitis.

b) emergency measures
Centrally 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 of the shock.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutical group: Third generation cephalosporins.
ATC classification: J01DD01

Mechanism of action
Cefotaxime inhibits the action of certain bacterial cell wall synthetic enzymes and so interrupts cell wall biosynthesis. Bacterial cell lysis results.

Mechanisms of resistance
Bacterial resistance to cefotaxime may be due to one or more of the following mechanisms:
- Hydrolysis by β-lactamases. Cefotaxime may be efficiently hydrolysed by the production of certain extended-spectrum β-lactamases. Also, the induction and/or constitutive expression of chromosomally-encoded (AmpC) enzymes can efficiently hydrolyse the drug.
- An impermeability-based mechanism of resistance.
- Efflux pump mechanisms.

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

Cefotaxime-resistant bacteria may exhibit varying degrees of cross-resistance with other β-lactams. Cefotaxime-resistant gram-negative bacteria show complete cross-resistance to other broad-spectrum third generation cephalosporins (e.g. ceftazidime, ceftriaxone).

The use of cefotaxime as monotherapy in infections caused by gram negative bacteria containing inducible encoded AmpC-like β-lactamases like *Enterobacter cloacae*, *Enterobacter* spp., *Serratia* spp., and *Citrobacter* spp. should be discouraged despite apparent *in vitro* susceptibility, as mutants with stably depressed (hyperproduced) β-lactamase may be selected during therapy.

Breakpoints
National Committee for Clinical Laboratory Standards (NCCLS):
Enterobacteriaceae*, *Pseudomonas aeruginosa* and other Non- Fermenters, *Staphylococcus* spp.: susceptible ≤ 8 mg/l; intermediate 16-32 mg/l; resistant ≥ 64 mg/l.

Haemophilus influenzae: susceptible ≤ 2 mg/l.
Neisseria gonorrhoeae: susceptible ≤ 0.5 mg/l.
Streptococcus pneumoniae (non-meningitis): susceptible ≤ 1 mg/l; intermediate 2 mg/l; resistant ≥ 4 mg/l.
Streptococcus pneumoniae (meningitis): susceptible ≤ 0.5 mg/l; intermediate 1 mg/l; resistant ≥ 2 mg/l.
Streptococcus spp. (beta-haemolytic group): susceptible ≤ 0.5 mg/l.
Streptococcus spp. (viridans group): susceptible ≤ 1 mg/l; intermediate 2 mg/l; resistant ≥ 4 mg/l.
*Strains of *Escherichia coli* and *Klebsiella* spp. that produce ESBLs may be clinically resistant to therapy with cefotaxime despite *in vitro* susceptibility.

In-vitro antibacterial spectrum
A general overview of the antibacterial spectrum of cefotaxime is given below. It should be considered that the prevalence of acquired resistance may vary geographically within the European Union and with time for selected species, so that local information on resistance is desirable, particularly when treating severe infections. The information given in the table below provides an approximate guidance on the probabilities whether microorganisms will be susceptible to cefotaxime.

Commonly susceptible species	
Gram positive aerobes	
Staphylococcus aureus (MSSA)	
Streptococcus agalactiae	
Streptococcus pneumoniae (including penicillin-resistant strains)	
Streptococcus pyogenes	
Gram-negative aerobes	
Haemophilus influenzae	
Moraxella catarrhalis°	
Morganella morganii	
Neisseria gonorrhoeae°	
Neisseria meningitidis°	
Proteus mirabilis [%]	
Species for which acquired resistance may be a problem	
Gram-positive aerobes	
Staphylococcus aureus [ɔ]	
Staphylococcus epidermidis[+]	
Staphylococcus haemolyticus[+]	
Staphylococcus hominis[+]	
Gram-negative aerobes	
Citrobacter freundii	
Enterobacter aerogenes	
Enterobacter cloacae	
Escherichia coli [%]	
Klebsiella oxytoca [%]	
Klebsiella pneumoniae [%]	
Proteus vulgaris	
Serratia marcescens	
Anaerobes	
Bacteroides fragilis	

Inherently resistant species ***Gram-positive aerobes*** *Enterococcus* spp. *Listeria monocytogenes* *Staphylococcus aureus* (MRSA) ***Gram-negative aerobes*** *Acinetobacter baumannii* *Pseudomonas aeruginosa* *Stenotrophomonas maltophilia* ***Anaerobes*** *Clostridium difficile* ***Others*** *Chlamydia* spp. *Chlamydophila* spp. *Legionella pneumophilia* *Mycoplasma* spp. *Treponema pallidum*	

° No current surveillance data available. Susceptibility is anticipated according to the current scientific knowledge.
+ In at least one region resistance rate is above 50%.

% Extended Spectrum beta-lactamase (ESBL) producing strains are always resistant.

ɜ resistance rates <10% in community acquired infections

5.2 Pharmacokinetic properties

Cefotaxime is applied parenterally.

Absorption
After intravenous injection of 1000 mg cefotaxime the serum concentrations after 5 min amounted to about 81-102 mg/l and after 15 min to 46 mg/l. 8 min after intravenous injection of 2000 mg cefotaxime, serum concentrations of 167-214 mg/l were recorded. After intramuscular administration, the maximum serum concentrations (approximately 20 mg/l after 1000 mg) were reached within 30 min.

Distribution
The apparent distribution volume is 21-37 l.

With infected meninges, cefotaxime and desacetyl-cefotaxime penetrate into the fluid space and then reach therapeutically effective concentrations there (e.g. with infections which are caused by gram-negative bacteria and pneumococci).

The serum protein binding amounts to approximately 25-40%.

Cefotaxime pervades tissue rapidly, passes the placenta barrier and reaches high concentrations in foetal tissues (up to 6 mg/kg). It is only expressed at a low percentage in the mother's milk (concentrations in the mother's milk: 0.4 mg/l after 2000 mg).

Biotransformation
Cefotaxime is metabolized to a considerable extent in man. Approximately 15-25% of a parenteral dose is excreted as O-desacetyl-cefotaxime. The metabolite possesses anti-bacterial activity.

In addition to desacetyl-cefotaxime, there are two other inactive lactones. From desacetyl-cefotaxime, a lactone is produced as an ephemeral intermediate, which still cannot be proven either in the urine or in the plasma, because it is subject to a rapid conversion to stereo isomers of the ring opening (betalactam ring) lactone. These are likewise eliminated in the urine.

Elimination
The excretion of cefotaxime and desacetyl-cefotaxime takes place mainly by the renal route. A small percentage (approximately 2%) is eliminated with bile. In the urine collected over 6-hours, 40-60% of a dose was recovered in unchanged form and approximately 20% as desacetyl-cefotaxime. After intravenous administration of radioactively marked cefotaxime somewhat more than 80% was recovered in the urine, from it, 50-60% appeared as unchanged mother substance and the remainder as 3 metabolites.

The total clearance of the cefotaxime amounts to 240-390 ml/ min and the renal clearance to 130-150 ml/min.

The serum half-lives of cefotaxime and its active metabolite amount to be 50-80 minutes and 125 minutes, respectively. In geriatric patients (> 80 years) the half-lives were found to be 120-150 minutes and 5 hours for the active metabolite.

With severe kidney malfunctions (creatinin clearance 3-10 mi/min) the half-life of the cefotaxime can be extended to 2.5-10 hours. Cefotaxime only accumulates under these conditions to a small extent, in contrast to the active and inactive metabolites.

Both cefotaxime and desacetyl-cefotaxime are removed by haemodialysis to a large extent from the blood.

5.3 Preclinical safety data

The toxicity of cefotaxime after single doses is very low. Cefotaxime has no mutagenic potential, as indicated by a negative micronucleus test. Studies in rats and mice gave no indication of cefotaxime having teratogenic properties. Fertility was not impaired. In perinatal and postnatal studies in rats, pups born to the high dose animals had significantly lower weights at birth and remained smaller than control pups during the 21 days of nursing.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Not applicable.

6.2 Incompatibilities

Cefotaxime should not be mixed in alkaline solutions such as sodium bicarbonate injection.
Cefotaxime should also not be admixed with aminoglycosides. However, they may be administered separately to the same patient.

6.3 Shelf life

Unopened
2 years

Opened and reconstituted product
From a microbiological point of view, the product should be used immediately. Discard any unused solution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Chemical and physical in-use stability has been demonstrated for 6 hours at 2-8 ºC, when dissolved in water for injection and 1% lidocaine HCl solution. When reconstituted with other compatible solutions (see section 6.6), the product should be used immediately.

The colour of the solution may change to light yellow, however, the efficacy and safety of the antibiotic are not influenced.

6.4 Special precautions for storage

Do not store above 25 °C.
Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

Transparent type II glass vial with bromobutyl rubber stopper and aluminium seal with a flip off cap, containing cefotaxime sodium, equivalent to 500 mg cefotaxime.
The vials are packed in a carton box containing 1, 5 or 10 vials.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The product is compatible with the following solutions:

- Water for Injections,
- Sodium chloride 9 mg/ml (0.9% w/v), solution for infusion
- Glucose 50 mg/ml (5% w/v), solution for infusion
- Lidocaine HCl 10 mg/ml (1% w/v), solution for injection (see also section 4.4 “Special warnings and precautions for use”).

The compatibility with other infusion fluids should be checked before use.

Reconstitute the powder with the solvent by shaking vigorously for at least 30 seconds to ensure complete dissolution. See also section 4.2 “Posology and method of administration” for further instructions. Only clear solutions, practically free from particles, should be used.

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

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.,
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