Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cefotaxime 1g Powder for solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains cefotaxime sodium equivalent to 1 g of cefotaxime

Excipient(s) with known effect
Each gram of cefotaxime contains approximately 48 mg (2.09 mmol) of sodium.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection or infusion (Powder for injection or infusion).

White to slightly yellow powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

1. Cefotaxime is indicated in the treatment of serious infections, either before the infecting organism has been identified or when caused by bacteria of established sensitivity, including
osteomyelitis,
septicaemia,
bacterial endocarditis,
meningitis, and
peritonitis.
and other serious bacterial infections suitable for parenteral antibiotic therapy.

2. Cefotaxime may be used for pre-operative prophylaxis in patients undergoing surgical procedures, that may be classified as contaminated or potentially so.

4.2 Posology and method of administration

Cefotaxime may be administered intravenously**,** by bolus injection or by infusion, or by intramuscular injection. 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.

Adults:

The recommended dosage for mild to moderate infections is 1g 12 hourly. However, dosage may be varied according to the severity of the infection, sensitivity of causative organisms and condition of the patient. Therapy may be initiated before the results of sensitivity tests are known.

In severe infections dosage may be increased up to 12g daily given in three or four divided doses. For infections caused by sensitive *Pseudomonas* species daily doses of greater than 6g will usually be required.

Children:

The usual dosage range is 100-150mg/kg/day in two to four divided doses. However, in very severe infection doses of up to 200mg/kg/day may be required.

Neonates: The recommended dosage is 50mg/kg/day in two to four divided doses. In severe infections 150-200mg/kg/day, in divided doses, have been given.

Dosage in renal impairment: Because of extra-renal elimination, it is only necessary to reduce the dosage of cefotaxime in severe renal failure (GFR <5ml/min = serum creatinine approximately 751 micromol/litre). After an initial loading dose of 1g, daily dose should be halved without change in the frequency of dosing, i.e. 1g twelve hourly becomes 0.5g twelve hourly, 1g eight hourly becomes 0.5g eight hourly, 2g eight hourly becomes 1g eight 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.

Dosage in hepatic impairment: No dosage adjustment is required.

Intravenous and Intramuscular Administration: Reconstitute cefotaxime with Water for Injections PhEur as directed in Section 6.6 (Instructions for use/handling). Shake well until dissolved and then withdraw the entire contents of the vial into the syringe.

Intravenous administration (Injection or Infusion): Cefotaxime may be administered by intravenous infusion using the fluids stated in Section 6.6 (Instructions for use/handling). The prepared infusion may be administered over 20-60 minutes.

For intermittent I.V. injections, the solution must be injected over a period of 3 to 5 minutes. During post-marketing surveillance, potentially life-threatening arrhythmia has been reported in a very few patients who received rapid intravenous administration of cefotaxime through a central venous catheter.
Cefotaxime and aminoglycosides should not be mixed in the same syringe or perfusion fluid.

4.3 Contraindications

Hypersensitivity to cephalosporins.

In patients with a history of hypersensitivity to Cefotaxime and/or to any of the excipients listed in section 6.1.
Allergic cross reactions can exist between penicillins and cephalosporins (see section 4.4).

Cefotaxime reconstituted with lidocaine is contraindicated in patients with:

- known history of hypersensitivity to lidocaine or other local anaesthetics of the amide type
- non-paced heart block
- severe heart failure
- administration by the intravenous route
- infants aged less than 30 months of age.

4.4 Special warnings and precautions for use

As with other antibiotics, the use of cefotaxime, especially if prolonged, may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken (see section 4.8).

Anaphylactic reactions:
Serious, including fatal hypersensitivity reactions have been reported in patients receiving cefotaxime (see sections 4.3 and 4.8).

If a hypersensitivity reaction occurs, treatment must be stopped.

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

Since cross allergy exists between penicillins and cephalosporins, use of the latter should be undertaken with extreme caution in penicillin sensitive subjects. Hypersensitivity reactions (anaphylaxis) occurring with these two antibiotic families may be serious or even fatal.

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.

Clostridioides 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 *Clostridioides difficile* associated disease (CDAD). CDAD may range in severity from mild to life threatening, the most severe form of which is pseudo-membranous colitis.

The diagnosis of this rare but possibly fatal condition can be confirmed by endoscopy and/or histology. It is important to consider this diagnosis in patients who present with 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. *Clostridioides difficile* associated disease can be favoured by faecal stasis. Medicinal products that inhibit peristalsis should not be given.

Blood disorders:
Leukopenia, neutropenia and, more rarely, bone marrow failure, pancytopenia or agranulocytosis may develop during treatment with cefotaxime. 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 dosage should be modified according to the creatinine clearance calculated (see section 4.2). Patients with severe renal dysfunction should be placed on the dosage schedule recommended in section 4.2.

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.

Encephalopathy:
Beta-lactams, including cefotaxime, predispose the patient to encephalopathy risk (which may include convulsions, confusion, impairment of consciousness, movement disorders), particularly in case of overdose or renal impairment (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 Cefotaxime when 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-oxydase specific method is used.

Sodium:
This medicinal product contains 48 mg sodium per vial, equivalent to 2.4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Probenecid interferes with renal tubular transfer of cephalosporins, thereby delaying their excretion and increasing their plasma concentrations.

As with other cephalosporins, cefotaxime may potentiate the nephrotoxic effects of nephrotoxic drugs such as aminogylcosides or potent diuretics (e.g. furosemide). Renal function must be monitored (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.

Lactation:
Cefotaxime passes into human breast milk.

Effects on the physiological intestinal flora of the breast-fed infant leading to diarrhoea, colonisation by yeast-like fungi, and sensitisation of the infant cannot be excluded. Therefore, a decision must be made whether to discontinue breast-feeding or to discontinue therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

In the case of adverse reactions such as dizziness or encephalopathy (which may include convulsions, confusion, impairment of consciousness, movement disorders) the patient should not operate machines or drive a vehicle. 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 (≥ 1/10,000 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) Candida infection
Blood and the lymphatic system disorders			Leukopenia Eosinophilia Thrombocytopenia			Bone marrow failure Pancytopenia Neutropenia Agranulocytosis (see section 4.4) Haemolytic anaemia
Immune system disorders			Jarisch-Herxheimer reaction			Anaphylactic reactions Angioedema Bronchospasm Anaphylactic shock
Nervous system disorders			Convulsions (see section 4.4)			Headache Dizziness Encephalopathy* (see section 4.4)
Cardiac disorders						Arrhythmia following rapid bolus infusion through central venous catheter
Gastrointestinal 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/orbilirubin			Hepatitis* (sometimes with jaundice)
Skin and subcutaneous			Rash Pruritus			Erythema multiforme

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)
disorders			Urticaria			Stevens-Johnson syndrome Toxic epidermal necrolysis (see section 4.4) Acute generalised exanthematous pustulosis (AGEP)
Renal and Urinary disorders			Decrease in renal function/increaseof creatinine (particularly when co-prescribed with aminoglycosides) (seesection 4.4)			Acute renal failure 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 (where lidocaine is used forreconstitution):* Systemic reactionsto lidocaine

* Beta-lactams, including cefotaxime, predispose the patient to encephalopathy risk (which may include convulsions, confusion, impairment of consciousness, movement disorders), particularly in case of overdose or renal impairment.
** postmarketing 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 week's treatment of borreliosis: skin rash, itching, fever, leucopenia, increase in liver enzymes, difficulty of breathing, joint discomfort.

Hepatobiliary disorders:

Increase in liver enzymes (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase) and/or bilirubin have been reported. 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.

Superinfection:

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.

For IM Formulations:

Since the solvent contains lidocaine, systemic reactions to lidocaine may occur, especially in the event of inadvertent intravenous injection or injection into highly vascularised tissue or in the event of an overdose.

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, Website: www.hpra.ie.

4.9 Overdose

Symptoms of overdose may largely correspond to the profile of side effects.

There is a risk of encephalopathy in cases of administration of β–lactam antibiotics including cefotaxime, particularly in case of overdose or renal impairment.

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

General Properties

ATC Classification
Pharmacotherapeutic group: Beta-lactam antibiotics, cephalosporins.
ATC Code: J01D A10

Mode of action
Cefotaxime is a third generation broad spectrum bactericidal cephalosporin antibiotic. The bactericidal properties are due to the inhibitory effect of cefotaxime on bacterial cell wall synthesis.

Mechanisms of resistance

Resistance to Cefotaxime may be due to production of extended-spectrum beta-lactamases that can efficiently hydrolyse the drug, to the induction and/or constitutive expression of AmpC enzymes, to impermeability or to efflux pump mechanisms. More than one of these possible mechanisms may co-exist in a single bacterium.

Breakpoints:

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

Susceptibility

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. This information gives only an approximate guidance on the probabilities whether micro-organisms will be susceptible to cefotaxime or not.

Species	Frequency of resistance ranges in EU (if > 10%) (extreme values)
Susceptible	
Gram-positive aerobes	
Staphylococcus aureus	
(Methicillin-susceptible) *	
Group A Streptococci (including Streptococcus pyogenes) *	
Group B Streptococci	
β-hemolytic Streptococci (Group C, F, G)	
Streptococcus pneumoniae *	12.7%
Viridans Group Streptococci	
Gram-negative aerobes	
Citrobacter spp. *	
Escherichia coli *	
Haemophilus influenzae *	

Haemophilus parainfluenzae *	
Klebsiella spp. *	
Moraxella catarrhalis *	
Neisseria gonorrhoeae *	
Neisseria meningitides *	
Proteus spp. *	
Providencia spp. *	
Yersinia enterocolitica	
Anaerobes	
Clostridium spp. (not Clostridium difficile)	
Peptostreptococcus spp.	
Propionibacterium spp.	
Others	
Borrelia spp.	

Resistant
Gram-positive aerobes
Enterococcus spp.
Enterococcus faecalis
Enterococcus faecium
Listeria spp.
Staphylococcus aureus (MRSA)
Staphylococcus epidermidis (MRSE)
Gram-negative aerobes
Acinetobacter spp.
Citrobacter spp.
Enterobacter spp.
Morganella morganii
Pseudomonas spp.
Serratia spp.
Xanthomonas 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 resistant to all currently available β-lactam antibiotics including cefotaxime.

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

5.2 Pharmacokinetic properties

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

The apparent volume of distribution at steady-state of cefotaxime is 21.6 litres/1.73m^2 after 1g 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 in levels above the minimum inhibitory concentration 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 2g. 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 390ml/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 are no pre-clinical data of relevance to the prescriber that are additional to those included in other sections.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Cefotaxime sodium should not be mixed with alkaline solutions such as sodium bicarbonate injection or solutions containing aminophylline.

Cefotaxime should not be admixed with aminoglycosides. If they are used concurrently they should be administered in separate site.

Cefotaxime should not be mixed with other medicinal products except those listed in *section 6.6*.

6.3 Shelf life

Unopened: 2years.
For the reconstituted solution, chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C. From a microbiological point of view, once opened, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Unopened: Do not store above 25°C. Keep the vials in the outer carton.

For storage times following reconstitution, *see section 6.3*.

6.5 Nature and contents of container

Cefotaxime is supplied in Type II 15ml glass vials, closed with a Type I rubber stopper (coated or uncoated with Omniflex) and sealed with an aluminium/plastic cap fitted with a detachable flip top.

The vials are boxed individually and in packs of 10, 25 or 50 vials.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only. Discard any unused contents.
When dissolved in Water for Injections PhEur, cefotaxime forms a straw-coloured solution suitable for intravenous and intramuscular injection. Variations in the intensity of colour of the freshly prepared solutions do not indicate a change in potency or safety.

Dilution Table:Intravenous Administration

Vial size	Diluent* to be added	Approx available volume	Approx displacement volume
1g	4ml	4.6ml	0.6ml

*Water for injection

Dilution Table: IntramuscularAdministration

Vial size	Diluent* to be added	Approx available volume	Approx displacement volume
1g	4ml	4.6ml	0.6ml

*Water for injection or 1% lidocaine
Reconstituted solution: Whilst it is preferable to use only freshly prepared solutions for both intravenous and intramuscular injection, cefotaxime is compatible with several commonly used intravenous infusion fluids and will retain satisfactory potency for up to 24 hours refrigerated (2°-8ºC) in the following:

Water for Injection***s*** Ph Eur
Sodium Chloride Intravenous Infusion BP
5% Glucose Intravenous Infusion BP
Sodium Chloride and Glucose Intravenous Infusion BP
Compound Sodium Lactate Intravenous Infusion BP (Ringer-lactate solution for injection)

Intravenous Infusion:
1-2g cefotaxime are dissolved in 40-100ml of infusion fluid.
After 24 hours any unused solution should be discarded.

Cefotaxime is compatible with 1% Lidocaine Injection BP; however freshly prepared solutions should be used.

Cefotaxime is also compatible with metronidazole infusion (500mg/100ml) and both will maintain potency when refrigerated (2°-8ºC)for up to 24 hours. Some increase in colour of prepared solutions may occur on storage. However, provided the recommended storage conditions are observed, this does not indicate change in potency or safety.

7 MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Ltd
Ballymacarbry
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 September 2003

Date of last renewal: 02 November 2005

10 DATE OF REVISION OF THE TEXT

March 2024