



**CEFOTAXIME 1G POWDER FOR SOLUTION FOR  
INJECTION OR INFUSION**

**PL 20117/0007**

**UKPAR**

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**CEFOTAXIME 1G POWDER FOR SOLUTION FOR  
INJECTION OR INFUSION**

**PL 20117/0007**

**LAY SUMMARY**

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Morningside Healthcare Limited a Marketing Authorisation (licence) for the medicinal product Cefotaxime 1g Powder for Solution for Injection or Infusion (PL 20117/0007). This medicine is available by prescription only.

Cefotaxime is an antibiotic that is used to treat a number of bacterial infections. It kills bacteria by interfering with the formation of the bacteria's cell wall, without this the bacteria disintegrate and die.

Cefotaxime 1g Powder for Solution for Injection or Infusion raised no clinically significant safety concerns and it was therefore judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.

**CEFOTAXIME 1G POWDER FOR SOLUTION FOR  
INJECTION OR INFUSION**

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**SCIENTIFIC DISCUSSION**

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## **INTRODUCTION**

Based on the review of the data on quality, safety and efficacy the UK granted a marketing authorisation for the medicinal product Cefotaxime 1g Powder for Solution for Injection or Infusion to Morningside Healthcare Limited on 24 August 2006. This product is a prescription only medicine.

This is a national application submitted under Article 10.1 of Directive 2001/83, claiming essential similarity to Claforan 1g Injection (PL 04425/0188) authorised in the UK to Aventis Pharma Ltd. This product was originally authorised in the UK in March 1981 to Roussel Laboratories Ltd.

Cefotaxime is a broad-spectrum bactericidal cephalosporin antibiotic. Cefotaxime is exceptionally active *in vitro* against gram-negative organisms sensitive or resistant to first or second generation cephalosporins. It is similar to other cephalosporins in activity against gram-positive organisms.

## **PHARMACEUTICAL ASSESSMENT**

### **1. INTRODUCTION**

This national standard abridged application is for powder for injection containing 1g of the cephalosporin antibiotic cefotaxime sodium. The full standard term is powder for solution for injection or infusion. The product is indicated for the treatment of a number of infections as described in the SPC, administered by IV bolus, IV infusion or by IM injection. The application has been made under the first paragraph of Article 10.1, claiming essential similarity to Claforan 1g Injection (PL 04425/0188) authorised in the UK to Aventis Pharma Ltd. This product was originally authorised in the UK in March 1981 (PL 00109/0074, Roussel Laboratories Ltd).

No genetically modified organisms are included in the product.

No paediatric development plan exists for this product.

The proposed product has not been authorised to the applicant or to a related company in any other European Union (EU) Member State, nor is it the subject of any pending application in any other EU Member State.

### **2. ACTIVE SUBSTANCE**

#### **2.1 General information**

##### 2.1.1 Nomenclature

rINN: cefotaxime sodium

CAS: 64485-93-4

Chemical name: 5-thia-1-azabicyclo [4,2,0] oct-2-ene-2-carboxylic acid, 3-[(acetyloxy)methyl]-[[2-amine-4-thiazolyl](methoxyimino)acetyl]amino]-8-oxo, [6R-[6 $\alpha$ ,7 $\beta$ (z)]]], sodium salt

##### 2.1.2 Structure

C<sub>16</sub>H<sub>16</sub>N<sub>5</sub>NaO<sub>7</sub>S<sub>2</sub>

MW: 477.46

##### 2.1.3 General properties

White or slightly yellow hygroscopic crystalline powder. It is freely soluble in water, sparingly soluble in methanol and practically insoluble in ether.

### **2.2 Manufacture**

### 2.2.1 Manufacturer

A suitable manufacturer is responsible for production of the active substance, cefotaxime sodium.

### 2.2.2 Manufacturing process description and process controls

In a letter dated 10 February 2004 the applicant requested that the application was assessed referring to the Certificate of Suitability issued to the active substance manufacturer (R0-CEP 1999-033-Rev 00) for Cefotaxime Sodium Sterile, a copy of this certificate has been provided.

Certificate R0-CEP 1999-033-Rev 00 required some additional tests and limits to supplement the control measures described in the Ph Eur monograph.

### 2.2.3 In-process controls for critical stage

Covered by the Certificate of Suitability.

### 2.2.4 Control of materials

Covered by the Certificate of Suitability.

## 2.3 Control of intermediates

Covered by the Certificate of Suitability.

## 2.4 Characterisation

Covered by the Certificate of Suitability.

## 2.5 Impurities

Details of the impurities that are potentially present in the active substance manufactured have been provided.

## **2.6 Control of active substance**

### **2.6.1 Specification**

An appropriate specification is provided, with all proposed limits being acceptable.

It is stated that N,N-dimethylaniline is not used in the manufacturing process, hence it is acceptable that a test for this residual solvent (included in the Ph Eur monograph) is not performed. It is also stated that no ICH Class I solvents are used.

### **2.6.2 Analytical procedures / validation**

The manufacturer of the finished product uses the Ph Eur methods for assay and related substances for the active substance and finished product. Validation data has been included in the dossier.

### **2.6.3 Batch analyses**

Satisfactory batch data have been provided for three batches (CFTS020060, CFTS020061 and CFTS020062) manufactured in 2002. The levels of impurities found have been summarised.

In addition, three Certificates of Analysis from the active substance manufacturer and from the manufacturer of the finished product have been provided. The results from the two analyses are similar and demonstrate compliance with the proposed active substance specification.

Satisfactory Certificates of Analysis have also been provided for four batches of active substance manufactured by an additional manufacturer that was used in manufacture of the stability batches.

## **2.7 Reference standards or materials**

Covered by the Certificate of Suitability.

## **2.8 Container closure system**

Bulk substance is stored in an appropriate container.

## **2.9 Stability**

Stability data have been generated by the active substance manufacturer. Data have been provided for three commercial scale batches manufactured in April

2002. These batches have been stored for up to 6 months at 40°C/75% and for up to 9 months at 25°C/60%.

Batches were tested for appearance, loss on drying, assay, related substances, pH, specific optical rotation and specific absorbance. All batches remained within specification under the above conditions. A retest period of 24 months was proposed and data have been provided that support this re-test period.

A commitment has been provided that the stability studies on the current batches will be continued to 48 months.

In addition, stress studies have been conducted exposing the active substance to acid, alkali, thermal, UV and oxidative stress. The substance was sensitive to all conditions except exposure to UV light. Specificity of the method has been demonstrated.

### 3. MEDICINAL PRODUCT

#### 3.1 Composition

Composition and function of ingredients

<b>Ingredient</b>	<b>Quantity (g)</b>	<b>Function</b>	<b>Reference Standard</b>
Cefotaxime sodium (equivalent to cefotaxime)	(1.0)	Active ingredient	Ph Eur

No overages are included. Nominal content of each vial is based on assay and moisture content of the batch of active substance.

#### 3.2 TSE Risk Materials

Declarations have been provided that the only materials of animal origin used in the fermentation stage or other stages are milk-derived materials. The risk of TSE may be considered to be minimised. A TSE declaration referring to EMEA/410/01 rev 02 has been provided and is satisfactory.

The media used for media fill studies (CASO broth) uses casein that is derived from milk fit for human consumption and peptone that is derived from casein (bovine source). The milk-derived substances are excluded from the scope of the guidance note. A TSE Certificate of Suitability has been issued to the supplier of Casein-Meat Peptone E2 Ref. 19501 (R1-CEP 2000-120-Rev 00), a copy of which has been provided.



### **3.3 Pharmaceutical Development**

Brief but satisfactory information has been provided.

The SPC for the reference product states that the product is compatible with water for injections, sodium chloride injection, 5% dextrose injection, dextrose and sodium chloride injection and compound sodium lactate injection (Ringer-lactate injection). It is proposed that once the product is opened it should be used immediately or within 24 hours if stored in a refrigerator. The SPC of the reference product also states that the product may be reconstituted with 1% lidocaine but must be used immediately. It is also compatible with metronidazole infusion 500mg/100ml, with both products being chemically stable if stored at 2-8°C for up to 24 hours.

The product may be administered intravenously, by bolus injection, by infusion or intramuscularly. For intravenous and intramuscular use it is recommended that the product is reconstituted with water for injections. The SPC for the reference product gives the following dilutions, that should also apply to this product: 1g plus 4ml; 2g plus 10ml. In addition, the reference SPC states that for intravenous infusion 1-2 g are dissolved in 40-100ml water for injections or in the infusion fluids listed above. The prepared infusion may be administered over 20-60 minutes.

### **3.4 Manufacture**

#### **3.4.1 Manufacturer**

A copy of the manufacturing authorisation for the site intended for manufacture and assembly has been provided issued by the relevant authorities, dated October 2003.

#### **3.4.2 Batch formula**

The filling process is considered as a continuous process, whereby a specific batch is produced using raw materials from only a single batch of active substance and is produced over not more than 5 days of continuous operation.

#### **3.4.3 Manufacturing process and process controls**

A flow chart of the manufacturing process has been provided. The manufacturing process consists of aseptic filling (Grade A area) of a single batch of active substance into washed, sterilised and depyrogenated vials. After filling, the vials are sealed with sterilised rubber stoppers and an aluminium overcap is applied.

Manufacture is in a facility dedicated to the manufacture of injectable cephalosporin products involving aseptic filling.

The conditions for sterilisation of the vials (and depyrogenisation), stoppers and removable parts of the filling machine are suitable.

#### 3.4.4 In-process controls for critical stages

Fill weight is checked on 12 vials every 30 minutes.

After capping and labelling periodic checks are made of the legibility of the labelling and seal integrity.

Filled and capped vials are subject to a 100% visual inspection.

Studies on seal force have been presented. and a suitable operating range has been established.

#### 3.4.5 Control of intermediates

There are no intermediate products.

#### 3.4.6 Process validation or evaluation

The manufacturing process has been validated through the successful manufacture of four 1g production batches (9,372 to 28,116 vials) between July 2001 and July 2002 using batches of active substance provided by the manufacturer of the stability batches. The batches comply with the proposed finished product specification and confirm the consistency of the manufacturing process.

Satisfactory validation reports have been provided for the autoclave (solid load, porous load, media fill load and rubber stoppers), vial washer, depyrogenation tunnel and filling/stoppering machine.

A satisfactory report has been provided covering seven consecutive media fill studies (13,150 vials of 10ml, 15ml or 20ml, filled over 3-4 days) with sterilised anhydrous lactose followed by a growth promotion medium. Two of the filling runs showed contamination; one vial out of 13,338 (0.008%) and two vials out of 13,228 vials (0.015%). Overall, the contamination rate was three vials out of 92,710 vials (0.003%). Revalidation is every 6 months using a single vial size; this is acceptable. Results of a revalidation media fill study (two runs) have been presented. No contamination was observed in either of the runs in which 13,150 vials were filled.

### 3.5 Control of excipients

### 3.5.1 Specification

There are no excipients in this product.

## **3.6 Control of drug product**

### 3.6.1 Specification

The finished product specification has been described and is based on the specification for the active substance. It complies with the BP monograph for Cefotaxime Sodium for Injection.

Absence of a limit for average weight is accepted, given that the fill weight is highly dependent on potency. A suitable measure of uniformity is included.

### 3.6.2 Analytical procedures / validation

The analytical methods have been suitably described.

A reverse phase HPLC method is used as the assay method and for determination of levels of related substances. The method is based on the method described in the Ph Eur monograph for cefotaxime sodium but with some changes made. The method has been validated in accordance with ICH and with respect to cefotaxime and impurities A and B (based on the available reference standards. System suitability parameters are included in the method). Forced degradation studies have been included. The method can detect impurities A, B and E as described in the Ph Eur.

The tests for sterility and bacterial endotoxins performed on the finished product are conducted and validated in accordance with the methods described in the European Pharmacopoeia.

Cefotaxime working standard used in the validation of the assay method was a standard production batch. A satisfactory Certificate of Analysis has been provided for this batch.

### 3.6.3 Batch analyses

Satisfactory batch analysis data have been provided for four 1g production batches (9,372-2,8116 vials) between July 2001 and July 2002. The batches comply with the proposed finished product specification and with the Ph Eur limits for sub-visible particles.

### 3.6.4 Justification

A comparison of monograph and proposed specification requirements has been provided. This can be considered as a justification for the finished product specifications.

### 3.7 Container closure system

The product is presented in clear borosilicate Type I glass vials (10 ml nominal capacity) with grey chlorobutyl stoppers (complying with the Ph Eur monograph for rubber closures, Type I) with an aluminium overcap. Packs contain 10 vials.

Satisfactory specifications have been provided for the vials and stoppers. Satisfactory batch data/Quality Certificates have been provided for batches of the vials and stoppers.

Satisfactory baseline microbial and endotoxin data have been provided for the vials and stoppers. Validation data have been provided for the methods used.

### 3.8 Stability

Stability data were provided for eight 1 g production batches (8,000-62,333 vials) manufactured between March 1997 and June 2000. Five batches were manufactured with active substance from the manufacturer that produced the active substance used in process validation, and the other three batches used active substance from the intended commercial supplier. All batches were manufactured at a manufacturing facility that has now been decommissioned and filled into containers/closures that are identical to those intended for commercialisation.

The analytical methods were as described for routine batch release.

Stability data provided: 25°C/60% (2 x 36, 6 x 24 months)

Test parameters: appearance of powder and constituted solution, pH, loss on drying or water content, assay, related substances, UV absorbance, visible particles, sterility, bacterial endotoxins

Only minor changes were seen in most of the test parameters. All batches comply with the specification throughout the test period. Limits for individual and total related substances were introduced part way through the stability studies and, therefore, are not available for all inspection points. The highest levels of individual and total impurities found over 24 months storage at 25°C/60% were 1.0% and 3.1%, respectively. Some batches showed an apparent fall in assay

values, although this was not reflected in a corresponding increase in the levels of related substances.

The applicant has confirmed that stability studies have been initiated with batches of 1g and 500mg product manufactured at the new proposed commercial facilities. Satisfactory results are available following 3-18 months storage at 25°C/60% and after 3-12 months storage at 40°C/75%.

Stability studies have been conducted following reconstitution of the powder with water for injections, 50ml 5% dextrose, 0.9% NaCl, 0.9% NaCl/5% dextrose and Lactated Ringer's Solution.

Stability data provided: room temperature (initial, 5 and 24 hours)  
refrigerated (initial, 6, 27 and 48 hours)

Test parameters: pH, assay, related substances, sterility, absorbance

The vials retained their physical, chemical and microbiological quality over less than 5 hours.

The applicant has proposed a shelf life of 24 months for product stored below 25°C. This proposal is accepted. The reconstituted product must be used within 4 hours. This is acceptable.

The licence holder also commits to carry out stability studies on a batch of reconstituted solution stored in an inverted position this year and to immediately notify the MHRA if any any out of specification results are observed. This is acceptable

### **3.9 Other information**

#### 3.9.1 Bioavailability, bioequivalence

Not relevant.

#### 3.9.3 Essential similarity

The requirements for essential similarity are met.

### **3.10 Product Literature**

#### 3.10.1 SPC

The SPC is satisfactory.

#### 3.10.2 PIL

The leaflet is satisfactory.

### 3.10.3 Labelling

The labelling is satisfactory.

## 3.11 Administrative

### 3.11.1 Comment on Expert Report

The Pharmaceutical Expert has suitable experience and the report is satisfactory.

### 3.11.2 MAA form

The MAA form is satisfactory.

### 3.11.3 GMP

The site for manufacture of the active substance has been inspected as part of the EDQM Certification scheme and documentation has been provided to support the satisfactory outcome of inspection of the manufacturing facilities.

A copy of the Manufacturing Authorisation for the manufacturing, assembly and release site has been provided. Manufacture is in accordance with the principles of Good Manufacturing Practice.

It is proposed that batch release will be performed at Medochemie Ltd, Iapetou St, V.I.P.E., Agios, Athanasios, Limassol, Cyprus. A copy of the relevant licence has been provided.

### 3.11.4 Guideline Compliance

This application generally complies with the requirements of the Notice to Applicants and relevant Notes for Guidance.

## 4. CONCLUSIONS

A Marketing Authorisation may be granted.

## **PRECLINICAL ASSESSMENT**

No new preclinical data have been supplied with this application and none is required for an application of this type.

## CLINICAL ASSESSMENT

### **1. Introduction**

Cefotaxime is a broad-spectrum bactericidal cephalosporin antibiotic. Cefotaxime is exceptionally active in vitro against gram-negative organisms sensitive or resistant to first or second-generation cephalosporins. It is similar to other cephalosporins in activity against gram-positive organisms.

This application is made under Article 10.1, first paragraph, claiming essential similarity to the innovator's product Claforan 1g Injection, authorised to Aventis Pharma Ltd in the UK (PL 04425/0188), the applicant has now submitted this application for a generic intravenous or intramuscular product.

### **2. Assessment**

The following is the comparison of the Summaries of Product Characteristics of the index product under assessment and of the corresponding innovator product (Claforan 1g Injection) from Aventis Pharma Ltd (PL 04425/0188) in the UK:

#### 2.1 Indications

Virtually identical

#### 2.2 Posology

Virtually identical

#### 2.3 Contraindications

Virtually identical

#### 2.4 Special warnings and precautions for use

Virtually identical

#### 2.5 Interactions

Virtually identical

#### 2.6 Use during pregnancy and lactation

Virtually identical

#### 2.7 Effect on the ability to drive and use machines



Virtually identical

#### 2.8 Undesirable effects

Virtually identical

#### 2.9 Overdose

Virtually identical

#### 2.10 Pharmacodynamic properties

Virtually identical

#### 2.11 Pharmacokinetic properties

Virtually identical

### **3. Discussion**

The Summaries of Product Characteristics of the index products are virtually identical.

For this parenteral formulation, there are no bioequivalence issues.

### **4. Patient Information Leaflet**

This is in compliance with Directive 92/27/EEC and is satisfactory.

### **5. Recommendations**

There are no major clinical public health issues and the recommendation is to grant a marketing authorisation for this preparation.

## **OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT**

### **QUALITY**

The important quality characteristics of Cefotaxime 1g Powder for Solution for Injection or Infusion are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

### **PRECLINICAL**

No new preclinical data were submitted and none are required for applications of this type.

### **EFFICACY**

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

### **RISK BENEFIT ASSESSMENT**

The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and some benefit has been shown to be associated with Cefotaxime 1g Powder for Solution for Injection or Infusion. The risk benefit is therefore considered to be positive.

**CEFOTAXIME 1G POWDER FOR SOLUTION FOR  
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**PL 20117/0007**

**STEPS TAKEN FOR ASSESSMENT**

1	The MHRA received the marketing authorisation application on 31 October 2003
2	Following initial assessment of the application the MHRA requested further information relating to the quality dossier on 24 November 2004
3	The applicant responded to the MHRA's request, providing further information on the quality dossier in June 2005
4	Following assessment of the response the MHRA requested further information relating to the quality dossier on 23 December 2005
5	The applicant responded to the MHRA's request, providing further information on the quality dossier on 5 April 2006 and 9 June 2006
6	Following assessment of the response the MHRA requested further information relating to the quality dossier on 26 June 2006
7	The applicant responded to the MHRA's request, providing further information on 10 July 2006
8	Following assessment of the response the MHRA requested further additional information relating to the quality dossier on 13 July 2006
9	The applicant responded to the MHRA's request, providing further information on 28 July 2006
10	The application was determined on 24 August 2006

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1. NAME OF THE MEDICINAL PRODUCT**

Cefotaxime 1g Powder for Solution for Injection or Infusion

### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Cefotaxime sodium equivalent to 1g of cefotaxime.

### **3. PHARMACEUTICAL FORM**

Powder for solution for injection or infusion. A white to slightly creamy powder.

### **4. CLINICAL PARTICULARS**

#### **4.1. Therapeutic indications**

##### **Properties:**

Cefotaxime is a broad-spectrum bactericidal cephalosporin antibiotic. Cefotaxime is exceptionally active *in vitro* against Gram-negative organisms sensitive or resistant to first or second generation cephalosporins. It is similar to other cephalosporins in activity against Gram-positive organisms.

##### **Indications:**

Cefotaxime is indicated in the treatment of the following infections either before the infecting organism has been identified or when caused by bacteria of established sensitivity.

##### **Septicaemias**

**Respiratory Tract Infections** such as acute and chronic bronchitis, bacterial pneumonia, infected bronchiectasis, lung abscess and post-operative chest infections.

**Urinary Tract Infections** such as acute and chronic pyelonephritis, cystitis and asymptomatic bacteriuria.

**Soft-Tissue Infections** such as cellulitis, peritonitis and wound infections.

**Bone and Joint Infections** such as osteomyelitis, septic arthritis.

**Obstetric and Gynaecological Infections** such as pelvic inflammatory disease.

**Gonorrhoea** particularly when penicillin has failed or is unsuitable.

**Other Bacterial Infections** meningitis and other sensitive infections suitable for parenteral antibiotic therapy.

**Prophylaxis:**

The administration of Cefotaxime prophylactically may reduce the incidence of certain post-operative infections in patients undergoing surgical procedures that are classified as contaminated or potentially contaminated or in clean operations where infection would have serious effects.

Protection is best ensured by achieving adequate local tissue concentrations at the time contamination is likely to occur. Cefotaxime should therefore be administered immediately prior to surgery and if necessary continued in the immediate post-operative period.

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.

**Bacteriology:**

The following organisms have shown *in vitro* sensitivity to Cefotaxime.

**Gram-positive:**

Staphylococci, including coagulase-positive, coagulase-negative and penicillinase-producing strains.

Beta-haemolytic and other streptococci such as *Streptococcus mitis* (*viridans*) (many strains of enterococci, e.g. *Streptococcus faecalis*, are relatively resistant).

*Streptococcus (Diplococcus) pneumoniae*

*Clostridium* spp.

**Gram-negative:**

*Escherichia coli*.

*Haemophilus influenzae* including ampicillin resistant strains.

*Klebsiella* spp.

*Proteus* spp. (both indole positive and indole negative).

*Enterobacter* spp.

*Neisseria* spp. (including  $\beta$ -lactamase producing strains of *N. gonorrhoea*).

*Salmonella* spp. (including *Sal. typhi*).

*Shigella* spp.

*Providencia* spp.

*Serratia* spp.

*Citrobacter* spp.

Cefotaxime has frequently exhibited useful *in vitro* activity against *Pseudomonas* and *Bacteroides* species although some strains of *Bacteroides fragilis* are resistant.

There is *in vitro* evidence of synergy between Cefotaxime and aminoglycoside antibiotics such as gentamicin against some species of Gram-negative bacteria including some strains of *Pseudomonas*. No *in vitro* antagonism has been noted. In severe infections caused by *Pseudomonas* spp. the addition of an aminoglycoside antibiotic may be indicated.

#### **4.2. Posology and method of administration**

Cefotaxime may be administered intravenously or 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.

##### ***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 3 or 4 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 2 to 4 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 2 to 4 divided doses. In severe infections 150-200mg/kg/day, in divided doses, have been given.

### ***Dosage in Gonorrhoea:***

A single injection of 1g may be administered intramuscularly or intravenously.

### ***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.

### ***Intravenous and Intramuscular Administration:***

Reconstitute cefotaxime with 4.0mL of Water for Injections 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 and use immediately.

### ***Intravenous 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. To produce an infusion using vials with an infusion connector, remove the safety cap and directly connect the infusion bag. The needle in the closure will automatically pierce the vial stopper. Pressing the infusion bag will transfer solvent into the vial. Reconstitute by shaking the vial and finally, transfer the reconstituted solution back to the infusion bag ready for use.

## **4.3. Contraindications**

Known or suspected allergy to cephalosporins.

## **4.4. Special warnings and precautions for use**

Preliminary enquiry about hypersensitivity to penicillin and other  $\beta$ -Lactam antibiotics is necessary before prescribing cephalosporins since cross allergy occurs in 5–10% of cases.

Hypersensitivity reactions (anaphylaxis) occurring with the two types of antibiotics can be serious and occasionally fatal. Hypersensitivity requires that treatment be stopped.

Patients with severe renal dysfunction should be placed on the dosage schedule recommended under “Posology and Method of Administration”.

As with other antibiotics, the use of cefotaxime, especially if prolonged, may result in overgrowth of non susceptible organisms, such as *Enterococcus* spp. Repeated evaluation of the condition of the patient is essential. If superinfection occurs during treatment with cefotaxime, specific antimicrobial therapy should be instituted if considered clinically necessary.

Cefotaxime reconstituted with lidocaine must never be used in the following:

- by the intravenous route
- in infants under 30 months
- in subjects with a previous history of hypersensitivity to this product
- in patients who have an unpaired heart block
- in patients with severe heart failure.

The sodium content of cefotaxime (2.09mmol/g) should be taken into account when prescribing to patients requiring sodium restriction.

Cefotaxime may predispose patients to pseudomembranous colitis. Although any antibiotic may predispose to pseudomembranous colitis, the risk is higher with broad spectrum drugs, such as cephalosporins. This side effect, which may occur more frequently in patients receiving higher doses for prolonged periods, should be considered as potentially serious. The presence of *C. difficile* toxin should be investigated, and treatment with cefotaxime stopped in cases of suspected colitis. Diagnosis can be confirmed by toxin detection and specific antibiotic therapy (e.g. oral vancomycin or metronidazole) should be initiated if considered clinically necessary. The administration of products which cause faecal stasis should be avoided.

#### **4.5. Interactions with other medicinal products and other forms of interaction**

Cephalosporin antibiotics at high dosage should be given with caution to patients receiving aminoglycoside antibiotics or potent diuretics such as furosemide as these combinations are suspected to adversely affect renal function. However, at the recommended doses, enhancement of nephrotoxicity is unlikely to be a problem with cefotaxime.

Probenecid interferes with renal tubular transfer of cefotaxime delaying its excretion and increasing the plasma concentration.



### **Interference with Laboratory Tests:**

A positive Coombs test may be seen during treatment with cephalosporins. This phenomenon may occur during treatment with cefotaxime.

A false positive reaction to glucose may occur with reducing substances but not with the use of specific glucose oxidase methods.

### **4.6. Pregnancy and lactation**

**Pregnancy:** It is known that cefotaxime crosses the placental barrier. Although studies in animals have not shown an adverse effect on the developing foetus, the safety of cefotaxime in human pregnancy has not been established. Consequently, cefotaxime should not be administered during pregnancy especially during the first trimester, without carefully weighing the expected benefit against possible risks.

**Lactation:** Cefotaxime is excreted in the milk.

### **4.7. Effects on ability to drive and use machines**

None known.

### **4.8. Undesirable effects**

Adverse reactions to cefotaxime have occurred relatively infrequently and have generally been mild and transient. Effects reported include candidiasis, nausea, vomiting, abdominal pain, diarrhoea (diarrhoea may sometimes be a symptom of pseudomembranous colitis (see warnings)), transient rises in liver transaminases, alkaline phosphatase and/or bilirubin.

As with other cephalosporins, changes in renal function have been rarely observed with high doses of cefotaxime, particularly when co-prescribed with aminoglycosides. Rare cases of interstitial nephritis have been reported in patients treated with cefotaxime. Administration of high doses of cephalosporins, particularly in patients with renal insufficiency, may result in encephalopathy (e.g. impairment of consciousness, abnormal movements and convulsions).

Hypersensitivity reactions have been reported. These include skin rashes, pruritus and less frequently urticaria, drug fever and very rarely anaphylaxis (e.g. angioedema and bronchospasm possibly culminating in shock).

As with other cephalosporins, occasional cases of bullous reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme have also been reported.

As with other beta-lactam antibiotics, granulocytopenia and more rarely agranulocytosis may develop during treatment with cefotaxime, particularly if given over long periods. A few cases of eosinophilia and neutropenia have been observed, reversible when treatment is ceased. Some cases of rapidly reversible eosinophilia and thrombocytopenia on stopping treatment have been reported. Rare cases of haemolytic anaemia have been reported. For cases of treatment lasting longer than 10 days, blood count should therefore be monitored.

Transient pain may be experienced at the site of injection. This is more likely to occur with higher doses. Occasionally, phlebitis has been reported in patients receiving intravenous cefotaxime. However, this has rarely been a cause for discontinuation of treatment.

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

The following symptoms have occurred after several weeks of treatment for borreliosis (Lyme's Disease): skin rash, itching, fever, leucopenia, increases in liver enzymes, difficulty of breathing, joint discomfort. To some extent these manifestations are consistent with the symptoms of the underlying disease, for which the patient is being treated.

#### **4.9. Overdose**

Serum levels of cefotaxime may be reduced by peritoneal dialysis or haemodialysis. In the case of overdosage, particularly in renal insufficiency, there is a risk of reversible encephalopathy.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1. Pharmacodynamic properties**

Cefotaxime is a broad spectrum bactericidal cephalosporin antibiotic. Cefotaxime is exceptionally active in vitro against Gram-negative organisms sensitive or resistant to first or second generation cephalosporins. It is similar to other cephalosporins in activity against Gram-positive bacteria.

#### **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<sup>2</sup> after a 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**

Not applicable.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1. List of excipients**

None

### **6.2. Incompatibilities**

Not applicable

### **6.3. Shelf life**

Unopened: 2 years

After reconstitution: Use immediately.

The product has shown chemical stability for up to 4 hours if stored between 2-8°C in the following infusion fluids:-

- Water for Injections.
- Sodium Chloride Injection.
- 5% Dextrose Injection.
- Dextrose and Sodium Chloride Injection.

### **6.4. Special precautions for storage**

Unreconstituted solution: Do not store above 25°C. Keep the container in the outer carton.

For storage conditions of the reconstituted medicinal product, see section 6.3

### **6.5. Nature and contents of container**

Cefotaxime is supplied in clear 10ml Type I glass vials with chlorobutyl rubber stoppers and an aluminium overseal. The vials are boxed individually and in packs of 10.

### **6.6 Special precautions for disposal of used medicinal product or waste materials derived from such medicinal product and other handling of the product**

Cefotaxime is supplied as a white to slightly creamy Powder for Solution for Injection or Infusion, which when dissolved in Water for Injections forms a straw-coloured solution suitable for IV or IM injection. Variations in the intensity of colour of the freshly prepared solution do not indicate a change in potency or safety.

Reconstituted Solutions should be used immediately

Cefotaxime is compatible with several commonly used intravenous infusion fluids as follows:

- Water for Injections
- Sodium Chloride Injection
- 5% Dextrose Injection
- Dextrose and Sodium Chloride Injection
- Cefotaxime is also compatible with 1% lidocaine, however only freshly prepared solutions should be used (see section 4.4)'.

Cefotaxime is also compatible with metronidazole infusion (500mg/100ml) some increase in colour of prepared solutions may occur on storage. However, this does not indicate change in potency or safety.

Any unused product or waste material should be disposed of in accordance with local requirements

**7. MARKETING AUTHORISATION HOLDER**

Morningside Healthcare Ltd  
115 Narborough Road  
Leicester  
LE3 0PA  
United Kingdom

**8. MARKETING AUTHORISATION NUMBER**

PL 20117/0007

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

24/08/2006

**10. DATE OF REVISION OF THE TEXT**

24/08/2006

## PATIENT INFORMATION LEAFLET

### PATIENT INFORMATION LEAFLET

#### **For Cefotaxime 1g Powder for solution for Injection or Infusion**

**Please read this entire leaflet when you start your course of treatment with 'Cefotaxime'. This is a summary of the information about this medicine. If you are not sure about anything or want to know more, ask your doctor or pharmacist.**

**Please keep this leaflet in a safe place; you may want to read it again.**

#### **Who makes Cefotaxime Injection?**

**Marketing Authorisation Holder:** Morningside Healthcare Ltd, 115 Narborough Road, Leicester, LE3 0PA.

**Manufacturer:** Medochemie Ltd, Iapetou St., V.I.P.E, Agios, Athanasios, Limassol, Cyprus

#### **What 'Cefotaxime' is and what is it used for?**

It is a white or off white which is made into solution to be given by injection into a vein or a muscle. Cefotaxime is an antibiotic, given for the treatment of a wide range of infections. Antibiotics kill bacteria, which cause infections in your body. It comes in a glass bottle and contains Cefotaxime Sodium equivalent to 1 g of Cefotaxime. There are no other ingredients.

#### **Before you take/use Cefotaxime**

##### **Do not take/use Cefotaxime if:**

- You have ever suffered a severe reaction to any other antibiotics particularly penicillins or cephalosporins.
- You are pregnant, trying for a baby or breast feeding
- You have kidney disease

#### **Take special care with Cefotaxime**

- Cefotaxime may cause you to become infected with *C. difficile*, a bacterial infection that can cause severe inflammation (colitis) of the colon (large intestine). If you have severe or bloody diarrhoea and suspect you have colitis contact your doctor immediately.
- Cefotaxime may cause you to become infected with *Enterococcus* spp so your doctor will monitor your condition. If you become infected, you may start on a specific therapy, if your doctor feels it is necessary.
- Tell your doctor if you are on a sodium-controlled diet.
- If you require any tests, blood, urine or diagnostic, whilst taking this medicine please ensure that the doctor knows that you are taking Cefotaxime

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

In particular, **are you taking any of the following?**

- diuretics (water tablets) e.g. furosemide,
- probenecid
- other antibiotics

#### **What if I am pregnant (or think I might be pregnant) or breast-feeding?**

Cefotaxime should not be taken during pregnancy, especially during the first 3 months without carefully weighing the expected benefit against possible risks. **If you are pregnant** or you think you may be pregnant or you are trying for a baby tell your doctor or pharmacists before taking this medicine.

Cefotaxime is excreted in human milk, and should be given to nursing mothers with caution. **Please tell your doctor if you are breastfeeding.**

#### **Can I drive or operate machinery?**

There are no known effects on your ability to drive or operate machinery whilst taking Cefotaxime Injection.

### How to take/use Cefotaxime

Cefotaxime is given intravenously (injection into a vein) or infusion (slow injection into a vein) or intramuscularly (injection into the muscle). Your treatment with Cefotaxime Injection will depend on the type of infection and how severe it is. Your doctor will decide what dosage is necessary, how often you will receive treatment and how long this should be continued.

### How much Cefotaxime will I be given?

**Adults:** The recommended dosage for mild to moderate infections is 1g every 12 hours. In severe infections this may be increased up to 12g per day given in 3 or 4 doses. For infections caused by sensitive *Pseudomonas* species daily doses of greater than 6g will usually be required.

**Children:** The dose will depend on the size of your body and the usual dose is 100-150mg/kg/day in 2 to 4 divided doses. However, in very severe infection doses of up to 200mg/kg/day may be required.

**Babies:** The recommended dosage is 50mg/kg/day in 2 to 4 divided doses. In severe infections this could be increased to 150-200mg/kg/day.

**Dosage in patients with kidney disorders:** It is only necessary to reduce the dosage of cefotaxime in severe kidney failure. After an initial dose of 1g, the daily dose should be halved without change in the frequency of dosing i.e. 1g every twelve hours becomes 0.5g every twelve hours, 1g every eight hours becomes 0.5g every eight hours, 2g every eight hours becomes 1g every eight hours etc.

### What if you stop taking Cefotaxime or are given too much

As this medicine will be given to you whilst you are in hospital, it is unlikely that you will stop taking your medicine or be given too much; however, if you have any concerns discuss this with your doctor or nurse.

### Possible side effects

Like all medicines, Cefotaxime can cause side effects, although not everybody gets them. Tell your doctor if you notice any of the following:

- Skin rash or itchy skin
- Infection, nausea, stomach pain, fever, diarrhoea
- Slight pain may be experienced at the site of injection.
- Your veins swelling following intravenous injection.
- Sore throat, fever, chills, rash with or without lesions around the mouth.
- If you take Cefotaxime for more than 10 days, your doctor may ask you to take a blood test.
- If you feel your heart flutter.
- Breathing difficulties or swelling of the neck, face or throat.
- Abnormal or sudden involuntary muscle contractions or you begin to lose consciousness.
- Tiredness (as you may have injury to your liver).

If you notice any of these side effects or any that are not mentioned in this leaflet, please inform your doctor or pharmacist.

### Storing Cefotaxime

Keep out of the reach and sight of children. The vials should be stored below 25°C and in the outer carton to protect from light.

### Use by date

Do not use this medicine after the expiry date stated on the carton.

This leaflet was revised in June 2006

# **TECHNICAL LEAFLET FOR PROFESSIONALS ADMINISTERING CEFOTAXIME 1G POWDER FOR SOLUTION FOR INJECTION OR INFUSION**

## **TECHNICAL LEAFLET**

### **Cefotaxime 1g Powder for solution for Injection or Infusion**

THIS SECTION CONTAINS INFORMATION FOR HEALTH PROFESSIONALS PLEASE DETACH BEFORE GIVING THE ABOVE SECTION TO THE PATIENT.

This is a summary of the information regarding the preparation, storage and administration of Cefotaxime 1g Powder for Solution for Injection or Infusion.

Please refer to Summary of Product Characteristics for full prescribing and other information.

### **INSTRUCTIONS FOR USE**

The contents of the vial should be reconstituted with Water for Injections 4.0mL should be added to the vial of Cefotaxime 1g Powder for Solution for Injection or Infusion). The vial should be shaken and if the powder does not dissolve immediately, be allowed to stand at room temperature until completely dissolved. Do not use if the solution is cloudy or the container is damaged.

Cefotaxime is compatible with several commonly used intravenous infusions as follows:

- Water for Injections
- Sodium Chloride Injection.
- 5% Dextrose Injection.
- Dextrose and Sodium Chloride Injection.
- Compound Sodium Lactate Injection (Ringer-lactate Injection).

Cefotaxime is compatible with metronidazole infusion (500mg/100ml). Some increase in colour of prepared solutions may occur; this does not indicate change in potency or safety.

Cefotaxime is also compatible with 1% lidocaine, however Cefotaxime reconstituted with lidocaine must never be used in the following:

- by the intravenous route
- in infants under 30 months
- in subjects with a previous history of hypersensitivity to either product
- in patients who have an unpaired heart block
- in patients with severe heart failure.

The sodium content of cefotaxime (2.09mmol/g) should be taken into account when prescribing to patients requiring sodium restriction.

### **STORAGE**

The unconstituted dry powder is stable for 24 months. Do not store above 25°C. Protect from light by keeping the container in the outer carton.

Reconstituted Solution: Once opened, the product should be used immediately and any unused drug should be discarded appropriately.

The product has shown chemical stability for up to 4 hours if stored between 2-8°C in the following infusion fluids:-

- Water for Injections
- Sodium Chloride Injection .
- 5% Dextrose Injection .
- Dextrose and Sodium Chloride Injection .

### **PARENTERAL ADMINISTRATION**

Cefotaxime may be administered intravenously or 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.

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**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 3 or 4 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 2 to 4 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 2 to 4 divided doses. In severe infections 150-200mg/kg/day, in divided doses, have been given.

**Dosage in Gonorrhoea:** A single injection of 1g may be administered intramuscularly or intravenously.

**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.

**Intravenous and Intramuscular Administration:** Reconstitute cefotaxime with 4.0mL of Water for Injections 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 and use immediately.

**Intravenous 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. To produce an infusion using vials with an infusion connector, remove the safety cap and directly connect the infusion bag. The needle in the closure will automatically pierce the vial stopper. Pressing the infusion bag will transfer solvent into the vial. Reconstitute by shaking the vial and finally, transfer the reconstituted solution back to the infusion bag ready for use.

**Marketing Authorisation Holder:**

Morningside Healthcare Ltd,  
115 Narborough Road, Leicester,  
LE3 0PA, UK

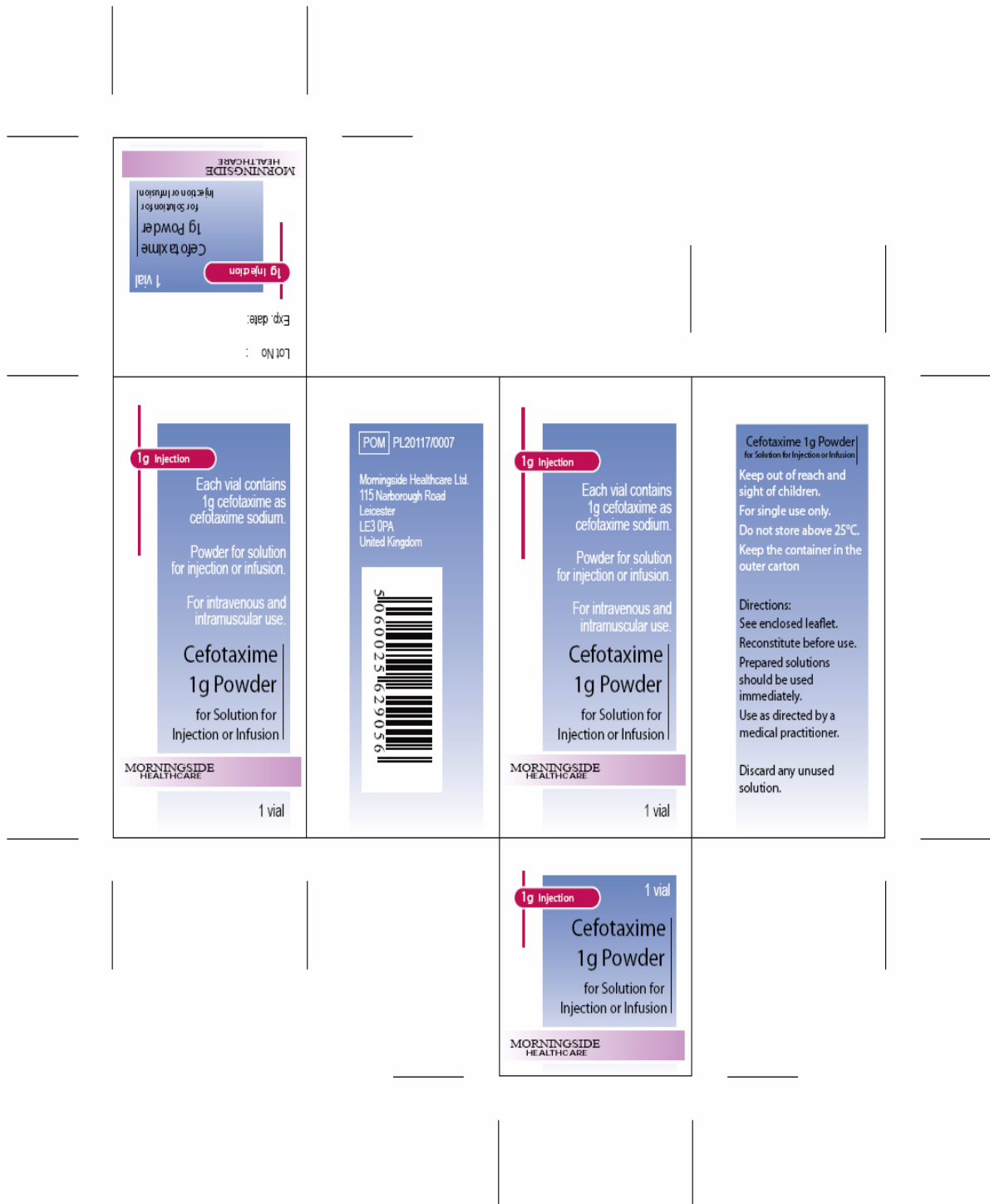
Date of preparation of information to health care professionals: June 2006

## PACKAGING

### Vial label:

<p><b>POM</b> PL20117/0007</p> <p>LOT:</p> <p>EXP:</p> <p>Each vial contains 1g cefotaxime as cefotaxime sodium.</p> <p>Powder for solution for injection or infusion.</p> <p>For intravenous and intramuscular use.</p>	<p><b>1g Injection</b></p> <p><b>Cefotaxime</b></p> <p><b>1g Powder</b></p> <p>for Solution for Injection or Infusion</p>	<p>Keep out of reach and sight of children.</p> <p>For single use only</p> <p>Do not store above 25°C.</p> <p>See enclosed leaflet.</p> <p>Reconstitute before use.</p> <p>Prepared solutions should be used immediately.</p> <p>Use as directed by a medical practitioner.</p> <p>Discard any unused solution.</p> <p>Keep the container in the outer carton</p> <p><b>MORNINGSIDE</b> HEALTHCARE</p>
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**Small pack carton:**



**Large pack carton:**

