CEFOTAXIME 1G POWDER FOR SOLUTION FOR INJECTION OR INFUSION
PL 14894/0397

CEFOTAXIME 2G POWDER FOR SOLUTION FOR INJECTION OR INFUSION
PL 14894/0398

UKPAR

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LAY SUMMARY

The Medicines Healthcare products Regulatory Agency granted Ranbaxy (UK) Limited Marketing Authorisations (licences) for the medicinal products Cefotaxime 1g Powder for Solution for Injection or Infusion (PL 14894/0397) and Cefotaxime 2g Powder for Solution for Injection or Infusion (PL 14894/0398) on 25\th\ February 2010. These are prescription-only medicines (POM).

Cefotaxime is an antibiotic that 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.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Cefotaxime 1g Powder for Solution for Injection or Infusion and Cefotaxime 2g Powder for Solution for Injection or Infusion outweigh the risks; hence Marketing Authorisations have been granted.
SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted Marketing Authorisations for the medicinal products Cefotaxime 1g Powder for Solution for Injection or Infusion and Cefotaxime 2g Powder for Solution for Injection or Infusion to Ranbaxy (UK) Limited on 25th February 2010. These products are prescription-only medicines.

These applications were submitted as abridged applications according to Article 10(1) of Directive 2001/83/EC. The products are claimed to be generic medicinal products of the original, Claforan Injection 1g & 2g (PL 00109/0074) authorised in the UK to Hoechst Marion Roussel Ltd. These products were originally authorised in the UK in March 1981 but to Roussel Laboratories Limited. The Marketing Authorisation holder was subsequently changed through a Change of Ownership to PL 04425/0188 (Aventis Pharma Limited). The reference products have been authorised in the EU for more than 10 years.

The product contains the active ingredient cefotaxime sodium. 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.

These applications were submitted at the same time and all sections of this scientific discussion refer to both products.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Oxytocin
INN: Cefotaxime sodium

Structure

![Structure of Cefotaxime sodium]

Molecular weight: 477.46
Molecular formula: C_{16}H_{16}N_{5}Na_{0.5}S_{2}
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-[6α,7β(z)]], sodium salt

Appearance: White or slightly yellow powder, hygroscopic
Solubility: Freely soluble in water, sparingly soluble in methanol and practically insoluble in ether.

Manufacture

All aspects of the manufacture, in-process controls, validation and active substance specification are covered by a Certificate of Suitability for the active substance manufacturer.

The Certificate of Suitability states that the drug substance is suitably controlled by its Ph.Eur. monograph. An appropriate specification is provided for the active substance, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specification.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

All potential known impurities have been identified and characterised. Suitable Certificates of Analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug and supporting an appropriate retest period.
DRUG PRODUCT

Other ingredients
No other ingredients or pharmaceutical excipients are used in the final drug product.

None of the starting materials or any part of the drug product contains material of animal or human origin.

Product development
The objective of the development programme was to produce products that could be considered generic medicinal products of Cefotaxime Claforan Injection 1g & 2g (PL 00109/0074) authorised in the UK to Hoechst Marion Roussel Ltd on 16th March 1981. Comparative analytical data has been provided to demonstrate that the proposed products are similar to the reference products.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

Impurity Profiles
Comparative impurity profiles between the proposed product and the reference product have been provided and are satisfactory.

Compatibility
Evidence of compatibility with commonly used intravenous fluids including those listed in the SmPC have been provided and is satisfactory.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on three production scale batches of each strength has been provided and demonstrate compliance with the release specification. Certificates of Analysis have been provided for any working standards used.

Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container Closure System
The product is filled in a transparent glass vial (Type II), with a bromobutyl stopper and a flip off aluminium and polypropylene cap.

The vials are packed in box of 10 and 50 vials. Specifications and Certificates of Analysis for all packaging types used have been provided. All primary product packaging complies with European Pharmacopoeia monograph 3.2.1 (glass containers for pharmaceutical use).
Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set, before opening the vial, with the following special storage precautions, “Do not store above 25°C. Keep the vial in the outer carton in order to protect from light.” After first opening the vial and after reconstitution, “The product should be used immediately”.

Bioequivalence/Bioavailability
The applicant has provided satisfactory justification for the bio waiver, based on 5.1.6 Parenteral solution CPMP/EWP/QWP/1401/98, page 13. The applicant’s product is an IV injection that contains the same active substance in the same concentration as the currently authorised reference product.

Essential Similarity
The drug substance complies with Ph Eur monograph for Cefotaxime. A biowaiver is claimed. Comparative analytical data for the proposed and reference products have been provided and are satisfactory. It is therefore considered that the proposed products are generic medicinal products of the reference products, Claforan Injection 1g & 2g.

ADMINISTRATIVE
Expert Report
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labelling are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA form
The MAA form is pharmaceutically satisfactory.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.
PRECLINICAL ASSESSMENT

These applications for Cefotaxime 1g and 2g Powder for Solution for Injection or Infusion were submitted as national abridged application, according to Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products of Claforan Injection 1g & 2g (PL 00109/0074) authorised in the UK to Hoechst Marion Roussel Ltd on 16th March 1981.

No new preclinical data have been supplied with these applications and none are required for applications of this type.

A preclinical expert report has been written by a suitably qualified person and is satisfactory.

The Marketing Authorisation Holder has been provided adequate justification for not submitting an Environmental Risk Assessment.
**CLINICAL ASSESSMENT**

1. **BACKGROUND**

Cefotaxime is a bacteriocidal broad-spectrum antibiotic, which is active against a wide range of Gram positive and Gram negative organisms.

Cefotaxime is the parent substance of aminothiazolyl-cephalosporins. It was the first parenteral third generation cephalosporin. When compared to first and second-generation cephalosporins, cefotaxime possesses a more extensive spectrum of activity against Gram positive and negative bacteria.

2. **THERAPEUTIC INDICATIONS**

Cefotaxime is indicated for the treatment of the following severe infections when known or thought very likely to be due to bacteria that are susceptible to cefotaxime (see section 5.1 – Pharmacodynamic properties):

- **Bacterial pneumonia.** Cefotaxime is not active against bacteria that cause atypical pneumonia or against several other bacterial species that may cause pneumonia, including *P. aeruginosa* (see section 5.1 – Pharmacodynamic properties).

- **Complicated infections of the kidneys and upper urinary tract.**

- **Severe infections of the skin and soft tissue**

- **Genital infections caused by gonococci, particularly when penicillin has failed or is unsuitable**

- **Intra-abdominal infections (such as peritonitis).** Cefotaxime should be used in combination with an antibiotic that is active against anaerobes in the treatment of intra-abdominal infections.

- **Acute bacterial meningitis** *(particularly if due to* *H. influenzae, N. meningitides, S. pneumoniae, E. coli, Klebsiella spp.)*

- **Septicaemia infections originating from the lungs, urinary tract, or bowel** *(in case of gram-negative organisms a combination with another suitable antibiotic should be considered).*

Consideration should be given to official guidance on the appropriate use of antibacterial agents.
Posology and method of administration
Cefotaxime may be administered by intravenous bolus injection, by intravenous infusion, or by intramuscular injection after reconstitution of the solution according to the directions given below. Dosage and mode of administration should be determined by the severity of the infection, susceptibility of the causative organism and the patient’s condition. Therapy may be started before the result of sensitivity tests are known.

Adults and children over 12 years
The usual dose in adults is for mild to moderate infections is 2 to 6g daily. However, dosage may be varied according to the severity of the infection, sensitivity of the causative organisms and conditions of the patient.

Guidelines for dosage:

Typical infection in presence (or suspicion) of a sensitive micro-organism: 1g every 12 hours corresponding to a total daily dosage of 2g intramuscularly or intravenously.

Infection in the presence (or suspicion) of sensitive or moderately sensitive multiple micro-organisms: 1-2g every 12 hours corresponding to a total daily dosage of 2-4g.

Severe infection by unidentified micro-organisms or for infections that cannot be localized: 2-3g as a single dose every 6 to 8 hours up to a maximum daily dosage of 12 g.

A combination of cefotaxime and other antibiotics in indicated in severe infections.

Infants and children up to 12 years
The usual dosage for infants and children <50 kg is 50-150 mg/kg/day in 2 to 4 divided doses. In very severe infections up to 200 mg/kg/day in divided doses may be required. In infants and children >50 kg the usual dose in adults, without exceeding the maximum daily dose of 12 g should be given.

Newborn infants and premature infants
The recommended dosage is 50 mg/kg/day in 2 to 4 divided doses. In case of life-threatening situations it may be necessary to increase the daily dose. In severe infections 150-200 mg/kg/day have been given: in those situations the following table may serve as a guide, since there are differences in kidney maturation.

<table>
<thead>
<tr>
<th>Age</th>
<th>Daily dose of Cefotaxime</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-7 days</td>
<td>50 mg/kg every 12 hours</td>
</tr>
</tbody>
</table>
8 days - 1 month | 50 mg/kg every 8 hours

_Elderly_
No dosage adjustment is required, provided that renal and hepatic function are normal.

_Other recommendations_

_Gonorrhoea:_
For gonorrhoea, a single injection (intramuscularly or intravenously) of 0.5g to 1 g cefotaxime. For complicated infections, consideration should be given to available official guidelines. Syphilis should be excluded before initiating treatment.

_Urinary tract infections:_
In uncomplicated UTI 1 g every 12 hours.

_Bacterial meningitis:_
In adults, daily doses of 6 to 12 g and in children daily doses of 150 to 200 mg/kg divided in equal doses every 6 to 8 hours are recommended. For the new-born, 50 mg/kg of cefotaxime can be given every 12 hours to infants 0-7 days old and every 8 hours to those 7-28 days old.

_Intra-abdominal infections:_
Intra-abdominal infection should be treated with Cefotaxime in combination with other appropriate antibiotics.

_Duration of therapy_
The duration of therapy with Cefotaxime depends on the clinical condition of the patient and varies according to the course of the disease. Administration of Cefotaxime should be continued until symptoms have subsided or evidence of bacterial eradication has been obtained. Treatment over at least 10 days is necessary in infections caused by _Streptococcus pyogenes_ (parenteral therapy may be switched to an adequate oral therapy before the end of the 10 day period).

_Dosage in renal function impairment_
In adult patients with a creatinine clearance of \( \leq 5 \) ml/min, the initial dose is similar to the recommended usual dose should be halved without change in the frequency of dosing.

_Dosage in dialysis or peritoneal dialysis_
In patients on haemodialysis and peritoneal dialysis an i.v. injection of 0.5-2 g, given at the end of each dialysis session and repeated every 24 hours, is sufficient to treat most infections efficaciously.

**Method of administration**

In order to prevent any risk of infection, the preparation of the infusion should be done in close aseptic conditions. Do not delay the infusion after the preparation of the solution.

- **Intravenous infusion**
  
  For *short intravenous infusion* 1g or Cefotaxime should be dissolved in 40-50 ml Water for Injections or in another compatible fluid (e.g. glucose 10%). After preparation the solution should be given as a 20 minute intravenous infusion.

  For *long lasting intravenous infusion* 2 g Cefotaxime should be dissolved in 100 ml of Water for Injections or another suitable fluid, e.g. 0.9% sodium chloride or isotonic glucose solution or other compatible fluids for infusions. After preparation, the solution may be given as a 50-60 minute intravenous infusion.

- **Intravenous injection**
  
  For intravenous injection Cefotaxime 1 g should be dissolved in 4 ml Water for Injections, Cefotaxime 2 g should be dissolved in 10 ml Water for Injections and should be injected over 3-5 minutes.

- **Intramuscular injection**
  
  Cefotaxime 1.0 g is dissolved in the 4ml Water for Injections. The solution should be administered by deep intramuscular injection. In order to prevent pain from the injection Cefotaxime 1.0 g may be dissolved in 4 ml % Lidocaine Hydrochloride (only for adults). Solutions with lidocaine must *not* be administered intravenously. If the total daily dose is more than 2g, then intravenous administration should be chosen. In the case of severe infections, intramuscular injection is not recommended.

The following table shows the volume of dilution

<table>
<thead>
<tr>
<th>Vial size</th>
<th>Short Intravenous Infusion</th>
<th>Long lasting Intravenous Infusion</th>
<th>Intravenous Injection</th>
<th>Intramuscular Injection</th>
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<tr>
<td>1 g</td>
<td>40-50 ml</td>
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<td>4 ml</td>
<td>4 ml</td>
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<tr>
<td>2 g</td>
<td>-</td>
<td>100 ml</td>
<td>10 ml</td>
<td>-</td>
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</table>
Assessor’s Comment
This is identical to the reference SmPC.

3. CLINICAL PHARMACOLOGY
Assessor’s Conclusion on Bioequivalence
For these intravenous products, there are no issues arising from bioequivalence provided that the pharmaceutical assessor has no concerns about similarity of the formulation with the reference product.

4. CLINICAL DATA - OVERVIEW
The Clinical Overview is translated from Spanish reviews the known clinical profile of cefotaxime antibiotic and cefotaxime for injection and the applicant product in relation to that. The reviewer concluded that cefotaxime powder for Injection ‘is suitable for inclusion in the Spanish pharmaceutical market as a generic specialty.’

5. EFFICACY
The efficacy profile of cefotaxime is well established. No new efficacy data are required for these applications.

6. SAFETY
The safety profile of cefotaxime is well established. No new efficacy data are required for these applications.

7. EXPERT REPORT
The clinical expert report has been written by a suitably qualified person and is satisfactory.

8. SUMMARY OF PRODUCT CHARACTERISTICS, PATIENT INFORMATION LEAFLET (PIL) AND LABELS.
The SmPC, PIL and labelling are medically acceptable.

9 CONCLUSION AND RECOMMENDATIONS
It is recommended that Marketing Authorisations are granted for these applications.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Cefotaxime 1g Powder for Solution for Injection or Infusion (PL 14894/0397) and Cefotaxime 2g Powder for Solution for Injection or Infusion (14894/0398) 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
Cefotaxime is a well-known drug and has been used for many years. No bioequivalence studies have been performed and none are required for these applications, as the product is administered as a parental aqueous solution rapidly \textit{in vivo}.

No formal data on clinical efficacy or safety have been presented for these applications and none are required.

No new or unexpected safety concerns arise from this application.

The SmPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the innovator products are interchangeable. Extensive clinical experience with cefotaxime sodium is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
## STEPS TAKEN FOR ASSESSMENT

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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 23rd December 2004.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant, the MHRA considered the application valid on 6th August 2006.</td>
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<td>3</td>
<td>Following assessment of the applications, the MHRA requested further information relating to the quality dossiers on 16th November 2005, 19th February 2007, 19th October 2007, 10th September 2008, and further information relating to the clinical dossiers on 6th October 2009.</td>
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<td>5</td>
<td>The applications were determined on 25th February 2010.</td>
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**CEFOTAXIME 1G POWDER FOR SOLUTION FOR INJECTION OR INFUSION**  
PL 14894/0397

**CEFOTAXIME 2G POWDER FOR SOLUTION FOR INJECTION OR INFUSION**  
PL 14894/0398

### STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
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CEFOTAXIME 1G POWDER FOR SOLUTION FOR INJECTION OR INFUSION
PL 14894/0397

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 1g cefotaxime.
Also contains 48 mg (2.09 mmol) of sodium per vial.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
White or slightly creamy powder.
Powder for solution for injection or infusion.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Cefotaxime is indicated for the treatment of the following severe infections when known or thought very likely to be due to bacteria that are susceptible to cefotaxime (see section 5.1 – Pharmacodynamic properties):

• Bacterial pneumonia; cefotaxime is not active against bacteria that cause atypical pneumonia or against several other bacterial species that may cause pneumonia, including P. aeruginosa (see section 5.1 – Pharmacodynamic properties).

• Complicated infections of the kidneys and upper urinary tract.

• Severe infections of the skin and soft tissue

• Genital infections caused by gonococci, particularly when penicillin has failed or is unsuitable

• Intra-abdominal infections (such as peritonitis). Cefotaxime should be used in combination with an antibiotic that is active against anaerobes in the treatment of intra-abdominal infections.

• Acute bacterial meningitis (particularly if due to H. influenzae, N. meningitides, S. pneumoniae, E. coli, Klebsiella spp.)

• Septicaemia infections originating from the lungs, urinary tract, or bowel (in case of gram-negative organisms a combination with another suitable antibiotic should be considered).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.
4.2 Posology and method of administration

Cefotaxime may be administered by intravenous bolus injection, by intravenous infusion, by intramuscular injection after reconstitution of the solution according to the directions given below. Dosage and mode of administration should be determined by the severity of the infection, susceptibility of the causative organism and the patient’s condition. Therapy may be started before the result of sensitivity tests are known.

**Adults and children over 12 years**

The usual dose in adults is for mild to moderate infections is 2 to 6g daily. However, dosage may be varied according to the severity of the infection, sensitivity of the causative organisms and conditions of the patient.

Guidelines for dosage:

Typical infection in presence (or suspicion) of a sensitive micro-organism: 1g every 12 hours corresponding to a total daily dosage of 2g intramuscularly or intravenously.

Infection in the presence (or suspicion) of sensitive or moderately sensitive multiple micro-organisms: 1-2g every 12 hours corresponding to a total daily dosage of 2-4g.

Severe infection by unidentified micro-organisms or for infections that cannot be localized: 2-3g as a single dose every 6 to 8 hours up to a maximum daily dosage of 12 g.

A combination of cefotaxime and other antibiotics in indicated in severe infections.

**Infants and children up to 12 years**

The usual dosage for infants and children <50 kg is 50-150 mg/kg/day in 2 to 4 divided doses. In very severe infections up to 200 mg/kg/day in divided doses may be required. In infants and children >50 kg the usual dose in adults, without exceeding the maximum daily dose of 12 g should be given.

**Newborn infants and premature infants**

The recommended dosage is 50 mg/kg/day in 2 to 4 divided doses. In case of life-threatening situations it may be necessary to increase the daily dose. In severe infections 150-200 mg/kg/day have been given: in those situations the following table may serve as a guide, since there are differences in kidney maturation.

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**Elderly**

No dosage adjustment is required, provided that renal and hepatic function are normal.
Other recommendations

Gonorrhoea:
For gonorrhoea, a single injection (intramuscularly or intravenously) of 0.5g to 1 g cefotaxime. For complicated infections, consideration should be given to available official guidelines. Syphilis should be excluded before initiating treatment.

Urinary tract infections:
In uncomplicated UTI 1 g every 12 hours.

Bacterial meningitis:
In adults, daily doses of 6 to 12 g and in children daily doses of 150 to 200 mg/kg divided in equal doses every 6 to 8 hours are recommended. For the new-born, 50 mg/kg of cefotaxime can be given every 12 hours to infants 0-7 days old and every 8 hours to those 7-28 days old.

Intra-abdominal infections:
Intra-abdominal infection should be treated with Cefotaxime in combination with other appropriate antibiotics.

Duration of therapy
The duration of therapy with Cefotaxime depends on the clinical condition of the patient and varies according to the course of the disease. Administration of Cefotaxime should be continued until symptoms have subsided or evidence of bacterial eradication has been obtained. Treatment over at least 10 days is necessary in infections caused by Streptococcus pyogenes (parenteral therapy may be switched to an adequate oral therapy before the end of the 10 day period).

Dosage in renal function impairment
In adult patients with a creatinine clearance of $\leq 5$ ml/min, the initial dose is similar to the recommended usual dose should be halved without change in the frequency of dosing.

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

Method of administration
In order to prevent any risk of infection, the preparation of the infusion should be done in close aseptic conditions. Do not delay the infusion after the preparation of the solution.

- Intravenous infusion
  For short intravenous infusion 1 g or Cefotaxime should be dissolved in 40-50 ml Water for Injections or in another compatible fluid (e.g. glucose 10%). After preparation the solution should be given as a 20 minute intravenous infusion.

  For long lasting intravenous infusion 2 g Cefotaxime should be dissolved in 100 ml of Water for Injections or another suitable fluid, e.g. 0.9% sodium chloride or isotonic glucose solution or other
compatible fluids for infusions. After preparation, the solution may be given as a 50-60 minute intravenous infusion.

- **Intravenous injection**
  For intravenous injection Cefotaxime 1 g should be dissolved in 4 ml Water for Injections, Cefotaxime 2 g should be dissolved in 10 ml Water for Injections and should be injected over 3-5 minutes.

- **Intramuscular injection**
  Cefotaxime 1.0 g is dissolved in the 4ml Water for Injections. The solution should be administered by deep intramuscular injection. In order to prevent pain from the injection Cefotaxime 1.0 g may be dissolved in 4 ml % Lidocaine Hydrochloride (only for adults). Solutions with lidocaine must not be administered intravenously. If the total daily dose is more than 2g, then intravenous administration should be chosen. In the case of severe infections, intramuscular injection is not recommended.

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<td>10 ml</td>
<td>-</td>
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4.3 **Contraindications**
- Cefotaxime should not be used in patients with a known or suspected hypersensitivity to cefotaxime or cephalosporins.

4.4 **Special warnings and precautions for use**
- Special care is indicated in patients who have had an anaphylactic response to penicillin. Preliminary enquiry about hypersensitivity to penicillin and other lactam antibiotics is necessary before prescribing cephalosporins since cross allergy occurs in 5-10% of cases. In case of allergic reaction, the treatment should be stopped immediately.

- Patients with severe renal dysfunction may need dosage adjustment (see sections 4.2 – Posology and method of administration).

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

- As with other broad-spectrum antibiotics, prolonged used may result in the overgrowth of non-susceptible organisms, which may require interruption of treatment. If super-infection occurs during treatment, specific anti-microbial therapy should be instituted if considered clinically necessary.

- Pseudomembranous colitis has been reported with the use of broad-spectrum antibiotics. Therefore, it is important to consider its diagnosis in patients who develop severe diarrhea during or after
The presence of *C. difficile* toxin should be investigated and treatment with cefotaxime stopped in cases of suspected colitis. The diagnosis can be confirmed by toxin detection and 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.

- Since haematological abnormalities may develop during treatment with cefotaxime, blood count should be monitored if treatment lasts for longer than 7 days. In case of neutropenia (< 1400 neutrophils/mm³), treatments should be interrupted.

- Do not mix aminoglycosides and cefotaxime in the same syringe of liquids for perfusion.

- Fast infusion in a central vein can cause arrhythmia

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

- Cefotaxime constituted with lidocaine must never be used:
  - by the intravenous route
  - in infants under 30 months
  - in subjects with a previous history of hypersensitivity to this product
  - in patients who have an unpaced heart block
  - in patients with severe heart failure.

4.5 Interaction with other medicinal products and other forms of interaction

*With other medicaments:*

- Concomitant administration of probenecid leads to an increase and prolongation of serum concentrations of cefotaxime by inhibition of renal elimination of cefotaxime.

- The efficacy of oral contraceptives may be decreased during concomitant use of cefotaxime. Therefore during therapy with Cefotaxime additional contraceptive measures should be used.

- Concurrent treatment with high doses of cephalosporins and nephrotoxic drugs such as aminoglycosides or potent diuretics (e.g. furosemide) may adversely affect renal function. The monitoring of the renal function if strictly recommended.

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

*Other forms of interaction:*

- 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.

- A false-positive reaction to glucose may occur with reducing substances (Benedict’s or Fehling’s solution, or with Clinistest tablets) but not with the use of specific enzyme-based tests (glucose oxidase methods).
4.6 Pregnancy and lactation
There are no adequate data to assess possible harmfulness of cefotaxime during pregnancy. To date, animal experiments show no indication for adverse effects. Caution should be exercised when prescribing to pregnant women.

Cefotaxime is excreted in human milk in low concentrations. Use during lactation can lead in infants to an effect on the physiological intestinal flora with diarrhoea, to Saccharomyces colinisation and may also lead to desensitization. A decision should be made whether to discontinue nursing or discontinue treatment taking into account the importance of cefotaxime to the nursing woman.

4.7 Effects on ability to drive and use machines
There have been no reports of the effects of Cefotaxime on the ability to drive.

4.8 Undesirable effects
Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, ≤1/100), rare (≥1/10000, ≤1/1000), very rare (≤1/10000), not known (cannot be estimated from the available data).

Infections and infestations
Rare
- Prolonged use may result in overgrowth of non-susceptible organisms (see section 4.4 – Special warnings and precautions for use).

Blood and lymphatic system disorders
Rare
- 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, but these were reversible when treatment was ceased. Rare cases of haemolytic anaemia have been reported. Rare cases of thrombocytopenia have been recorded, but these were rapidly reversible on withdrawal of treatment. It is therefore recommended that blood count should be monitored if treatment lasts for longer than 7 days.

Nervous system disorders
Rare
Administration of high doses of antibiotic belonging to this group (particularly in patients with renal insufficiency) may result in encephalopathy, which may result in dizziness, convulsions and fatigue.

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

Gastrointestinal disorders
Common
- Commonly, patients receiving cefotaxime experience gastrointestinal disturbance such as candidasis, nausea, vomiting abdominal pain, diarrhea. If severe and persistent diarrhea occurs, pseudomenbranous
colitis should be considered. In cases or suspicion of pseudomembranous colitis, treatment with cefotaxime should be discontinued and appropriate therapy should be initiated.

**Hepato-biliary disorders**

*Rare*

- Moderate and transient increase in bilirubin, liver transaminase and other enzymes has been observed rarely (ALT, AST, LDH, GGT, alkaline phosphatase).

**Skin and cutaneous tissue disorders**

*Common*

- Hypersensitivity reactions have been reported, these include cutaneous reactions such as skin rashes, pruritus, urticaria
- Drug fever

*Very rare*

- Erythema multiforme exsudativum,
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
- Anaphylactic shock (see section 4.9 Overdose)

In patients with allergic diathesis, hypersensitivity reactions after administration of Cefotaxime are more likely to occur.

During therapy of infections with spirochetes, a Herxheimer-like reaction may occur. This may result in fever, shivering, headache and joint pain.

**Renal and urinary disorders**

*Rare*

- There may be a temporary increase in creatinine and urea in the serum

*Very rare*

- There have been very rare reports of reversible interstitial nephritis.

**General disorder and administration site conditions**

*Common*

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

4.9 **Overdose**

**Symptoms of intoxication**
Cefotaxime has a wide margin of safety. Cases of acute intoxication with cefotaxime have not been published. Symptoms of overdose may largely correspond to the profile of side effects.

In cases of overdosage (particularly in renal insufficiency) there is a risk of reversible encephalopathy.

*Therapy of intoxication*

There is no specific antidote for overdose. Serum levels of cefotaxime can be reduced by haemodialysis or peritoneal dialysis.

*Therapy of hypersensitivity reactions*

Anaphylactic shock requires immediate countermeasures. Upon first signs of hypersensitivity reactions (e.g. cutaneous reactions such as skin rashes or urticaria, headache, nausea, restlessness) the administration of Cefotaxime should be discontinued. In cases of severe hypersensitivity reactions or anaphylactic reactions, emergency treatment should be initiated, such as administration of epinephrine and/or glucocorticoids.

According to the clinical severity additional therapeutic measures may be required (e.g. artificial breathing, application of histamine-receptor antagonists). In cases of circulatory collapse, resuscitation must be initiated according to the current guidelines.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: J01DA10

Pharmacotherapeutic group: Beta-lactam antibiotics, cephalosporins

General properties:

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.

Breakpoints:

According to the EUCAST (European Committee on Antimicrobial Susceptibility Testing) Clinical MIC breakpoints (v 2.0, dated 25-05-2009) the following breakpoints have been identified for cefotaxime:

<table>
<thead>
<tr>
<th>Organism</th>
<th>Susceptible ($\leq$)/Resistant ($\geq$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae$^2$</td>
<td>$1/2$</td>
</tr>
<tr>
<td><em>Pseudomonas</em></td>
<td>-</td>
</tr>
<tr>
<td><em>Acinetobacter</em></td>
<td>-</td>
</tr>
<tr>
<td><em>Staphylococcus</em> $^3$</td>
<td>Note$^3$</td>
</tr>
<tr>
<td><em>Enterococcus</em></td>
<td>-</td>
</tr>
<tr>
<td>Species</td>
<td>Susceptible</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td><strong>Streptococcus A, B, C, G</strong></td>
<td>0.5/2</td>
</tr>
<tr>
<td><strong>Streptococcus pneumoniae</strong></td>
<td>0.5/0.5</td>
</tr>
<tr>
<td><strong>Other streptococci</strong></td>
<td>0.12/0.12</td>
</tr>
<tr>
<td><strong>Haemophilus influenzae</strong></td>
<td>1/2</td>
</tr>
<tr>
<td><strong>Moraxella Catarrhalis</strong></td>
<td>0.12/0.12</td>
</tr>
<tr>
<td><strong>Neisseria gonorrhoeae</strong></td>
<td>0.12/0.12</td>
</tr>
<tr>
<td><strong>Neisseria Meningitidis</strong></td>
<td>0.12/0.12</td>
</tr>
<tr>
<td><strong>Gram-positive, anaerobes</strong></td>
<td>-</td>
</tr>
<tr>
<td><strong>Gram-negative, anaerobes</strong></td>
<td>-</td>
</tr>
<tr>
<td><strong>Non-species related breakpoints¹</strong></td>
<td>1/2</td>
</tr>
</tbody>
</table>

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 not mentioned in the table or footnotes.

2. The cephalosporin breakpoints for Enterobacteriaceae will detect reduced susceptibility mediated by most clinically important beta-lactamases in Enterobacteriaceae. Occasional ESBL-producing strains will be reported susceptible. For purposes of infection control, epidemiology and surveillance, laboratories may wish to use specific tests to screen for and confirm ESBL-production.

3. Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility.

4. The susceptibility of streptococcus groups A, B, C and G can be inferred from their susceptibility to benzylpenicillin.

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

**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.

<table>
<thead>
<tr>
<th>Species</th>
<th>Susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram-positive aerobes</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td></td>
</tr>
<tr>
<td><em>(Methicillin-susceptible)</em></td>
<td></td>
</tr>
<tr>
<td><strong>Group A Streptococci</strong> (including Streptococcus pyogenes)*</td>
<td></td>
</tr>
<tr>
<td><strong>Group B Streptococci</strong></td>
<td></td>
</tr>
</tbody>
</table>

MHRA-UKPAR – Cefotaxime 1g and 2g Powder for Solution for Injection or Infusion

PL 14894/0397-8
β-hemolytic Streptococci (Group C,F, G)

*Streptococcus pneumoniae*

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 morgani*

*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.

$ Frequency of resistance ranges in EU is >10% (extreme values); Streptococcus pneumoniae show a variable degree of resistance - 12.7%

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

Absorption

Cefotaxime is for parenteral application. Mean peak concentrations 5 minutes after intravenous injection are about 81-102 mg/l following a 1 g dose cefotaxime and about 167-214 mg/l 8 minutes after a 2 g dose. Intramuscular injection produces mean peak plasma concentrations of 20 mg/l within 30 minutes following a 1 g dose.

Distribution

Cefotaxime gives good penetration into different compartments. Therapeutic drug levels exceeding the minimum inhibitory levels for common pathogens can rapidly be achieved. Cerebrospinal fluid concentrations are low when the meninges are not inflamed but cefotaxime usually passes the blood-brain barrier in levels above the MIC of the sensitive pathogens when the meninges are inflamed (3-30 μg/ml). Cefotaxime concentrations (0.2-5.4 μg/ml), inhibitory for most Gram-negative bacteria, are attained in purulent sputum, bronchial secretions and pleural fluid after doses of 1 or 2 g. Concentrations likely to be effective against most sensitive organisms are similarly attained in female reproductive organs, otitis media effusions, prostatic tissue, interstitial fluid, peritoneal fluid and gall bladder wall, after therapeutic doses. High concentrations of cefotaxime and O-desacetylcefotaxime are attained in bile. Cefotaxime passes the placenta and attains high concentrations in foetal fluid and tissues (up to 6 mg/kg). Small amounts of cefotaxime diffuses into the breast milk.

Protein binding for cefotaxime is approximately 25-40%.

The apparent distribution volume for cefotaxime is 21-37 l after 1g intravenous infusion over 30 minutes.

Biotransformation

Cefotaxime is partly metabolized in human beings. Approximately 15-25% of a parenteral dose is metabolized to the O-desacetylcefotaxime metabolite, which also has antibiotic properties.
Elimination

The main route of excretion of cefotaxime and O-desacetylcefotaxime is the kidney. Only a small amount (2%) of cefotaxime is excreted in the bile. In the urine collected within 6 hours 40-60% of the administered dose of cefotaxime is recovered as unchanged cefotaxime and 20% is found as O-desacetylcefotaxime. After administration of radioactive labeled cefotaxime more than 80% can be recovered in the urine, 50-60% of this fraction is unchanged cefotaxime and the rest contains metabolites.

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

The serum half-lives of cefotaxime and O-desacetylcefotaxime are normally about 50-80 and 90 minutes respectively. In the elderly, the serum half-life of cefotaxime is 120-150 min.

In patients with impaired renal function (creatinine clearance 3-10ml/min) the serum half-life of cefotaxime can be increased to 2.5-3.6 hours.

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

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat dose toxicity, genotoxicity, and toxicity to reproduction.

Cefotaxime passes through the placenta. After intravenous administration of 1 g cefotaxime during the birth values of 14 µg/ml were measures in the umbilical cord serum in the first 90 minutes after application, which dropped to approximately 2.5 µg/ml by the end of the second hour after application. In the amniotic fluid, the highest concentration of 6.9 µg/ml was measured after 3-4 hours. This value exceeds the MIC for most gram-negative bacteria.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6

6.3 Shelf life

Vial before opening: 2 years.
Vial after first opening: The product should be used immediately.
After reconstitution: The product should be used immediately.

From a microbiological point of view, 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 to 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 vial in the outer carton in order to protect from light.
For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 **Nature and contents of container**
Type II transparent glass vial, with a bromobutyl stopper and a flip off aluminum and polypropylene cap.
Packs of 10 or 50 vials.

6.6 **Special precautions for disposal**
Cefotaxime is supplied as a white to slightly creamy powder, which when dissolved in Water for Injections Ph. Eur. 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.
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:
- Water for Injections Ph. Eur.
- Sodium Chloride Injection BP.
- 5% Dextrose Injection BP.
- Dextrose and Sodium Chloride Injection BP.
- Compound Sodium Lactate Injection BP (Ringer-lactate Injection).
Any unused solution should be discarded.
Cefotaxime is also compatible with 1% lignocaine, however freshly prepared solutions should be used.
Cefotaxime is also compatible with metronidazole infusion (500mg/100ml). 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.
This medicinal product is for single use only; Discard any contents remaining in the vial immediately after use.
The reconstituted solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.
CEFOTAXIME 2G POWDER FOR SOLUTION FOR INJECTION OR INFUSION
PL 14894/0398

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Cefotaxime 2g Powder for Solution for Injection or Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains Cefotaxime sodium equivalent to 2g cefotaxime.
Also contains 96 mg (4.18 mmol) of sodium per vial.
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
White or slightly creamy powder.
Powder for solution for injection or infusion.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Cefotaxime is indicated for the treatment of the following severe infections when known or thought very likely to be due to bacteria that are susceptible to cefotaxime (see section 5.1 – Pharmacodynamic properties):

- Bacterial pneumonia; cefotaxime is not active against bacteria that cause atypical pneumonia or against several other bacterial species that may cause pneumonia, including P. aeruginosa (see section 5.1 – Pharmacodynamic properties).

- Complicated infections of the kidneys and upper urinary tract.

- Severe infections of the skin and soft tissue

- Genital infections caused by gonococci, particularly when penicillin has failed or is unsuitable

- Intra-abdominal infections (such as peritonitis). Cefotaxime should be used in combination with an antibiotic that is active against anaerobes in the treatment of intra-abdominal infections.

- Acute bacterial meningitis (particularly if due to H. influenzae, N. meningitides, S. pneumoniae, E. coli, Klebsiella spp.)

- Septicaemia infections originating from the lungs, urinary tract, or bowel (in case of gram-negative organisms a combination with another suitable antibiotic should be considered).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.
4.2 Posology and method of administration

Cefotaxime may be administered by intravenous bolus injection, by intravenous infusion, by intramuscular injection after reconstitution of the solution according to the directions given below. Dosage and mode of administration should be determined by the severity of the infection, susceptibility of the causative organism and the patient’s condition. Therapy may be started before the result of sensitivity tests are known.

*Adults and children over 12 years*

The usual dose in adults is for mild to moderate infections is 2 to 6g daily. However, dosage may be varied according to the severity of the infection, sensitivity of the causative organisms and conditions of the patient.

*Guidelines for dosage:*

Typical infection in presence (or suspicion) of a sensitive micro-organism: 1g every 12 hours corresponding to a total daily dosage of 2g intramuscularly or intravenously.

Infection in the presence (or suspicion) of sensitive or moderately sensitive multiple micro-organisms: 1-2g every 12 hours corresponding to a total daily dosage of 2-4g.

Severe infection by unidentified micro-organisms or for infections that cannot be localized: 2-3g as a single dose every 6 to 8 hours up to a maximum daily dosage of 12 g.

A combination of cefotaxime and other antibiotics in indicated in severe infections.

*Infants and children up to 12 years*

The usual dosage for infants and children <50 kg is 50-150 mg/kg/day in 2 to 4 divided doses. In very severe infections up to 200 mg/kg/day in divided doses may be required. In infants and children >50 kg the usual dose in adults, without exceeding the maximum daily dose of 12 g should be given.

*Newborn infants and premature infants*

The recommended dosage is 50 mg/kg/day in 2 to 4 divided doses. In case of life-threatening situations it may be necessary to increase the daily dose. In severe infections 150-200 mg/kg/day have been given: in those situations the following table may serve as a guide, since there are differences in kidney maturation.

<table>
<thead>
<tr>
<th>Age</th>
<th>Daily dose of Cefotaxime</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-7 days</td>
<td>50 mg/kg every 12 hours</td>
</tr>
<tr>
<td>8 days- 1 month</td>
<td>50 mg/kg every 8 hours</td>
</tr>
</tbody>
</table>

*Elderly*
No dosage adjustment is required, provided that renal and hepatic function are normal.

**Other recommendations**

**Gonorrhoea:**
For gonorrhoea, a single injection (intramuscularly or intravenously) of 0.5g to 1 g cefotaxime. For complicated infections, consideration should be given to available official guidelines. Syphilis should be excluded before initiating treatment.

**Urinary tract infections:**
In uncomplicated UTI 1 g every 12 hours.

**Bacterial meningitis:**
In adults, daily doses of 6 to 12 g and in children daily doses of 150 to 200 mg/kg divided in equal doses every 6 to 8 hours are recommended. For the new-born, 50 mg/kg of cefotaxime can be given every 12 hours to infants 0-7 days old and every 8 hours to those 7-28 days old.

**Intra-abdominal infections:**
Intra-abdominal infection should be treated with Cefotaxime in combination with other appropriate antibiotics.

**Duration of therapy**
The duration of therapy with Cefotaxime depends on the clinical condition of the patient and varies according to the course of the disease. Administration of Cefotaxime should be continued until symptoms have subsided or evidence of bacterial eradication has been obtained. Treatment over at least 10 days is necessary in infections caused by *Streptococcus pyogenes* (parenteral therapy may be switched to an adequate oral therapy before the end of the 10 day period).

**Dosage in renal function impairment**
In adult patients with a creatinine clearance of ≤ 5 ml/min, the initial dose is similar to the recommended usual dose should be halved without change in the frequency of dosing.

**Dosage in dialysis or peritoneal dialysis**
In patients on haemodialysis and peritoneal dialysis an i.v. injection of 0.5-2 g, given at the end of each dialysis session and repeated every 24 hours, is sufficient to treat most infections efficaciously.

**Method of administration**
In order to prevent any risk of infection, the preparation of the infusion should be done in close aseptic conditions. Do not delay the infusion after the preparation of the solution.

- **Intravenous infusion**
  
  For *short intravenous infusion* 1 g or Cefotaxime should be dissolved in 40-50 ml Water for Injections or in another compatible fluid (e.g. glucose 10%). After preparation the solution should be given as a 20 minute intravenous infusion.

  For *long lasting intravenous infusion* 2 g Cefotaxime should be dissolved in 100 ml of Water for Injections or another suitable fluid, e.g. 0.9% sodium chloride or isotonic glucose solution or other
compatible fluids for infusions. After preparation, the solution may be given as a 50-60 minute intravenous infusion.

- **Intravenous injection**
  For intravenous injection Cefotaxime 1 g should be dissolved in 4 ml Water for Injections, Cefotaxime 2 g should be dissolved in 10 ml Water for Injections and should be injected over 3-5 minutes.

- **Intramuscular injection**
  Cefotaxime 1.0 g is dissolved in the 4ml Water for Injections. The solution should be administered by deep intramuscular injection. In order to prevent pain from the injection Cefotaxime 1.0 g may be dissolved in 4 ml % Lidocaine Hydrochloride (only for adults). Solutions with lidocaine must not be administered intravenously. If the total daily dose is more than 2g, then intravenous administration should be chosen. In the case of severe infections, intramuscular injection is not recommended.

The following table shows the volume of dilution

<table>
<thead>
<tr>
<th>Vial size</th>
<th>Short Intravenous Infusion</th>
<th>Long lasting Intravenous Infusion</th>
<th>Intravenous Injection</th>
<th>Intramuscular Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 g</td>
<td>40-50 ml</td>
<td>-</td>
<td>4 ml</td>
<td>4 ml</td>
</tr>
<tr>
<td>2 g</td>
<td>-</td>
<td>100 ml</td>
<td>10 ml</td>
<td>-</td>
</tr>
</tbody>
</table>

4.3 **Contraindications**
- Cefotaxime should not be used in patients with a known or suspected hypersensitivity to cefotaxime or cephalosporins.

4.4 **Special warnings and precautions for use**
- Special care is indicated in patients who have had an anaphylactic response to penicillin. Preliminary enquiry about hypersensitivity to penicillin and other lactam antibiotics is necessary before prescribing cephalosporins since cross allergy occurs in 5-10% of cases. In case of allergic reaction, the treatment should be stopped immediately.

- Patients with severe renal dysfunction may need dosage adjustment (see sections 4.2 – Posology and method of administration).

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

- As with other broad-spectrum antibiotics, prolonged used may result in the overgrowth of non-susceptible organisms, which may require interruption of treatment. If super-infection occurs during treatment, specific anti-microbial therapy should be instituted if considered clinically necessary.

- Pseudomembranous colitis has been reported with the use of broad-spectrum antibiotics. Therefore, it is important to consider its diagnosis in patients who develop severe diarrhea during or after antibiotic use. The presence of *C. difficile* toxin should be investigated and treatment with
cefotaxime stopped in cases of suspected colitis. The diagnosis can be confirmed by toxin detection and antibiotic therapy (e.g. oral vancomycin or metronidazole) should be initiated if considered clinically necessary. The administration of products which cause fecal stasis should be avoided.

- Since haematological abnormalities may develop during treatment with cefotaxime, blood count should be monitored if treatment lasts for longer than 7 days. In case of neutropenia (< 1400 neutrophils/mm³), treatments should be interrupted.

- Do not mix aminoglycosides and cefotaxime in the same syringe of liquids for perfusion.

- Fast infusion in a central vein can cause arrhythmia

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

- Cefotaxime constituted with lidocaine must never be used:
  - by the intravenous route
  - in infants under 30 months
  - in subjects with a previous history of hypersensitivity to this product
  - in patients who have an unpaced heart block
  - in patients with severe heart failure.

### 4.5 Interaction with other medicinal products and other forms of interaction

**With other medicaments:**

- Concomitant administration of probenecid leads to an increase and prolongation of serum concentrations of cefotaxime by inhibition of renal elimination of cefotaxime.

- The efficacy of oral contraceptives may be decreased during concomitant use of cefotaxime. Therefore during therapy with Cefotaxime additional contraceptive measured should be used.

- Concurrent treatment with high doses of cephalosporins and nephrotoxic drugs such as aminoglycosides or potent diuretics (e.g. furosemide) may adversely affect renal function. The monitoring of the renal function if strictly recommended.

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

**Other forms of interaction:**

- 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.

- A false-positive reaction to glucose may occur with reducing substances (Benedict’s or Fehling’s solution, or with Clinistest tablets) but not with the use of specific enzyme-based tests (glucose oxidase methods).
4.6 Pregnancy and lactation
There are no adequate data to assess possible harmfulness of cefotaxime during pregnancy. To date, animal experiments show no indication for adverse effects. Caution should be exercised when prescribing to pregnant women.

Cefotaxime is excreted in human milk in low concentrations. Use during lactation can lead in infants to an effect on the physiological intestinal flora with diarrhoea, to *Saccharomyces* colonisation and may also lead to desensitization. A decision should be made whether to discontinue nursing or discontinue treatment taking into account the importance of cefotaxime to the nursing woman.

4.7 Effects on ability to drive and use machines
There have been no reports of the effects of Cefotaxime on the ability to drive.

4.8 Undesirable effects
Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, ≤1/100), rare (≥1/10000, ≤1/1000), very rare (≤1/10000), not known (cannot be estimated from the available data).

**Infections and infestations**

Rare

- Prolonged use may result in overgrowth of non-susceptible organisms (see section 4.4 – Special warnings and precautions for use).

**Blood and lymphatic system disorders**

Rare

- 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, but these were reversible when treatment was ceased. Rare cases of haemolytic anaemia have been reported. Rare cases of thrombocytopenia have been recorded, but these were rapidly reversible on withdrawal of treatment. It is therefore recommended that blood count should be monitored if treatment lasts for longer than 7 days.

**Nervous system disorders**

Rare

Administration of high doses of antibiotic belonging to this group (particularly in patients with renal insufficiency) may result in encephalopathy, which may result in dizziness, convulsions and fatigue.

**Cardiac disorders**

Very rare

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

**Gastrointestinal disorders**
Common

- Commonly, patients receiving cefotaxime experience gastrointestinal disturbance such as candidasis, nausea, vomiting, abdominal pain, diarrhea. If severe and persistent diarrhea occurs, pseudomembranous colitis should be considered. In cases or suspicion of pseudomembranous colitis, treatment with cefotaxime should be discontinued and appropriate therapy should be initiated.

Hepato-biliary disorders

Rare

- Moderate and transient increase in bilirubin, liver transaminase and other enzymes has been observed rarely (ALT, AST, LDH, GGT, alkaline phosphatase).

Skin and cutaneous tissue disorders

Common

- Hypersensitivity reactions have been reported, these include cutaneous reactions such as skin rashes, pruritus, urticaria
- Drug fever

Very rare

- Erythema multiforme exsudativum,
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
- Anaphylactic shock (see section 4.9 Overdose)

In patients with allergic diathesis, hypersensitivity reactions after administration of Cefotaxime are more likely to occur.

During therapy of infections with spirochetes, a Herxheimer-like reaction may occur. This may result in fever, shivering, headache and joint pain.

Renal and urinary disorders

Rare

- There may be a temporary increase in creatinine and urea in the serum

Very rare

- There have been very rare reports of reversible interstitial nephritis.

General disorder and administration site conditions

Common

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

Symptoms of intoxication

Cefotaxime has a wide margin of safety. Cases of acute intoxication with cefotaxime have not been published. Symptoms of overdose may largely correspond to the profile of side effects.

In cases of overdosage (particularly in renal insufficiency) there is a risk of reversible encephalopathy.

Therapy of intoxication:

There is no specific antidote for overdose. Serum levels of cefotaxime can be reduced by haemodialysis or peritoneal dialysis.

Therapy of hypersensitivity reactions:

Anaphylactic shock requires immediate countermeasures. Upon first signs of hypersensitivity reactions (e.g. cutaneous reactions such as skin rashes or urticaria, headache, nausea, restlessness) the administration of Cefotaxime should be discontinued. In cases of severe hypersensitivity reactions or anaphylactic reactions, emergency treatment should be initiated, such as administration of epinephrine and / or glucocorticoids.

According to the clinical severity additional therapeutic measures may be required (e.g. artificial breathing, application of histamine-receptor antagonists). In cases of circulatory collapse, resuscitation must be initiated according to the current guidelines.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: J01D A10

Pharmacotherapeutic group: Beta-lactam antibiotics, cephalosporins

General properties:

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.

Breakpoints:

According to the EUCAST (European Committee on Antimicrobial Susceptibility Testing) Clinical MIC breakpoints (v 2.0, dated 25-05-2009) following breakpoints have been identified for cefotaxime:

<table>
<thead>
<tr>
<th>Enterobacteriaceae²</th>
<th>Susceptible (≤) / Resistant (≥)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>1/2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pseudomonas</th>
<th>-</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Acinetobacter</th>
<th>-</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Staphylococcus³</th>
<th>Note³</th>
</tr>
</thead>
</table>
Enterococcus -

Streptococcus A, B, C, G Note ¹

Streptococcus pneumoniae 0.5/2

Other streptococci 0.5/0.5

Haemophilus influenzae 0.12/0.12

Moraxella Catarrhalis 1/2

Neisseria gonorrhoeae 0.12/0.12

Neisseria Meningitidis 0.12/0.12

Gram-positive, anaerobes -

Gram-negative, anaerobes -

Non-species related breakpoints¹ 1/2

S<\R>

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 not mentioned in the table or footnotes.

2. The cephalosporin breakpoints for Enterobacteriaceae will detect reduced susceptibility mediated by most clinically important beta-lactamases in Enterobacteriaceae. Occasional ESBL-producing strains will be reported susceptible. For purposes of infection control, epidemiology and surveillance, laboratories may wish to use specific tests to screen for and confirm ESBL-production.

3. Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility.

4. The susceptibility of streptococcus groups A, B, C and G can be inferred from their susceptibility to benzylpenicillin.

**S<\R>** = Susceptibility testing not recommended as the species is a poor target for therapy with the drug

### 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

<table>
<thead>
<tr>
<th>Susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive aerobes</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>(Methicillin-susceptible)*</td>
</tr>
<tr>
<td>Group A Streptococci (including <em>Streptococcus pyogenes)</em></td>
</tr>
</tbody>
</table>

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 not mentioned in the table or footnotes.
<table>
<thead>
<tr>
<th><strong>Group B Streptococci</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-hemolytic Streptococci (Group C,F, G)</strong></td>
</tr>
<tr>
<td><strong>Streptococcus pneumoniae</strong></td>
</tr>
<tr>
<td><strong>Viridans Group Streptococci</strong></td>
</tr>
</tbody>
</table>

**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.*
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

Absorption
Cefotaxime is for parenteral application. Mean peak concentrations 5 minutes after intravenous injection are about 81-102 mg/l following a 1 g dose cefotaxime and about 167-214 mg/l 8 minutes after a 2 g dose. Intramuscular injection produces mean peak plasma concentrations of 20 mg/l within 30 minutes following a 1 g dose.

Distribution
Cefotaxime gives good penetration into different compartments. Therapeutic drug levels exceeding the minimum inhibitory levels for common pathogens can rapidly be achieved. Cerebrospinal fluid concentrations are low when the meninges are not inflamed but cefotaxime usually passes the blood-brain barrier in levels above the MIC of the sensitive pathogens when the meninges are inflamed (3-30 µg/ml). Cefotaxime concentrations (0.2-5.4 µg/ml), inhibitory for most Gram-negative bacteria, are attained in purulent sputum, bronchial secretions and pleural fluid after doses of 1 or 2 g.

Concentrations likely to be effective against most sensitive organisms are similarly attained in female reproductive organs, otitis media effusions, prostatic tissue, interstitial fluid, peritoneal fluid and gall bladder wall, after therapeutic doses. High concentrations of cefotaxime and O-desacytylecefotaxime are attained in bile. Cefotaxime passes the placenta and attains high concentrations in foetal fluid and tissues (up to 6 mg/kg). Small amounts of cefotaxime diffuses into the breast milk.

Protein binding for cefotaxime is approximately 25-40%.

The apparent distribution volume for cefotaxime is 21-37 l after 1g intravenous infusion over 30 minutes.

Biotransformation
Cefotaxime is partly metabolized in human beings. Approximately 15-25% of a parenteral dose is metabolized to the O-desacytylecefotaxime metabolite, which also has antibiotic properties.
Elimination

The main route of excretion of cefotaxime and O-desacetylcefotaxime is the kidney. Only a small amount (2%) of cefotaxime is excreted in the bile. In the urine collected within 6 hours 40-60% of the administered dose of cefotaxime is recovered as unchanged cefotaxime and 20% is found as O-desacetylcefotaxime. After administration of radioactive labeled cefotaxime more than 80% can be recovered in the urine, 50-60% of this fraction is unchanged cefotaxime and the rest contains metabolites.

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

The serum half-lives of cefotaxime and O-desacetylcefotaxime are normally about 50-80 and 90 minutes respectively. In the elderly, the serum half-life of cefotaxime is 120-150 min.

In patients with impaired renal function (creatinine clearance 3-10ml/min) the serum half-life of cefotaxime can be increased to 2.5-3.6 hours.

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

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat dose toxicity, genotoxicity, and toxicity to reproduction.

Cefotaxime passes through the placenta. After intravenous administration of 1 g cefotaxime during the birth values of 14 µg/ml were measures in the umbilical cord serum in the first 90 minutes after application, which dropped to approximately 2.5 µg/ml by the end of the second hour after application. In the amniotic fluid, the highest concentration of 6.9 µg/ml was measured after 3-4 hours. This value exceeds the MIC for most gram-negative bacteria.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6

6.3 Shelf life

Vial before opening: 2 years.

Vial after first opening: The product should be used immediately.

After reconstitution: The product should be used immediately.

From a microbiological point of view, 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 to 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 vial in the outer carton in order to protect from light.

For storage conditions of the reconstituted medicinal product, see section 6.3.
6.5 Nature and contents of container
Type II transparent glass vial, with a bromobutyl stopper and a flip off aluminum and polypropylene cap.
Packs of 10 vials.

6.6 Special precautions for disposal
Cefotaxime is supplied as a white to slightly creamy powder, which when dissolved in Water for Injections Ph. Eur. 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.

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

Any unused solution should be discarded.

Cefotaxime is also compatible with 1% lignocaine, however freshly prepared solutions should be used.

Cefotaxime is also compatible with metronidazole infusion (500mg/100ml). 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.

This medicinal product is for single use only; Discard any contents remaining in the vial immediately after use.

The reconstituted solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.

7 MARKETING AUTHORISATION HOLDER
Ranbaxy (UK) Limited
Building 4, Chiswick High Road
London, W4 5YE
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 14894 / 0398

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
25/02/2010

10 DATE OF REVISION OF THE TEXT
25/02/2010
CEFOTAXIME 1G & 2G POWDER FOR SOLUTION FOR INJECTION OR INFUSION
PL 14894/0397-8

PATIENT INFORMATION LEAFLET

Read all of this leaflet carefully before you start using this medicine.
• Keep this leaflet. You may need to read it again.
• If you have any further questions, please ask your doctor or your pharmacist.
• This medicine has been prescribed for you. Do not use it on others.
• It may harm them, even if their symptoms are the same as yours.

If any of the side effects get worse, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

1. WHAT CEFOTAXIME IS AND WHAT IT IS USED FOR

Cefotaxime is an antibiotic belonging to the cephalosporin group of antibiotics. It is used for the treatment of:
- Bacterial infections of the chest (bronchitis, pneumonia), skin, bone, or joint.
- Complicated infections of the urinary tract and wounds.
- Other infections that are resistant to other antibiotics.

2. BEFORE YOU USE CEFOTAXIME

Do not use Cefotaxime if:
- you are allergic to Cefotaxime or any of the other ingredients.
- you are allergic to any cephalosporin or penicillin.
- you have had an allergic reaction to any penicillin.
- you are taking other medicines.

Take special care with Cefotaxime:
- check with your doctor or pharmacist before using it.
- if you have diabetes.
- if you have liver or kidney problems.
- if you have had an allergic reaction to the medicine.
- if you have had a severe allergic reaction to any of the ingredients.

3. HOW TO USE CEFOTAXIME

This medicine will always be administered by a doctor or nurse because it needs to be given either as an injection or by drip. In adults, Cefotaxime will usually be given every 6-8 hours. In children, Cefotaxime is normally given every 2-4 days.

Children
- The usual dosage range is 50-150mg/kg/day in 2-4 divided doses. However, in very severe infections, doses of up to 200mg/kg/day in divided doses may be required.

Young babies (under 1 month):
- The recommended dosage is 50mg/kg/day in 2-4 divided doses. In severe infections, 150-200mg/kg/day, in divided doses, may be given.

Adults:
- The recommended dosage for mild to moderate infections is 1g-2g 12-hourly. However, dosage may be varied according to the severity of the infection and condition of the patient.
In severe infections dosage may be increased up to 12g daily given in 3 or 4 divided doses.

**Dosage in General:**
A single injection of Cefotaxime may be administered intravenously or intramuscularly. It can also be given by intravenous infusion over 20 minutes.

**If you use more Cefotaxime than you should:**
It is most unlikely that you will be given too much medicine by the nurse or doctor. Your doctor and nurse will be monitoring your progress, and checking the medicine that you are given. Always ask if you are not sure why you are getting a dose of medicine.

**If you forget to use Cefotaxime:**
Your doctor or nurse will give you instructions when to give your medicine. It is most unlikely that you will not be given the medicine as it has been prescribed. If you think that you may have missed a dose then talk to your nurse or doctor. It is important that the course of treatment your doctor has prescribed is taken. You may start to feel better but it is important not to stop taking this medicine until the doctor advises otherwise your condition may get worse again.

**If you have any further questions on the use of this product, ask your doctor or pharmacist.**

### 4. Possible Side Effects

Like all medicines, Cefotaxime can cause side effects although not everybody gets them.

Contact your doctor or nearest hospital emergency department immediately if you experience swelling of the face and/or throat when given Cefotaxime, since this may be due to a serious allergic reaction.

The following side effects may occur in some patients during treatment:

**Common side effects:**

- Stomach problems:
  - Abdominal pain, diarrhoea, nausea (feeling sick) and vomiting (being sick), candidiasis. You may develop severe and persistent diarrhoea during or after treatment, especially if you notice blood or mucus (manifestations of pseudomembranous colitis).
- Skin problems:
  - Rash, itching, hives (urticaria), allergic reactions and swelling of the neck, face or throat.
- Injection site problems:
  - Pain, redness and swelling.
- Other problems:
  - Drug fever.

**Rare side effects:**

- Changes in the amount of blood cells. This may cause sore throat and mouth ulcers. If your treatment is more than 7 days your doctor should monitor your blood counts. Cefotaxime may also lead to increased risk of infection. Your doctor may carry out blood tests to identify the specific problem with your blood.
- Nervous system problems:
  - Patients with kidney problems may experience dizziness, convulsions and fatigue when taking high doses of Cefotaxime.
- Liver problems:
  - Nodules and transient increase in liver enzymes (increase in bilirubin, liver transaminases and may increase in ALT (AST), (GGT)).

**Kidney problems:**

- Temporary increase in kidney function parameters (urine creatinine, urea).

**Very rare side effects**

- Heart problems
- Kidney problems
- Dark discoloration of urine, bloody or cloudy urine or any change in the urine output (this may be due to a condition called crystalluria).
- Other:
  - Fever, rash, a salty taste, headache, joint pain, move abnormally or involuntary muscle contractions, breathing difficulties and feel tired.

If any of these side effects gets worse, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

### 5. How to Store Cefotaxime

Keep out of the reach and sight of children.

Do not use Cefotaxime after the expiry date which is stated on the label after 2013. The expiry date refers to the last day of that month.

Always keep this medicine in the original packaging, in order to protect from light. Do not store above 25°C.

Once reconstituted, this medicine should be used immediately.

This medicine is for single use only; discard any remaining solution immediately after use. Medicines should not be disposed of via waste water or household waste. Ask your pharmacist (or disposal of medicines no longer required). These measures will help to protect the environment.

### 6. Further Information

**What Cefotaxime contains:**

- The active ingredient is Cefotaxime Sodium.
- Cefotaxime 1g powder for solution for injection or infusion contains Cefotaxime sodium equivalent to 1 g of Cefotaxime.
- Cefotaxime 2g powder for solution for injection or infusion contains 2 g of Cefotaxime sodium Ph. Eur., equivalent to 2 g of Cefotaxime base.

There are no other ingredients.

**What Cefotaxime looks like and contents of the pack:**

Cefotaxime is a white or slightly creamy powder which turns a straw-coloured solution on reconstitution.

Cefotaxime 1g powder for injection or infusion is available in packs of 10 or 50 vials.

Cefotaxime 2g powder for injection or infusion is available in packs of 10 vials.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer:**

**Marketing Authorisation holder:**

Pharmacia (UK) Limited, Building 4, Cheswick High Road, London W4 5YE

**Manufacturer:**

Laboratory J&J, Gran Capita, 10-0870 Sant Joan Despi, Barcelona, Spain

This leaflet was last approved in 05/2010.