Public Assessment Report

Decentralised Procedure

CEFUROXIME 250 MG POWDER FOR SOLUTION FOR INJECTION
CEFUROXIME 750 MG POWDER FOR SOLUTION FOR INJECTION
CEFUROXIME 1.5 G POWDER FOR SOLUTION FOR INJECTION/INFUSION
CEFUROXIME 1.5 G POWDER FOR SOLUTION FOR INJECTION/INFUSION

Procedure No: UK/H/1485/001-4/DC

UK Licence No: PL 22805/0023-6

ORCHID EUROPE LTD
LAY SUMMARY

On 01 September 2010, Belgium, Germany, Spain, Italy, The Netherlands, Poland and the UK agreed to grant Marketing Authorisations to Orchid Europe Ltd for the medicinal products Cefuroxime 250 mg Powder for solution for injection, Cefuroxime 750 mg Powder for solution for injection and Cefuroxime 1.5 g Powder for solution for injection/infusion (PL 22805/0023-6; UK/H/1485/001-4/DC). The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, Marketing Authorisations were granted in the UK on 05 October 2010.

These products are prescription-only medicines to treat some infections of the:
- lungs
- urinary tract
- skin and layers of flesh immediately under the skin
- bones and joints
- membranes and fluid surrounding the brain and spinal cord (this infection is called meningitis)
- female reproductive tract and the nearby structures in the lower abdomen

Cefuroxime is sometimes given before some surgical operations to prevent infections.

Cefuroxime belongs to a group of antibacterial agents called cephalosporins, which act by killing bacteria. Like all antibiotics, cefuroxime is only effective against some types of bacteria, thus it is only suitable for treating some types of infections.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Cefuroxime 250 mg Powder for solution for injection, Cefuroxime 750 mg Powder for solution for injection and Cefuroxime 1.5 g Powder for solution for injection/infusion outweigh the risks, hence Marketing Authorisations have been granted.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Module 1: Information about initial procedure</th>
<th>Page 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Module 2: Summary of Product Characteristics</td>
<td>Page 5</td>
</tr>
<tr>
<td>Module 3: Product Information Leaflets</td>
<td>Page 29</td>
</tr>
<tr>
<td>Module 4: Labelling</td>
<td>Page 38</td>
</tr>
<tr>
<td>Module 5: Scientific Discussion</td>
<td>Page 50</td>
</tr>
<tr>
<td>1 Introduction</td>
<td></td>
</tr>
<tr>
<td>2 Quality aspects</td>
<td></td>
</tr>
<tr>
<td>3 Non-clinical aspects</td>
<td></td>
</tr>
<tr>
<td>4 Clinical aspects</td>
<td></td>
</tr>
<tr>
<td>5 Overall conclusions</td>
<td></td>
</tr>
<tr>
<td>Module 6 Steps taken after initial procedure</td>
<td>Page 57</td>
</tr>
</tbody>
</table>
# Module 1

| **Product Name** | Cefuroxime 250 mg Powder for solution for injection  
Cefuroxime 750 mg Powder for solution for injection  
Cefuroxime 1.5 g Powder for solution for injection/infusion |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td><strong>Active Substances</strong></td>
<td>Cefuroxime sodium</td>
</tr>
</tbody>
</table>
| **Form** | 250mg and 750mg: Powder for solution for injection  
1.5g: Powder for injection or infusion |
| **Strength** | 250mg, 750mg and 1.5g. |
| **MA Holder** | Orchid Europe Ltd, Building 3, Chiswick Park,  
566, Chiswick High Road, Chiswick, London, W4 5YA,  
UK. |
| **Reference Member State (RMS)** | UK |
| **CMS** | UK/H/1485/001-2 & 004/DC: Belgium, Germany, Spain,  
Italy, The Netherlands and Poland.  
UK/H/1485/003/DC: Germany, Spain, Italy, The  
Netherlands and Poland. |
| **Procedure Number** | UK/H/1485/001-4/DC |
| **Timetable** | Day 210 – 01 September 2010 |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Cefuroxime 250 mg Powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 263 mg of cefuroxime sodium equivalent to 250mg of cefuroxime.

Also contains 0.59 mmol (13.56 mg) of sodium per vial.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Powder for solution for injection
White to faintly yellow, amorphous powder

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Cefuroxime sodium for injection is indicated for the treatment of the following infections caused by susceptible organisms:
- Lower respiratory tract infections: acute exacerbation of chronic bronchitis, bacterial pneumonia.
- Urinary tract infections.
- Soft tissue infections.
- Bone and joint infections.
- Obstetric and gynaecological infections.
- Meningitis.
- Prophylaxis against infection in abdominal, pelvic, orthopaedic, cardiac, pulmonary, oesophageal and vascular surgery.

Consideration should be given to official local guidance (e.g., national recommendations) on the appropriate use of antibacterial agents.

4.2 Posology and method of administration
Usually cefuroxime is effective when administered alone, but when appropriate it may be used in combination with metronidazole or an aminoglycoside.

General Dosage
Adults: Many infections will respond to 750mg three times daily by intramuscular or intravenous injection. For more severe infections this dose should be increased to 1.5g three times daily intravenously.

The intramuscular method of administration is reserved to exceptional clinical situations and should undergo a risk-benefit assessment.

Special advise for intramuscular injection has to be regarded (see section 6.6).

The frequency of dosage may be increased to six-hourly injections, intramuscular or intravenous, giving total daily doses of 3g to 6g.

Infants and children: Doses of 30 to 100mg/kg/day given in three or four divided doses. A dose of 60mg/kg/day will be appropriate for most infections.

Neonates: Doses of 30 to 100mg/kg/day given in two or three divided doses. In the first weeks of life the serum half-life of cefuroxime can be three to five times that in adults.

Meningitis
Cefuroxime therapy is suitable for sole therapy of bacterial meningitis due to sensitive strains.

Infants and children: 200 to 240mg/kg/day intravenously in three or four divided doses. This dosage may be reduced to 100mg/kg/day after three days or when clinical improvement occurs.
Neonates: The initial dosage should be 100mg/kg/day intravenously. This dosage may be reduced to 50mg/kg/day after three days or when clinical improvement occurs.

Adults: 3g intravenously every eight hours. No data is currently available to recommend a dose for intrathecal administration.

Prophylaxis
1500 mg intravenously 30-60 minutes before surgery. For orthopaedic, pelvic and abdominal operations this may be followed with two 750mg doses 8 and 16 hours later. For vascular, cardiac, oesophageal and pulmonary operations this may be supplemented with 750mg intramuscularly three times a day for a further 24 to 48 hours.

Dosage in Impaired Renal Function
As cefuroxime is excreted by the kidneys, the dosage should be reduced to allow for slower excretion in patients with impaired renal function, once creatinine clearance falls below 20ml/min, as follows:

| Marked impairment (creatinine clearance 10 to 20ml/min) | 750mg twice daily |
| Severe impairment (creatinine clearance of less than 10ml/min)* | 750mg once daily |
| Continuous peritoneal dialysis | 750mg twice daily |
| Renal failure on continuous arteriovenous haemodialysis or high-flux haemofiltration in intensive therapy units | 750mg twice daily |
| Low-flux haemofiltration | As for impaired renal function |

*For patients on haemodialysis, a further 750mg should be given at the end of each dialysis session.

4.3 Contraindications
Hypersensitivity to cefuroxime or to any other cephalosporin antibiotics.
Previous, immediate and/or severe hypersensitivity reaction to penicillin or any beta-lactam antibiotic.

4.4 Special warnings and precautions for use
Special care is indicated in patients who have experienced any kind of hypersensitivity reaction to penicillins or any other beta-lactam antibiotics as cross-reactions may occur (for contraindications due to known hypersensitivity see section 4.3).

In case of severe hypersensitivity reaction to cefuroxime, treatment with cefuroxime must be discontinued immediately and appropriate emergency measures must be initiated.

As with other broad spectrum antibiotics, prolonged use of cefuroxime sodium may result in overgrowth of non-susceptible organisms (e.g. Candida, Enterococci, Clostridium difficile), which may require interruption of treatment.

In patients who develop severe diarrhoea during or after use of cefuroxime sodium, the risk of life threatening pseudo-membranous colitis should be taken into account. The use of cefuroxime sodium should be discontinued and the appropriate treatment established. The use of preparations inhibiting the intestinal peristaltism is contra-indicated.

Cephalosporin antibiotics at high dosage should be given with caution to patients receiving potent diuretics or aminoglycosides, as these combinations are suspected of adversely affecting renal function. Clinical experience has shown that this is not likely to be a problem at the recommended dose levels.

Delayed sterilisation of the CSF in patients with Haemophilus influenzae meningitis may result in an adverse outcome such as deafness and/or neurological sequelae. Persistence of positive CSF cultures of H. influenzae at 18-36 hours has been noted in some patients treated with cefuroxime sodium injection and, as with other therapeutic regimens used in the treatment of meningitis, hearing loss has been reported in some children.

Cefuroxime 250 mg powder for Solution for Injection contains 0.59 mmol (13.56 mg) of sodium per vial. This should be taken into consideration in patients under sodium controlled diet.
4.5 Interaction with other medicinal products and other forms of interaction

Cephalosporin antibiotics at high dosage should be given with caution to patients receiving concurrent treatment with potent diuretics such as furosemide and aminoglycosides, as these combinations are suspected of adversely affecting renal function.

Bacteriostatic antibiotics may interfere with the bactericidal action of cephalosporins, it is advisable to avoid giving tetracyclines, macrolides, or chloramphenicol in conjunction with cefuroxime.

Probenicid inhibits the tubular excretion of cefuroxime, when probenicid is administered concomitantly plasma concentrations are enhanced.

Cefuroxime does not interfere in enzyme-based tests for glycosuria. Slight interference with copper reduction methods (Benedict's, Fehling's, Clinitest) may be observed. However, this should not lead to false-positive results, as may be experienced with some other cephalosporins.

It is recommended that either the glucose oxidase or hexokinase methods are used to determine blood/plasma glucose levels in patients receiving cefuroxime. This antibiotic does not interfere in the alkaline picrate assay for creatinine.

4.6 Pregnancy and lactation

Pregnancy

Data on a limited number of exposed pregnancies indicate no adverse effects of cefuroxime on the pregnancy or on the health of the fetus/newborn child. To date no other relevant epidemiological data are available. Animal studies do not show any harmful effects on embryonal and fetal development (see section 5.3). Cefuroxime reaches the embryo/fetus via the placenta. Due to the limited clinical experience cefuroxime should only be used during pregnancy after careful risk/benefit, especially during the first trimester.

Lactation:

Cefuroxime is excreted in human milk. Cefuroxime should only be used during lactation after careful risk/benefit assessment. Diarrhoea and fungus infection of the mucous membranes could occur in the breast-fed infant, so that nursing might have to be discontinued. The possibility of sensitization should be borne in mind.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Adverse drug reactions are very rare (<1/10,000) and are generally mild and transient in nature.

The frequency categories assigned to the adverse reactions below are estimates, as for most reactions suitable data for calculating incidence are not available. In addition the incidence of adverse reactions associated with cefuroxime sodium may vary according to the indication.

The following convention has been used for the classification of frequency:

- very common ≥ 1/10
- common ≥ 1/100 and <1/10,
- uncommon ≥ 1/1,000 and <1/100,
- rare ≥1/10,000 and <1/1,000,
- very rare <1/10,000

Not known (cannot be estimated from the available data)
### System Organ Class

<table>
<thead>
<tr>
<th>Adverse drug reactions</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
</tr>
<tr>
<td>Superinfection, candida overgrowth</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Blood and the lymphatic system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Neutropenia, eosinophilia</td>
<td>Common</td>
</tr>
<tr>
<td>Leukopenia, haemoglobin decreased, Coomb’s test positive</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Rare</td>
</tr>
<tr>
<td>Haemolytic anaemia</td>
<td>Very rare</td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity (including skin reactions and urticaria)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Anaphylactic reaction</td>
<td>Very rare</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disturbance</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Pseudomembranous colitis</td>
<td>Very rare</td>
</tr>
<tr>
<td><strong>Hepato-biliary disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Hepatic enzymes increased transient</td>
<td>Common</td>
</tr>
<tr>
<td>Blood bilirubin increased transient</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Rash, urticaria, pruritus (see also immune system disorders)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Erythema multiforme, toxic epidermal necrolysis, Stevens Johnson Syndrome</td>
<td>Very rare</td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Nephritis interstitial, blood creatinine increased, blood urea increased, creatinine clearance decreased</td>
<td>Very rare</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Injection site reactions, pain</td>
<td>Common</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>Rare</td>
</tr>
</tbody>
</table>

### 4.9 Overdose

Overdose of cephalosporins can cause cerebral irritation leading to convulsions. Serum levels of cefuroxime can be reduced by haemodialysis or peritoneal dialysis.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

**Pharmacotherapeutic Group:** Second generation Cephalosporin, J01DC02

**Mode of action**

Cefuroxime is a semisynthetic derivative of cephalosporanic acid. Cefuroxime exerts antibacterial activity by inhibition of bacterial cell wall synthesis in susceptible species. Cefuroxime has good stability to several bacterial beta-lactamase enzymes and, consequently, is active against many penicillin-resistant or ampicillin and amoxicillin-resistant strains of susceptible species.

Cefuroxime binds to cell receptors, called penicillin-binding proteins. After a \( \beta \)-lactam antibiotic has bound to these receptors, the transpeptidation reaction is inhibited and peptidoglycan synthesis is blocked. This results in bacterial lysis.
Mechanism of resistance
Bacterial resistance to cefuroxime may be due to one or more of the following mechanisms:
• hydrolysis by beta-lactamases. Cefuroxime may be efficiently hydrolysed by certain of the extended-spectrum beta-lactamases (ESBLs) and by the chromosomally-encoded (AmpC) enzyme that may be induced or stably derepressed in certain aerobic gram-negative bacterial species
• reduced affinity of penicillin-binding proteins for cefuroxime
• outer membrane impermeability, which restricts access of cefuroxime to penicillin binding proteins in gram-negative organisms
• drug efflux pumps

Methicillin-resistant staphylococci (MRS) are resistant to all currently available β-lactam antibiotics including cefuroxime.

Penicillin-resistant Streptococcus pneumoniae are cross-resistant to cephalosporins such as cefuroxime through alteration of penicillin binding proteins.

Beta-lactamase negative, ampicillin resistant (BLNAR) strains of H. influenzae should be considered resistant to cefuroxime despite apparent in vitro susceptibility.

Strains of Enterobacteriaceae, in particular Klebsiella spp. and Escherichia coli that produce ESBLs (extended spectrum β-lactamase) may be clinically resistant to therapy with cephalosporins despite apparent in vitro susceptibility and should be considered as resistant.

PK/PD relationship
For beta-lactam antibacterial agents, bactericidal activity is more dependent upon the time that serum drug concentrations remain above the MIC of a given organism than on a simple comparison of MIC values with plasma drug concentrations.

Breakpoints
Clinical minimum inhibitory concentration (MIC) breakpoints established by EUCAST (April 2010) for cefuroxime are as follows:

<table>
<thead>
<tr>
<th>Organisms</th>
<th>MIC breakpoint (mg/L)</th>
<th>Sensitive ≤</th>
<th>Resistant ≥</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus spp.¹</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Streptococcus groups A, B, C and G²</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>0.5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other streptococci</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Non-species related breakpoints</td>
<td>4</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

¹ - The breakpoint relates to a dosage of 1.5 g x 3 and to E. coli, P. mirabilis and Klebsiella spp. only.
² - The beta-lactam susceptibility of beta-haemolytic streptococcus groups A, B, C and G is inferred from the penicillin susceptibility.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

The following table gives only an approximate guidance on probabilities whether microorganisms will be susceptible to cefuroxime or not.
<table>
<thead>
<tr>
<th>Species for which resistance may be a problem</th>
</tr>
</thead>
</table>

### Commonly susceptible species

**Aerobes, Gram positive:**
- *Staphylococcus aureus* (methicillin sensitive)
- *Staphylococcus saprophyticus*
- *Streptococcus agalactiae*
- *Streptococcus pyogenes*

**Aerobes, Gram negative:**
- *Proteus mirabilis*

### Species for which resistance may be a problem

**Aerobes, Gram positive:**
- *Staphylococcus epidermidis* +
- *Staphylococcus haemolyticus* +
- *Staphylococcus hominis* +
- *Streptococcus pneumoniae* +,2

**Aerobes, Gram negative:**
- *Citrobacter freundii* +
- *Citrobacter koseri* +
- *Enterobacter aerogenes* +
- *Enterobacter cloacae* +
- *Escherichia coli*
- *Haemophilus influenzae*
- *Klebsiella oxytoca*
- *Klebsiella pneumoniae* +
- *Moraxella catarrhalis*

### Resistant species

**Aerobes, Gram positive:**
- *Enterococcus spp.*
- *Listeria monocytogenes*
- *Staphylococcus aureus* (methicillin resistant)1
- *Staphylococcus epidermidis* (methicillin resistant)

**Aerobes, Gram negative:**
- *Acinetobacter baumannii*
- *Burkholderia cepacia*
- *Campylobacter spp.*
- *Morganella Morganii*
- *Proteus vulgaris*
- *Pseudomonas aeruginosa*
- *Serratia spp.*
- *Stenotrophomonas maltophilia*

**Anaerobes:**
- *Bacteroides spp.*
- *Clostridium difficile*

**Others:**
- *Chlamydia spp.*
- *Chlamydomphila spp.*
- *Legionella spp.*
- *Mycoplasma spp.*

---

+ Prevalence of bacterial resistance is > 50% in at least one European country.
1 Methicillin resistant staphylococci are resistant to other beta-lactams.
2 Streptococcus resistant to penicillin, are always resistant to cefuroxime.
5.2 Pharmacokinetic properties

Peak levels of cefuroxime are achieved within 30 to 45 minutes after intramuscular administration. The serum half-life after either intramuscular or intravenous injection is approximately 70 minutes. Concurrent administration of probenecid prolongs the excretion of the antibiotic and produces an elevated peak serum level. There is almost complete recovery of unchanged cefuroxime in the urine within 24 hours of administration, the major part being eliminated in the first six hours. Approximately 50% is excreted through the renal tubules and approximately 50% by glomerular filtration. Concentrations of cefuroxime in excess of the minimum inhibitory levels for common pathogens can be achieved in bone, synovial fluid and aqueous humor. Cefuroxime passes the blood-brain barrier when the meninges are inflamed.

5.3 Preclinical safety data

Preclinical nephrotoxicity studies showed the product can cause renal damage in some species when administered in very high doses. Its nephrotoxicity increases when administered in combination with glycerol and furosemide.

A cefuroxime ester did not show clinically relevant effects when tested in vitro and in vivo for genotoxic potential. No long-term investigations for the determination of a tumorigenic potential were performed. Investigations in rabbits and mice did not demonstrate reproductive toxicity or teratogenic effects.

Gamma-glutamyl transpeptidase activity in rat urine is inhibited by various cephalosporins, however, the level of inhibition is less with cefuroxime. This may have significance in the interference in clinical laboratory tests in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

The pH of 2.74% w/v sodium bicarbonate injection BP considerably affects the colour of solutions and therefore this solution is not recommended for the dilution of cefuroxime powder for solution for Injection. However, if required, for patients receiving sodium bicarbonate injection by infusion the cefuroxime powder for solution for Injection may be introduced into the tube of the giving set.

Cefuroxime powder for solution for Injection should not be mixed in the syringe with aminoglycoside antibiotics.

Unless compatibility is proven, the injection should always be administered separately.

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

6.3 Shelf life

For Dry Powder: 2 years

After Reconstitution: When prepared under aseptic condition, reconstituted product has demonstrated chemical and physical stability for 24 hours when stored in a refrigerator at 2-8°C.

From a microbiological point of view, once opened, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, when prepared in Water for Injections or any of the injections listed in Section 6.6.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

Keep vial in the outer carton.

For storage conditions of the reconstituted/diluted product see section 6.3.

6.5 Nature and contents of container

20 ml Type I glass vials with a Grey bromo butyl rubber stopper and flip off seal.
6.6 Special precautions for disposal

Intramuscular
Add 1ml water for injection to 250mg Cefuroxime Powder for solution for injection Shake gently to produce an opaque suspension.

Intravenous
Dissolve Cefuroxime 250mg Powder for solution for injection in 2ml of water for injection

The contents and concentrations of cefuroxime as a suspension/solution are shown in the table below:

<table>
<thead>
<tr>
<th>Cefuroxime per vial (mg)</th>
<th>Route of administration</th>
<th>Volume of solvent to be added (mL)</th>
<th>Final volume of suspension/solution (mL)</th>
<th>Concentration of suspension/solution (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td>IM</td>
<td>1</td>
<td>1.2</td>
<td>208</td>
</tr>
<tr>
<td></td>
<td>IV Bolus</td>
<td>2</td>
<td>2.2</td>
<td>114</td>
</tr>
</tbody>
</table>

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

7 MARKETING AUTHORISATION HOLDER
Orchid Europe Ltd
Building 3, Chiswick Park,
566, Chiswick High Road,
Chiswick, London, W4 5YA
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 22805/0023

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
05/10/2010

10 DATE OF REVISION OF THE TEXT
05/10/2010
1 NAME OF THE MEDICINAL PRODUCT
Cefuroxime 750 mg Powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 789 mg of cefuroxime sodium equivalent to 750 mg of cefuroxime.

Also contains 1.77 mmol (40.69 mg) of sodium per vial.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Powder for solution for injection
White to faintly yellow, amorphous powder

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Cefuroxime sodium for injection is indicated for the treatment of the following infections caused by susceptible organisms:
- Lower respiratory tract infections: acute exacerbation of chronic bronchitis, bacterial pneumonia.
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- Soft tissue infections.
- Bone and joint infections.
- Obstetric and gynaecological infections.
- Meningitis.
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Consideration should be given to official local guidance (eg, national recommendations) on the appropriate use of antibacterial agents.

4.2 Posology and method of administration
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The intramuscular method of administration is reserved to exceptional clinical situations and should undergo a risk-benefit assessment.
Special advise for intramuscular injection has to be regarded (see section 6.6 ).

The frequency of dosage may be increased to six-hourly injections, intramuscular or intravenous, giving total daily doses of 3g to 6g.

Infants and children: Doses of 30 to 100mg/kg/day given in three or four divided doses. A dose of 60mg/kg/day will be appropriate for most infections.

Neonates: Doses of 30 to 100mg/kg/day given in two or three divided doses. In the first weeks of life the serum half-life of cefuroxime can be three to five times that in adults.

Meningitis
Cefuroxime therapy is suitable for sole therapy of bacterial meningitis due to sensitive strains.

Infants and children: 200 to 240mg/kg/day intravenously in three or four divided doses. This dosage may be reduced to 100mg/kg/day after three days or when clinical improvement occurs.

Neonates: The initial dosage should be 100mg/kg/day intravenously. This dosage may be reduced to 50mg/kg/day after three days or when clinical improvement occurs.

Adults: 3g intravenously every eight hours. No data is currently available to recommend a dose for intrathecal administration.
Prophylaxis
1500 mg intravenously 30-60 minutes before surgery. For orthopaedic, pelvic and abdominal operations this may be followed with two 750mg doses 8 and 16 hours later. For vascular, cardiac, oesophageal and pulmonary operations this may be supplemented with 750mg intramuscularly three times a day for a further 24 to 48 hours.

Dosage in Impaired Renal Function
As cefuroxime is excreted by the kidneys, the dosage should be reduced to allow for slower excretion in patients with impaired renal function, once creatinine clearance falls below 20ml/min, as follows:

<table>
<thead>
<tr>
<th>Impairment</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marked impairment (creatinine</td>
<td>750mg twice daily</td>
</tr>
<tr>
<td>clearance 10 to 20ml/min)</td>
<td></td>
</tr>
<tr>
<td>Severe impairment (creatinine</td>
<td>750mg once daily</td>
</tr>
<tr>
<td>clearance of less than 10ml/min)</td>
<td></td>
</tr>
<tr>
<td>Continuous peritoneal dialysis</td>
<td>750mg twice daily</td>
</tr>
<tr>
<td>Renal failure on continuous</td>
<td>750mg twice daily</td>
</tr>
<tr>
<td>arteriovenous haemodialysis or</td>
<td></td>
</tr>
<tr>
<td>high-flux haemofiltration in</td>
<td></td>
</tr>
<tr>
<td>intensive therapy units</td>
<td></td>
</tr>
<tr>
<td>Low-flux haemofiltration</td>
<td>As for impaired renal function</td>
</tr>
</tbody>
</table>

For patients on haemodialysis, a further 750mg should be given at the end of each dialysis session.

4.3 Contraindications
Hypersensitivity to cefuroxime or to any other cephalosporin antibiotics.
Previous, immediate and/or severe hypersensitivity reaction to penicillin or any beta-lactam antibiotic.

4.4 Special warnings and precautions for use
Special care is indicated in patients who have experienced any kind of hypersensitivity reaction to penicillins or any other beta-lactam antibiotics as cross-reactions may occur (for contraindications due to known hypersensitivity see section 4.3).

In case of severe hypersensitivity reaction to cefuroxime, treatment with cefuroxime must be discontinued immediately and appropriate emergency measures must be initiated.

As with other broad spectrum antibiotics, prolonged use of cefuroxime sodium may result in overgrowth of non-susceptible organisms (e.g. Candida, Enterococci, Clostridium difficile), which may require interruption of treatment.

In patients who develop severe diarrhoea during or after use of cefuroxime sodium, the risk of life threatening pseudo-membranous colitis should be taken into account. The use of cefuroxime sodium should be discontinued and the appropriate treatment established. The use of preparations inhibiting the intestinal peristaltism is contra-indicated.

Cephalosporin antibiotics at high dosage should be given with caution to patients receiving potent diuretics or aminoglycosides, as these combinations are suspected of adversely affecting renal function. Clinical experience has shown that this is not likely to be a problem at the recommended dose levels.

Delayed sterilisation of the CSF in patients with Haemophilus influenzae meningitis may result in an adverse outcome such as deafness and/or neurological sequelae. Persistence of positive CSF cultures of H. influenzae at 18-36 hours has been noted in some patients treated with cefuroxime sodium injection and, as with other therapeutic regimens used in the treatment of meningitis, hearing loss has been reported in some children.

Cefuroxime sodium for injection contains sodium and this should be taken into consideration in patients under sodium controlled diet.

Cefuroxime 750 mg powder for solution for injection contains 1.77 mmol (40.69 mg) of sodium per vial. This should be taken into consideration in patients under sodium controlled diet.

4.5 Interaction with other medicinal products and other forms of interaction
Cephalosporin antibiotics at high dosage should be given with caution to patients receiving concurrent treatment with potent diuretics such as furosemide and aminoglycosides, as these combinations are suspected of adversely affecting renal function.

Bacteriostatic antibiotics may interfere with the bactericidal action of cephalosporins, it is advisable to avoid giving tetracyclines, macrolides, or chloramphenicol in conjunction with cefuroxime.
Probenicid inhibits the tubular excretion of cefuroxime, when probenicid is administered concomitantly plasma concentrations are enhanced.

Cefuroxime does not interfere in enzyme-based tests for glycosuria. Slight interference with copper reduction methods (Benedict's, Fehling's, Clinitest) may be observed. However, this should not lead to false-positive results, as may be experienced with some other cephalosporins.

It is recommended that either the glucose oxidase or hexokinase methods are used to determine blood/plasma glucose levels in patients receiving cefuroxime. This antibiotic does not interfere in the alkaline picrate assay for creatinine.

4.6 Pregnancy and lactation

Pregnancy

Data on a limited number of exposed pregnancies indicate no adverse effects of cefuroxime on the pregnancy or on the health of the fetus/newborn child. To date no other relevant epidemiological data are available. Animal studies do not show any harmful effects on embryonal and fetal development (see section 5.3). Cefuroxime reaches the embryo/fetus via the placenta. Due to the limited clinical experience cefuroxime should only be used during pregnancy after careful risk/benefit, especially during the first trimester.

Lactation:

Cefuroxime is excreted in human milk. Cefuroxime should only be used during lactation after careful risk/benefit assessment. Diarrhoea and fungus infection of the mucuos membranes could occur in the breast-fed infant, so that nursing might have to be discontinued. The possibility of sensitization should be borne in mind.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Adverse drug reactions are very rare (<1/10,000) and are generally mild and transient in nature.

The frequency categories assigned to the adverse reactions below are estimates, as for most reactions suitable data for calculating incidence are not available. In addition the incidence of adverse reactions associated with cefuroxime sodium may vary according to the indication.

The following convention has been used for the classification of frequency:

- very common ≥ 1/10
- common ≥ 1/100 and <1/10,
- uncommon ≥ 1/1,000 and <1/100,
- rare ≥1/10,000 and <1/1,000,
- very rare <1/10,000

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse drug reactions</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Superinfection, candida overgrowth</td>
<td>Rare</td>
</tr>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Neutropenia, eosinophilia</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Leukopenia, haemoglobin decreased, Coomb’s test positive</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Haemolytic anaemia</td>
<td>Very rare</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity (including skin reactions and urticaria)</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Anaphylactic reaction</td>
<td>Very rare</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Adverse drug reactions</td>
<td>Frequency</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>-------------------------------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Thrombophlebitis</td>
<td>Common</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Gastrointestinal disturbance</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Pseudomembranous colitis</td>
<td>Very rare</td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td>Hepatic enzymes increased transient</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Blood bilirubin increased transient</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash, urticaria, pruritus (see also immune system disorders)</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Erythema multiforme, toxic epidermal necrolysis, Stevens</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>Johnson Syndrome</td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Nephritis interstitial, blood</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>creatinine increased, blood urea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>creatinine clearance decreased</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site</td>
<td>Injection site reactions, pain</td>
<td>Common</td>
</tr>
<tr>
<td>conditions</td>
<td>Pyrexia</td>
<td>Rare</td>
</tr>
</tbody>
</table>

4.9 Overdose
Overdose of cephalosporins can cause cerebral irritation leading to convulsions. Serum levels of cefuroxime can be reduced by haemodialysis or peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic Group: Second generation Cephalosporin, J01DC02

Mode of action
Cefuroxime is a semisynthetic derivative of cephalosporanic acid. Cefuroxime exerts antibacterial activity by inhibition of bacterial cell wall synthesis in susceptible species. Cefuroxime has good stability to several bacterial beta-lactamase enzymes and, consequently, is active against many penicillin-resistant or ampicillin and amoxicillin-resistant strains of susceptible species.

Cefuroxime binds to cell receptors, called penicillin-binding proteins. After a beta-lactam antibiotic has bound to these receptors, the transpeptidation reaction is inhibited and peptidoglycan synthesis is blocked. This results in bacterial lysis.

Mechanism of resistance
Bacterial resistance to cefuroxime may be due to one or more of the following mechanisms:

- hydrolysis by beta-lactamases. Cefuroxime may be efficiently hydrolysed by certain of the extended-spectrum beta-lactamases (ESBLs) and by the chromosomally-encoded (AmpC) enzyme that may be induced or stably derepressed in certain aerobic gram-negative bacterial species
- reduced affinity of penicillin-binding proteins for cefuroxime
- outer membrane impermeability, which restricts access of cefuroxime to penicillin binding proteins in gram-negative organisms
- drug efflux pumps

Methicillin-resistant staphylococci (MRS) are resistant to all currently available beta-lactam antibiotics including cefuroxime.
Penicillin-resistant Streptococcus pneumoniae are cross-resistant to cephalosporins such as cefuroxime through alteration of penicillin binding proteins.

Beta-lactamase negative, ampicillin resistant (BLNAR) strains of H. influenzae should be considered resistant to cefuroxime despite apparent in vitro susceptibility.

Strains of Enterobacteriaceae, in particular Klebsiella spp. and Escherichia coli that produce ESBLs (extended spectrum β-lactamase) may be clinically resistant to therapy with cephalosporins despite apparent in vitro susceptibility and should be considered as resistant.

PK/PD relationship
For beta-lactam antibacterial agents, bactericidal activity is more dependent upon the time that serum drug concentrations remain above the MIC of a given organism than on a simple comparison of MIC values with plasma drug concentrations.

Breakpoints
Clinical minimum inhibitory concentration (MIC) breakpoints established by EUCAST (April 2010) for cefuroxime are as follows:

<table>
<thead>
<tr>
<th>Organisms</th>
<th>MIC breakpoint (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitive ≤</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>8</td>
</tr>
<tr>
<td>Staphylococcus spp. *</td>
<td>-</td>
</tr>
<tr>
<td>Streptococcus groups A, B, C and G *</td>
<td>-</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>0.5</td>
</tr>
<tr>
<td>Other streptococci</td>
<td>0.5</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>1</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>1</td>
</tr>
<tr>
<td>Non-species related break points</td>
<td>4</td>
</tr>
</tbody>
</table>

* - The breakpoint relates to a dosage of 1.5 g x 3 and to E. coli, P. mirabilis and Klebsiella spp. only.
1 - Susceptibility of staphylococci is inferred from the methicillin susceptibility.
2 - The beta-lactam susceptibility of beta-haemolytic streptococcus groups A, B, C and G is inferred from the penicillin susceptibility.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

The following table gives only an approximate guidance on probabilities whether microorganisms will be susceptible to cefuroxime or not.

<table>
<thead>
<tr>
<th>Commonly susceptible species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobes, Gram positive:</td>
</tr>
<tr>
<td>Staphylococcus aureus (methicillin sensitive)</td>
</tr>
<tr>
<td>Staphylococcus saprophyticus</td>
</tr>
<tr>
<td>Streptococcus agalactiae</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
</tr>
<tr>
<td>Aerobes, Gram negative:</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Species for which resistance may be a problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobes, Gram positive:</td>
</tr>
<tr>
<td>Staphylococcus epidermidis *</td>
</tr>
<tr>
<td>Staphylococcus haemolyticus +</td>
</tr>
<tr>
<td>Staphylococcus hominis *</td>
</tr>
<tr>
<td>Streptococcus pneumoniae +,2</td>
</tr>
<tr>
<td>Aerobes, Gram negative:</td>
</tr>
<tr>
<td>Citrobacter freundii</td>
</tr>
<tr>
<td>Citrobacter koser</td>
</tr>
<tr>
<td>Enterobacter aerogenes</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
</tr>
<tr>
<td>Escherichia coli</td>
</tr>
</tbody>
</table>
Haemophilus influenzae
Klebsiella oxytoca
Klebsiella pneumoniae
Moraxella catarrhalis

Resistant species

Aerobes, Gram positive:
Enterococcus spp.
Listeria monocytogenes
Staphylococcus aureus (methicillin resistant)
Staphylococcus epidermidis (methicillin resistant)

Aerobes, Gram negative:
Acinetobacter baumannii
Burkholderia cepacia
Campylobacter spp.
Morganella Morganii
Proteus vulgaris
Pseudomonas aeruginosa
Serratia spp.
Stenotrophomonas maltophilia

Anaerobes:
Bacteroides spp.
Clostridium difficile

Others:
Chlamydia spp.
Chlamyphila spp.
Legionella spp.
Mykobacterium spp.
Mycoplasma spp.

+ Prevalence of bacterial resistance is > 50% in at least one European country.
1 Methicillin resistant staphylococci are resistant to other beta-lactams.
2 Streptococcus resistant to penicillin, are always resistant to cefuroxime.

5.2 Pharmacokinetic properties
Peak levels of cefuroxime are achieved within 30 to 45 minutes after intramuscular administration. The serum half-life after either intramuscular or intravenous injection is approximately 70 minutes. Concurrent administration of probenecid prolongs the excretion of the antibiotic and produces an elevated peak serum level. There is almost complete recovery of unchanged cefuroxime in the urine within 24 hours of administration, the major part being eliminated in the first six hours. Approximately 50% is excreted through the renal tubules and approximately 50% by glomerular filtration. Concentrations of cefuroxime in excess of the minimum inhibitory levels for common pathogens can be achieved in bone, synovial fluid and aqueous humor. Cefuroxime passes the blood-brain barrier when the meninges are inflamed.

5.3 Preclinical safety data
Preclinical nephrotoxicity studies showed the product can cause renal damage in some species when administered in very high doses. Its nephrotoxicity increases when administered in combination with glycerol and furosemide.

A cefuroxime ester did not show clinically relevant effects when tested in vitro and in vivo for genotoxic potential. No long-term investigations for the determination of a tumorigenic potential were performed. Investigations in rabbits and mice did not demonstrate reproductive toxicity or teratogenic effects.

Gamma-glutamyl transpeptidase activity in rat urine is inhibited by various cephalosporins, however, the level of inhibition is less with cefuroxime. This may have significance in the interference in clinical laboratory tests in humans.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
None
6.2 Incompatibilities
The pH of 2.74% w/v sodium bicarbonate injection BP considerably affects the colour of solutions and therefore this solution is not recommended for the dilution of cefuroxime powder for solution for Injection. However, if required, for patients receiving sodium bicarbonate injection by infusion the cefuroxime powder for solution for Injection may be introduced into the tube of the giving set.

Cefuroxime powder for solution for Injection should not be mixed in the syringe with aminoglycoside antibiotics.

Unless compatibility is proven, the injection should always be administered separately.

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

6.3 Shelf life
For Dry Powder: 2 years

After Reconstitution: When prepared under aseptic condition, reconstituted product has demonstrated chemical and physical stability for 24 hours when stored in a refrigerator at 2-8°C.

From a microbiological point of view, once opened, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, when prepared in water for Injections or any of the injections listed in Section 6.6.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.
Keep vial in the outer carton.
For storage conditions of the reconstituted/diluted product see section 6.3.

6.5 Nature and contents of container
20 ml Type I glass vials with a Grey bromo butyl rubber stopper and flip off seal.
Pack size: 1 vial per carton.

6.6 Special precautions for disposal
Intramuscular
Add 3ml water for injection to 750mg Cefuroxime Powder for Solution for Injection Shake gently to produce an opaque suspension.

Intravenous
Dissolve Cefuroxime 750mg Powder for solution for injection in 6ml of water for injection

The contents and concentrations of cefuroxime as a suspension/solution are shown in the table below:

<table>
<thead>
<tr>
<th>Cefuroxime per vial (mg)</th>
<th>Route of administration</th>
<th>Volume of solvent to be added (mL)</th>
<th>Final volume of suspension/solution (mL)</th>
<th>Concentration of suspension/solution (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>750</td>
<td>IM</td>
<td>3</td>
<td>3.5</td>
<td>214</td>
</tr>
<tr>
<td></td>
<td>IV Bolus</td>
<td>6</td>
<td>6.7</td>
<td>112</td>
</tr>
</tbody>
</table>

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

7 MARKETING AUTHORISATION HOLDER
Orchid Europe Ltd
Building 3, Chiswick Park, 566, Chiswick High Road, Chiswick, London, W4 5YA
United Kingdom
8 MARKETING AUTHORIZATION NUMBER(S)
   PL 22805/0024

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
   05/10/2010

10 DATE OF REVISION OF THE TEXT
    05/10/2010
1 NAME OF THE MEDICINAL PRODUCT
Cefuroxime 1.5 g Powder for solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 1.578 g of cefuroxime sodium equivalent to 1.5 g of cefuroxime.

Also contains 3.54 mmol (81.38 mg) of sodium per vial.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Powder for solution for injection or infusion.
White to faintly yellow, amorphous powder.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Cefuroxime sodium for injection is indicated for the treatment of the following infections caused by susceptible organisms:

Lower respiratory tract infections: acute exacerbation of chronic bronchitis, bacterial pneumonia.

Urinary tract infections.

Soft tissue infections.

Bone and joint infections.

Obstetric and gynaecological infections.

Meningitis.

Prophylaxis against infection in abdominal, pelvic, orthopaedic, cardiac, pulmonary, oesophageal and vascular surgery.

Consideration should be given to official local guidance (eg, national recommendations) on the appropriate use of antibacterial agents.

4.2 Posology and method of administration
Usually cefuroxime is effective when administered alone, but when appropriate it may be used in combination with metronidazole or an aminoglycoside.

General Dosage
Adults: Many infections will respond to 750mg three times daily by intramuscular or intravenous injection. For more severe infections this dose should be increased to 1.5g three times daily intravenously.

The intramuscular method of administration is reserved to exceptional clinical situations and should undergo a risk-benefit assessment.
Special advise for intramuscular injection has to be regarded (see section 6.6 ).

The frequency of dosage may be increased to six-hourly injections, intramuscular or intravenous, giving total daily doses of 3g to 6g.

Infants and children: Doses of 30 to 100mg/kg/day given in three or four divided doses. A dose of 60mg/kg/day will be appropriate for most infections.

Neonates: Doses of 30 to 100mg/kg/day given in two or three divided doses. In the first weeks of life the serum half-life of cefuroxime can be three to five times that in adults.

Meningitis
Cefuroxime therapy is suitable for sole therapy of bacterial meningitis due to sensitive strains.
Infants and children: 200 to 240mg/kg/day intravenously in three or four divided doses. This dosage may be reduced to 100mg/kg/day after three days or when clinical improvement occurs.

Neonates: The initial dosage should be 100mg/kg/day intravenously. This dosage may be reduced to 50mg/kg/day after three days or when clinical improvement occurs.

Adults: 3g intravenously every eight hours. No data is currently available to recommend a dose for intrathecal administration.

Prophylaxis
1500 mg intravenously 30-60 minutes before surgery. For orthopaedic, pelvic and abdominal operations this may be followed with two 750mg doses 8 and 16 hours later. For vascular, cardiac, oesophageal and pulmonary operations this may be supplemented with 750mg intramuscularly three times a day for a further 24 to 48 hours.

Dosage in Impaired Renal Function
As cefuroxime is excreted by the kidneys, the dosage should be reduced to allow for slower excretion in patients with impaired renal function, once creatinine clearance falls below 20ml/min, as follows:

<table>
<thead>
<tr>
<th>Impairment Condition</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marked impairment (creatinine clearance 10 to 20ml/min)</td>
<td>750mg twice daily</td>
</tr>
<tr>
<td>Severe impairment (creatinine clearance of less than 10ml/min)*</td>
<td>750mg once daily</td>
</tr>
<tr>
<td>Continuous peritoneal dialysis</td>
<td>750mg twice daily</td>
</tr>
<tr>
<td>Renal failure on continuous arteriovenous haemodialysis or high-flux haemofiltration in intensive therapy units</td>
<td>750mg twice daily</td>
</tr>
<tr>
<td>Low-flux haemofiltration</td>
<td>As for impaired renal function</td>
</tr>
</tbody>
</table>

*For patients on haemodialysis, a further 750mg should be given at the end of each dialysis session.

4.3 Contraindications
Hypersensitivity to cefuroxime or to any other cephalosporin antibiotics. Previous, immediate and/or severe hypersensitivity reaction to penicillin or any beta-lactam antibiotic.

4.4 Special warnings and precautions for use
Special care is indicated in patients who have experienced any kind of hypersensitivity reaction to penicillins or any other beta-lactam antibiotics as cross-reactions may occur (for contraindications due to known hypersensitivity see section 4.3).

In case of severe hypersensitivity reaction to cefuroxime, treatment with cefuroxime must be discontinued immediately and appropriate emergency measures must be initiated.

As with other broad spectrum antibiotics, prolonged use of cefuroxime sodium may result in overgrowth of non-susceptible organisms (e.g. Candida, Enterococci, Clostridium difficile), which may require interruption of treatment.

In patients who develop severe diarrhoea during or after use of cefuroxime sodium, the risk of life threatening pseudo-membranous colitis should be taken into account. The use of cefuroxime sodium should be discontinued and the appropriate treatment established. The use of preparations inhibiting the intestinal peristalsis is contra-indicated.

Cephalosporin antibiotics at high dosage should be given with caution to patients receiving potent diuretics or aminoglycosides, as these combinations are suspected of adversely affecting renal function. Clinical experience has shown that this is not likely to be a problem at the recommended dose levels.

Delayed sterilisation of the CSF in patients with Haemophilus influenzae meningitis may result in an adverse outcome such as deafness and / or neurological sequelae. Persistence of positive CSF cultures of H. influenzae at 18-36 hours has been noted in some patients treated with cefuroxime sodium injection and, as with other therapeutic regimens used in the treatment of meningitis, hearing loss has been reported in some children.

Cefuroxime 1.5 g Powder for solution for injection/infusion contains 3.54 mmol (81.38 mg) of sodium per vial. This should be taken into consideration in patients under sodium controlled diet.
4.5 Interaction with other medicinal products and other forms of interaction
Cephalosporin antibiotics at high dosage should be given with caution to patients receiving concurrent treatment with potent diuretics such as furosemide and aminoglycosides, as these combinations are suspected of adversely affecting renal function.

Bacteriostatic antibiotics may interfere with the bactericidal action of cephalosporins, it is advisable to avoid giving tetracyclines, macrolides, or chloramphenicol in conjunction with cefuroxime.

Probenicid inhibits the tubular excretion of cefuroxime, when probenicid is administered concomitantly plasma concentrations are enhanced.

Cefuroxime does not interfere in enzyme-based tests for glycosuria. Slight interference with copper reduction methods (Benedict's, Fehling's, Clinitest) may be observed. However, this should not lead to false-positive results, as may be experienced with some other cephalosporins.

It is recommended that either the glucose oxidase or hexokinase methods are used to determine blood/plasma glucose levels in patients receiving cefuroxime. This antibiotic does not interfere in the alkaline picrate assay for creatinine.

4.6 Pregnancy and lactation
Pregnancy
Data on a limited number of exposed pregnancies indicate no adverse effects of cefuroxime on the pregnancy or on the health of the fetus/newborn child. To date no other relevant epidemiological data are available. Animal studies do not show any harmful effects on embryonal and fetal development (see section 5.3). Cefuroxime reaches the embryo/fetus via the placenta. Due to the limited clinical experience cefuroxime should only be used during pregnancy after careful risk/benefit, especially during the first trimester.

Lactation:
Cefuroxime is excreted in human milk. Cefuroxime should only be used during lactation after careful risk/benefit assessment. Diarrhoea and fungus infection of the mucous membranes could occur in the breast-fed infant, so that nursing might have to be discontinued. The possibility of sensitization should be borne in mind.

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects
Adverse drug reactions are very rare (<1/10,000) and are generally mild and transient in nature.

The frequency categories assigned to the adverse reactions below are estimates, as for most reactions suitable data for calculating incidence are not available. In addition the incidence of adverse reactions associated with cefuroxime sodium may vary according to the indication.

The following convention has been used for the classification of frequency:

- very common \(\geq 1/10\)
- common \(\geq 1/100 \text{ and } <1/10\),
- uncommon \(\geq 1/1,000 \text{ and } <1/100\),
- rare \(\geq 1/10,000 \text{ and } <1/1,000\),
- very rare <1/10,000

Not known (cannot be estimated from the available data)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse drug reactions</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Superinfection, candida overgrowth</td>
<td>Rare</td>
</tr>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Neutropenia, eosinophilia</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Leukopenia, haemoglobin decreased, Coomb’s test positive</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Condition</td>
<td>Frequency</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Haemolytic anaemia</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity (including skin reactions and urticaria)</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Anaphylactic reaction</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disturbance</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Pseudomembranous colitis</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic enzymes increased transient</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Blood bilirubin increased transient</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash, urticaria, pruritus (see also immune system disorders)</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Erythema multiforme, toxic epidermal necrolysis, Stevens Johnson Syndrome</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephritis interstitial, blood creatinine increased, blood urea increased, creatinine clearance decreased</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site reactions, pain</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>Rare</td>
<td></td>
</tr>
</tbody>
</table>

4.9 Overdose
Overdose of cephalosporins can cause cerebral irritation leading to convulsions. Serum levels of cefuroxime can be reduced by haemodialysis or peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties

**Pharmacotherapeutic Group:** Second generation Cephalosporin, J01DC02

**Mode of action**
Cefuroxime is a semisynthetic derivative of cephalosporanic acid. Cefuroxime exerts antibacterial activity by inhibition of bacterial cell wall synthesis in susceptible species. Cefuroxime has good stability to several bacterial beta-lactamase enzymes and, consequently, is active against many penicillin-resistant or ampicillin and amoxicillin-resistant strains of susceptible species.

Cefuroxime binds to cell receptors, called penicillin-binding proteins. After a beta-lactam antibiotic has bound to these receptors, the transpeptidation reaction is inhibited and peptidoglycan synthesis is blocked. This results in bacterial lysis.

**Mechanism of resistance**

Bacterial resistance to cefuroxime may be due to one or more of the following mechanisms:
- hydrolysis by beta-lactamas. Cefuroxime may be efficiently hydrolysed by certain of the extended-spectrum beta-lactamases (ESBLs) and by the chromosomally-encoded (AmpC) enzyme that may be induced or stably derepressed in certain aerobic gram-negative bacterial species.
• reduced affinity of penicillin-binding proteins for cefuroxime
• outer membrane impermeability, which restricts access of cefuroxime to penicillin binding proteins in gram-negative organisms
• drug efflux pumps

Methicillin-resistant *Staphylococci* (MRS) are resistant to all currently available β-lactam antibiotics including cefuroxime.

Penicillin-resistant *Streptococcus pneumoniae* are cross-resistant to cephalosporins such as cefuroxime through alteration of penicillin binding proteins.

Beta-lactamase negative, ampicillin resistant (BLNAR) strains of *H. influenzae* should be considered resistant to cefuroxime despite apparent in vitro susceptibility.

Strains of *Enterobacteriaceae*, in particular *Klebsiella* spp. and *Escherichia coli* that produce ESBLs (extended spectrum β-lactamase) may be clinically resistant to therapy with cephalosporins despite apparent in vitro susceptibility and should be considered as resistant.

**PK/PD relationship**
For beta-lactam antibacterial agents, bactericidal activity is more dependent upon the time that serum drug concentrations remain above the MIC of a given organism than on a simple comparison of MIC values with plasma drug concentrations.

**Breakpoints**
Clinical minimum inhibitory concentration (MIC) breakpoints established by EUCAST (April 2010) for cefuroxime are as follows:

<table>
<thead>
<tr>
<th>Organisms</th>
<th>MIC breakpoint (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitive ≤</td>
</tr>
<tr>
<td><em>Enterobacteriaceae</em></td>
<td>8</td>
</tr>
<tr>
<td><em>Staphylococcus</em> spp.†</td>
<td>-</td>
</tr>
<tr>
<td><em>Streptococcus</em> groups A, B, C and G‡</td>
<td>-</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>0.5</td>
</tr>
<tr>
<td><em>Other streptococci</em></td>
<td>0.5</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>1</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>1</td>
</tr>
<tr>
<td>Non-species related break points</td>
<td>4</td>
</tr>
</tbody>
</table>

* - The breakpoint relates to a dosage of 1.5 g x 3 and to *E. coli, P. mirabilis* and *Klebsiella* spp. only.
† - Susceptibility of staphylococci is inferred from the methicillin susceptibility.
‡ - The beta-lactam susceptibility of beta-haemolytic streptococcus groups A, B, C and G is inferred from the penicillin susceptibility.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

The following table gives only an approximate guidance on probabilities whether microorganisms will be susceptible to cefuroxime or not.

<table>
<thead>
<tr>
<th>Commonly susceptible species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobes, Gram positive:</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> (methicillin sensitive)</td>
</tr>
<tr>
<td><em>Staphylococcus saprophyticus</em></td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em></td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
</tr>
<tr>
<td>Aerobes, Gram negative:</td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
</tr>
<tr>
<td>Species for which resistance may be a problem</td>
</tr>
<tr>
<td>Aerobes, Gram positive:</td>
</tr>
</tbody>
</table>
Staphylococcus epidermidis
Staphylococcus haemolyticus
Staphylococcus hominis
Streptococcus pneumoniae

**Aerobes, Gram negative:**
- Citrobacter freundii
- Citrobacter koseri
- Enterobacter aerogenes
- Enterobacter cloacae
- Escherichia coli
- Haemophilus influenzae
- Klebsiella oxytoca
- Klebsiella pneumoniae
- Moraxella catarrhalis

**Aerobes, Gram positive:**
- Enterococcus spp.
- Listeria monocytogenes
- Staphylococcus aureus (methicillin resistant)
- Staphylococcus epidermidis (methicillin resistant)

**Anaerobes:**
- Bacteroides spp.
- Clostridium difficile

**Others:**
- Chlamydia spp.
- Chlamydophila spp.
- Legionella spp.
- Mycobacterium spp.
- Mycoplasma spp.

^ Prevalence of bacterial resistance is > 50% in at least one European country.
1 Methicillin resistant staphylococci are resistant to other beta-lactams.
2 Streptococcus resistant to penicillin, are always resistant to cefuroxime.

### 5.2 Pharmacokinetic properties

Peak levels of cefuroxime are achieved within 30 to 45 minutes after intramuscular administration. The serum half-life after either intramuscular or intravenous injection is approximately 70 minutes. Concurrent administration of probenecid prolongs the excretion of the antibiotic and produces an elevated peak serum level. There is almost complete recovery of unchanged cefuroxime in the urine within 24 hours of administration, the major part being eliminated in the first six hours. Approximately 50% is excreted through the renal tubules and approximately 50% by glomerular filtration. Concentrations of cefuroxime in excess of the minimum inhibitory levels for common pathogens can be achieved in bone, synovial fluid and aqueous humor. Cefuroxime passes the blood-brain barrier when the meninges are inflamed.

### 5.3 Preclinical safety data

Preclinical nephrotoxicity studies showed the product can cause renal damage in some species when administered in very high doses. Its nephrotoxicity increases when administered in combination with glycerol and furosemide.

A cefuroxime ester did not show clinically relevant effects when tested *in vitro* and *in vivo* for genotoxic potential. No long-term investigations for the determination of a tumorigenic potential were
performed. Investigations in rabbits and mice did not demonstrate reproductive toxicity or teratogenic effects.

Gamma-glutamyl transpeptidase activity in rat urine is inhibited by various cephalosporins, however, the level of inhibition is less with cefuroxime. This may have significance in the interference in clinical laboratory tests in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
None

6.2 Incompatibilities
The pH of 2.74% w/v sodium bicarbonate injection BP considerably affects the colour of solutions and therefore this solution is not recommended for the dilution of cefuroxime powder for solution for Injection. However, if required, for patients receiving sodium bicarbonate injection by infusion the cefuroxime powder for solution for injection may be introduced into the tube of the giving set.

Cefuroxime powder for solution for injection should not be mixed in the syringe with aminoglycoside antibiotics.

Unless compatibility is proven, the injection should always be administered separately.

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

6.3 Shelf life
For Dry Powder: 2 years

After Reconstitution: When prepared under aseptic condition, reconstituted product has demonstrated chemical and physical stability for 24 hours when stored in a refrigerator at 2-8°C.

From a microbiological point of view, once opened, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, when prepared in water for Injections or any of the injections listed in Section 6.6.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.
Keep vial in the outer carton.
For storage conditions of the reconstituted/diluted product see section 6.3.

6.5 Nature and contents of container
For 1.5g Injection: 20 ml Type I glass vials with a Grey bromo butyl rubber stopper and flip off seal.
For 1.5g Infusion: 100ml Type I glass vials with a Grey bromo butyl rubber stopper and flip off seal.
Pack size: 1 vial per carton.

6.6 Special precautions for disposal
For 1.5g Injection:
Dissolve Cefuroxime 1.5g Powder for solution for injection in 15 ml of water for injection

For 1.5g Infusion:
Dissolve 1.5g of Cefuroxime powder for solution for infusion in 15ml water for injections. Add the reconstituted solution of cefuroxime sodium to 50 or 100 ml to any of the compatible infusion solution mentioned below. These solutions may be given directly into the vein or introduced into the tubing of the giving set of a compatible parenteral infusion (see below).

5% glucose injection
0.9% sodium chloride injection
0.18% sodium chloride + 4% glucose
Hartman’s Solution
The contents and concentrations of cefuroxime as a solution are shown in the table below:

<table>
<thead>
<tr>
<th>Cefuroxime per vial (mg)</th>
<th>Route of administration</th>
<th>Volume of solvent to be added (mL)</th>
<th>Final Volume of solution (mL)</th>
<th>Concentration of solution (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1500</td>
<td>IV Bolus</td>
<td>15</td>
<td>16.2</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>IV Infusion</td>
<td>15 + 50</td>
<td>66.5</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 + 100</td>
<td>116.4</td>
<td>13</td>
</tr>
</tbody>
</table>

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

7 MARKETING AUTHORISATION HOLDER
Orchid Europe Ltd
Building 3, Chiswick Park,
566, Chiswick High Road,
Chiswick, London, W4 5YA
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 22805/0025
PL 22805/0026

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
05/10/2010

10 DATE OF REVISION OF THE TEXT
05/10/2010
Module 3
PACKAGE LEAFLET: INFORMATION FOR THE USER

Cefuroxime 250mg Powder for Solution for Injection
Cefuroxime 750mg Powder for Solution for Injection
Cefuroxime 1.5g Powder for Solution for Injection/Infusion

Cefuroxime

The name of your medicine is Cefuroxime Powder for Solution for Injection 250mg, 750mg & Cefuroxime Powder for Solution for Injection/Infusion 1.5g which will be referred to as Cefuroxime throughout the rest of this document.

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Cefuroxime is and what it is used for
2. Before you use Cefuroxime
3. How to use Cefuroxime
4. Possible side effects
5. How to store Cefuroxime
6. Further information

1. WHAT CEFUROXIME IS AND WHAT IT IS USED FOR
Cefuroxime belongs to a group of antibacterial agents called cephalosporins, which act by killing the bacteria. Like all antibiotics, Cefuroxime is only effective against some types of bacteria, thus it is only suitable for treating some types of infections.

Cefuroxime is used to treat some infections of the:
- lungs
- urinary tract
- skin and layers of flesh immediately under the skin
- bones and joints
- membranes and fluid surrounding the brain and spinal cord (this infection is called meningitis)
- female reproductive tract and the nearby structures in the lower abdomen

It is sometimes given before some surgical operations to prevent infections.

2. BEFORE YOU USE CEFUROXIME
Do not take Cefuroxime if
- you are allergic (hypersensitive) to cefuroxime or to any other cephalosporins antibiotics.
- you have ever had a severe allergic reaction to any penicillin or any other beta-lactam antibiotics.

Take special care with Cefuroxime if you
- have allergies, especially to cefuroxime, any other cephalosporin, or to any penicillin like drugs (Not all people who are allergic to penicillins are also allergic to cephalosporins.)
However, you should not take this medicine if you ever had a severe allergic reaction to any penicillin. This is because you might also be allergic to this medicine.

In patients who develop severe allergic reaction after administration of Cefuroxime, the medicine should be withdrawn and appropriate treatment should be given.
- have to take this medicine for longer periods. You may develop resistant germs, which may need to be treated with other drugs.
- have severe or persistent diarrhoea with stomach pain or cramps during or shortly after treatment. Stop taking Cefuroxime and contact your doctor immediately. Medicines which may slow or stop bowel movements must not be taken.
- have been told that your kidneys are not working as well as they should be.
- are taking diuretics (water tablets/injections which cause increased urination), or other antibiotics called aminoglycosides. It might be necessary to check your kidneys often during treatment.

Cefuroxime is not suitable for everyone. Before treatment with Cefuroxime, talk to your doctor or pharmacist if any of the above applies to you.

Like all medicines used to treat meningitis (infection of the membranes and fluid surrounding the brain and spinal cord), Cefuroxime treatment may take a while to clear the body of all the meningitis infection. Because of this, hearing loss caused by meningitis has occurred in a few patients after using Cefuroxime to treat the disease.

Blood and urine tests
This medicine can also alter the results of urine tests for sugar (such as Benedict's, Fehling's or Clinitest). If you have diabetes and routinely test your urine, tell your doctor. This is because, other tests may have to be used to monitor your diabetes while you are taking this medicine.

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

This medicine when given at high dosage can be affected by other medicines that are removed by the kidneys. This is especially true if these other medicines also affect how well the kidneys work. There are many medicines that can do this. Tell your doctor or pharmacist if you are taking any of the following:
- Diuretics (water tablets/injections which cause increased urination) such as furosemide.
- Antibiotics called aminoglycosides. It might be necessary to check your kidneys often during treatment. This can be done with blood and urine tests.
- Antibiotics such as tetracyclines, macrolides and chloramphenicol.
- Probenecid (drug used in the treatment of gout).

Taking Cefuroxime with food and drink
Food/meals have no influence on the effectiveness of Cefuroxime as it is given by injection or infusion.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine. Before starting treatment, you must tell your doctor if you are pregnant or if you intend to become pregnant. Cefuroxime is not known to harm the unborn child, but has not been deemed as safe. It will only be given to a pregnant woman if it is absolutely necessary.

Mothers who wish to breast-feed should discuss with their doctor. Small amounts of Cefuroxime enter the milk. Inform your doctor if your baby develops diarrhoea or if you notice anything unusual.
Driving and using machines
There is currently no information available about the effect of Cefuroxime on the ability to drive and use machines. However, if you feel light-headed or dizzy, do not drive and check with your doctor.

Important information about some of the ingredients of this product:
To be taken into consideration by patients under controlled sodium diet:

Cefuroxime 250 mg Powder for Solution for Injection:
This medicinal product contains 0.59 mmol (13.56 mg) of sodium per vial

Cefuroxime 750 mg Powder for Solution for Injection:
This medicinal product contains 1.77 mmol (40.69 mg) of sodium per vial

Cefuroxime 1.5 g Powder for Solution for Injection / Infusion:
This medicinal product contains 3.54 mmol (81.38 mg) of sodium per vial

3. HOW TO USE CEFUROXIME
Dosage
A doctor or nurse will usually administer the correct dose of Cefuroxime depending on the nature and severity of your illness, weight, age, and your general condition, including your kidney function. Always take Cefuroxime exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Your doctor may sometimes need to use Cefuroxime at the same time as other antibiotics (such as metronidazole or aminoglycoside) to help treat or prevent infection.

The usual dose is:

Adults
The usual dose for adults is 750mg given three times daily, either by intramuscular (into the muscle) or intravenous (into a vein) injection. For severe infections, a higher dose may be used, such as 1.5g (1500mg) three times daily. Bigger or more frequent doses are sometimes needed.

To treat meningitis (infection of the membranes and fluid surrounding the brain and spinal cord), 3g will be given three times daily intravenously (into a vein).

If Cefuroxime is given before an operation to prevent infection, it will be given as an injection of 1.5g in to the vein, 30-60 minutes before operation. Smaller doses of Cefuroxime may be given for one or two days after some surgical operations.

Infants and children
The dose for children is based on their weight. It is usually between 30 mg and 100 mg per kg body weight daily, divided in to three or four doses.

The usual dose for children for treatment of meningitis (infection of the membranes and fluid surrounding the brain and spinal cord) is 200 mg to 240 mg per kg body weight daily, in three or four divided doses intravenously (into a vein).

Newborns
For newborn babies, the dose is the same as for infants and children (between 30 mg and 100 mg per kg body weight daily), but divided in to two or three doses.

The usual dose for newborn babies for treatment of meningitis (infection of the membranes and fluid surrounding the brain and spinal cord) is 100mg per kg body weight daily intravenously (into a vein).

Patients with impaired kidney function
In patients with impaired kidney function, the dosage of Cefuroxime is usually reduced to compensate for its slower excretion. Depending upon the extent of kidney dysfunction, Cefuroxime 750 mg may
be given once or twice daily. Your doctor will calculate the right dose for you according to the results of blood or urine tests that measure how well your kidneys are functioning.

**Patients receiving dialysis**
For patients with renal failure on continuous arteriovenous haemodialysis or high-flux haemofiltration the dose is 750mg twice daily.

For patients who have haemodialysis courses, the appropriate dose is repeated after each haemodialysis period. This is because some of the Cefuroxime may be removed from the body during this type of dialysis and thus needs to be replaced.

**How to prepare and administer Cefuroxime**
Cefuroxime is supplied as a powder, so it must be made into a solution before it can be given. Only some types of solutions can be used to mix with the powder to make it ready for use. Your doctor or nurse will use the proper solutions to prepare a fresh solution of Cefuroxime for administration.

If you have been instructed to give Cefuroxime to yourself, make sure that you understand how to mix the powder with the solutions that you are given.

Cefuroxime will usually be given by a doctor or nurse either intramuscularly (into the large muscles of the leg or buttock) or intravenously (into a vein). In some infections, your medicine will be given to you through a “drip” intravenous infusion over a longer period of time (up to 30 minutes).

**How frequently you should be given Cefuroxime**
Cefuroxime is usually given two to three times a day.

**Duration of treatment**
Your doctor will advise you on how long your treatment should last. The duration of therapy will depend on how severe your infection is, and how well you are responding to the treatment.

**If you take more Cefuroxime than you should**
Since a doctor or nurse will give you Cefuroxime, it is very unlikely that you will be given too much Cefuroxime. Rarely, you may be asked by your doctor or nurse to give yourself Cefuroxime at home. If you think you or someone you know has received too much medicine, please tell your doctor or nurse immediately or contact the nearest hospital emergency department.

The following reactions and symptoms have been seen when very high doses of Cefuroxime have been given by mistake, or if large amounts of the medicine are accidentally taken: irritation of the brain and shaking fits (convulsions). In addition to treatment of the symptoms of overdose, the doctor may also try to reduce the levels of Cefuroxime in the blood by dialysis.

**If you forget to take Cefuroxime**
Since a doctor or nurse will give you Cefuroxime, it is very unlikely that you will miss a dose. If you think you may have missed a dose please tell your doctor or nurse. A double dose should not be used to make up for a forgotten dose.

**If you stop taking Cefuroxime**
You must use your medication exactly as directed. Do not stop your therapy on your own for any reason because your infection could worsen and result in hospitalization. Do not change your dosage schedule without talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.
4. POSSIBLE SIDE EFFECTS
Like all medicines, Cefuroxime can cause side effects, although not everybody gets them.

Serious side effects
Serious allergic reactions to Cefuroxime are very rare (affect fewer than one in ten thousand people). These can include:
- Sudden wheezing and tightness of the chest
- Swelling of eyelids, face or lips
- Severe skin rashes that can blister and may include the eyes, mouth, throat and genitals
- Loss of consciousness (fainting)

All of these allergic reactions need urgent medical attention. If you think you are having any of these reactions, you must tell your doctor or nurse immediately. If you are giving yourself Cefuroxime at home, stop taking Cefuroxime and contact your doctor or nearest hospital emergency department.

Common side effects (affect fewer than one in a ten people)
- Neutropenia (reduction in the number of a type of white blood cell called neutrophil)
- Eosinophilia (abnormal increase in the number of a type of white blood cell called eosinophil)
- Blood tests which show changes in certain liver enzymes
- Pain or inflammation at the site of injection

Uncommon side effects (affect fewer than one in a hundred people)
- Reduced number of different white blood cells, which makes infections more likely
- Reduced haemoglobin (a chemical present in the red blood cells which binds to oxygen, and takes oxygen from the lungs to all parts of the body)
- Digestive system problems like feeling sick (nausea) or being sick (vomiting), diarrhoea, stomach and intestinal discomfort
- Liver and bile problems: a reversible increase in bilirubin (this chemical gives bile its yellow/green colour) in your blood
- Skin rashes
- Lumpy rash (hives)
- Itching
- This medicine can also alter the results of some blood tests (such as Coombs’ test and cross-matching blood test). If you are having a blood test for any reason, tell the person who is taking your blood sample that you are taking this medicine as it may affect your result

Rare side effects (affect fewer than one in a thousand people)
- Infections: having a course of Cefuroxime can temporarily increase the risk of getting infections caused by other types of germs. For example, thrush (an infection caused by yeast called Candida) in the mouth or vagina can occur
- Reduction in blood platelets, which increases the risk of bleeding or bruising
- Fever

Very rare side effects (affect fewer than one in ten thousand people)
- Anaemia (reduction in red blood cells, which can make the skin pale or yellow and cause weakness or breathlessness)
- Serious allergic reactions, which cause difficulty breathing or dizziness
- Very rare infection of the large bowel that needs special treatment. So, if you have severe diarrhoea or if you see blood in your diarrhoea, you should stop taking this medicine and contact your doctor immediately
- Serious illness with swelling, reddening and blistering of the skin, mouth, eyes and genitals
- Inflammation of the kidney affecting its structure and function
- Changes in blood tests that check how your kidneys are working
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CEFUROXIME
Keep out of reach and sight of children.
Do not use Cefuroxime after the expiry date, which is stated on the label.
The expiry date refers to the last day of that month.
This medicinal product does not require any special storage conditions.
Keep vial(s) in the outer carton.
After the solution is made, it may be stored at 2-8°C for up to 24 hours.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION
What Cefuroxime contains:
The active substance is Cefuroxime Sodium. There are no other ingredients.
Each vial of 250mg, 750mg & 1.5g contains 263mg, 789mg & 1.578g of cefuroxime sodium equivalent to 250mg, 750mg & 1.5g of cefuroxime, respectively.

What Cefuroxime looks like and contents of the pack
Cefuroxime is a white to faint yellow, amorphous sterile powder packaged in 20ml / 100ml clear glass vial and sealed with grey bromo butyl rubber stopper and coloured flip off seal.

Pack of 1 vial in a carton along with the PIL.

Marketing Authorisation Holder and Manufacturer
Orchid Europe Ltd
Building 3, Chiswick Park,
566, Chiswick High Road,
Chiswick, London, W4 5YA
United Kingdom.

This medicinal product is authorised in the Member States of the EEA under the following names:
Belgium:
Cefuroxime Orchid Europe Ltd 250 mg Poeder voor oplossing voor injectie
Cefuroxime Orchid Europe Ltd 750 mg Poeder voor oplossing voor injectie
Cefuroxime Orchid Europe Ltd 1.5 g Poeder voor oplossing voor injectie of infusie

Cefuroxime Orchid Europe Ltd 250 Poudre pour solution pour injectable
Cefuroxime Orchid Europe Ltd 750 Poudre pour solution pour injectable
Cefuroxime Orchid Europe Ltd 1.5 g Poudre pour solution injectable ou pour perfusion

Cefuroxime Orchid Europe Ltd 250 Pulver zur Herstellung einer Injektionslösung
Cefuroxime Orchid Europe Ltd 750 Pulver zur Herstellung einer Injektionslösung
Cefuroxime Orchid Europe Ltd 1.5 g Pulver zur Herstellung einer injektionslösung/ Infusionslösung

Germany:
Cefuroxime Orchid Europe Ltd 250 mg Pulver zur Herstellung einer injektionslösung
Cefuroxime Orchid Europe Ltd 750 mg Pulver zur Herstellung einer injektionslösung
Cefuroxime Orchid Europe Ltd 1.5 g Pulver zur Herstellung einer Injektionslösung/ Infusionslösung

Spain:
Cefuroxime 250 mg polvo para solución inyectable
Cefuroxime 750 mg polvo para solución inyectable
Cefuroxime 1.5 g polvo para solución inyectable o para perfusión
The Netherlands:
Cefuroxime Orchid Europe Ltd 250 mg Poeder voor oplossing voor injectie
Cefuroxime Orchid Europe Ltd 750 mg Poeder voor oplossing voor injectie
Cefuroxime Orchid Europe Ltd 1.5 g Poeder voor oplossing voor injectie of infusie

United Kingdom:
Cefuroxime 250 mg Powder for solution for injection
Cefuroxime 750 mg Powder for solution for injection
Cefuroxime 1.5 g Powder for solution for injection/infusion

Italy:
Cefuroxime Orchid Europe Ltd 250 mg Polvere per soluzione iniettabile
Cefuroxime Orchid Europe Ltd 750 mg Polvere per soluzione iniettabile
Cefuroxime Orchid Europe Ltd 1.5 g Polvere per soluzione iniettabile/infusion

Poland:
Cerufoksym Orchid Europe Ltd

This leaflet was last approved in {09/2010}
INFORMATION FOR THE HEALTHCARE PROFESSIONAL
The following information is intended for medical or healthcare professionals only.

Instructions for use and handling:
For single use only: Any unused product or waste material should be disposed of in accordance with local requirements, immediately after use.

Intramuscular use
Add 1ml water for injection to Cefuroxime 250mg or at least 3ml for Cefuroxime 750mg Powder for Injection.

Shake gently to produce an opaque suspension.

Intravenous use
Dissolve in water for Injection using at least 2 ml for Cefuroxime 250mg, 6ml for Cefuroxime 750mg or 15ml for Cefuroxime 1.5g to produce a clear solution. For short intravenous infusion (e.g. up to 30 minutes), Cefuroxime 1.5g may be dissolved in 15ml water for injection, add the reconstituted solution of Cefuroxime sodium to 50 or 100ml of any of the compatible infusion solution mentioned below.

Reconstituted solution may be diluted with:

- 5% glucose injection
- 0.9% sodium chloride injection
- 0.18% sodium chloride + 4% glucose
- Hartman’s solution

The contents and concentrations of cefuroxime as a suspension/solution are shown in the table below:

<table>
<thead>
<tr>
<th>Cefuroxime per vial (mg)</th>
<th>Route of administration</th>
<th>Volume of solvent to be added (mL)</th>
<th>Final volume of suspension/solution (mL)</th>
<th>Concentration of suspension/solution (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td>IM</td>
<td>1</td>
<td>1.2</td>
<td>208</td>
</tr>
<tr>
<td></td>
<td>IV Bolus</td>
<td>2</td>
<td>2.2</td>
<td>114</td>
</tr>
<tr>
<td>750</td>
<td>IM</td>
<td>3</td>
<td>3.5</td>
<td>214</td>
</tr>
<tr>
<td></td>
<td>IV Bolus</td>
<td>6</td>
<td>6.7</td>
<td>112</td>
</tr>
<tr>
<td>1500</td>
<td>IV Bolus</td>
<td>15</td>
<td>16.2</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>IV Infusion</td>
<td>15 + 50</td>
<td>66.5</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>IV Infusion</td>
<td>15 +100</td>
<td>116.4</td>
<td>13</td>
</tr>
</tbody>
</table>

These solutions may be given directly into the vein or introduced into the tubing of the giving set of a compatible parenteral infusion.

Storing Cefuroxime Injection:
This medicinal product does not require any special storage conditions.
Keep vial(s) in outer carton.

Reconstituted solution: Chemical and physical stability has been demonstrated for 24 hours at 2°C-8°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally be no longer than 24 hours at 2-8°C unless reconstitution has taken place in controlled and validated aseptic conditions.
Incompatibilities
Solutions containing Cefuroxime should not be mixed with or added to solutions containing other agents other than those mentioned above.

The pH of 2.74% w/v sodium bicarbonate injection BP considerably affects the colour of solutions and therefore this solution is not recommended for the dilution of Cefuroxime powder for injection. However, if required, for patients receiving sodium bicarbonate injection by infusion, the Cefuroxime powder for injection may be introduced into the tube of the giving set.

Cefuroxime powder for injection should not be mixed in the same syringe with aminoglycoside antibiotics.

Usually Cefuroxime is effective when administered alone, but when appropriate it may be used in combination with metronidazole or an aminoglycoside apart from each other.
### Module 4
Labelling

<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS (Vial)</th>
</tr>
</thead>
</table>

#### 1. NAME OF THE MEDICINAL PRODUCT

Cefuroxime 250mg Powder for solution for injection
Cefuroxime

#### 2. STATEMENT OF ACTIVE SUBSTANCE (S)

Each vial contains 263 mg of cefuroxime sodium equivalent to 250mg of cefuroxime. Also contains 0.59 mmol (13.56 mg) of sodium per vial.

#### 3. LIST OF EXCIPIENTS

--

#### 4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection

#### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous or intramuscular use
Read the package leaflet before use

#### 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

#### 7. OTHER SPECIAL WARNING(S), IF NECESSARY

--

#### 8. EXPIRY DATE

EXP:
After Reconstitution: Store at 2 - 8°C for up to 24 hours

#### 9. SPECIAL STORAGE CONDITIONS

This medicinal product does not require any special storage conditions.
Keep the vial in the outer carton.
Use as directed by the physician.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

The vial is for single use only. Discard any unused portion

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Orchid Europe Ltd.
UK.

12. MARKETING AUTHORISATION NUMBER(S)

PL 22805/0023

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE
PARTICULARS TO APPEAR ON THE OUTER PACKAGING (Carton)

1. NAME OF THE MEDICINAL PRODUCT

Cefuroxime 250mg Powder for solution for injection
Cefuroxime

2. STATEMENT OF ACTIVE SUBSTANCE (S)

Each vial contains 263 mg of cefuroxime sodium equivalent to 250mg of cefuroxime. Also contains 0.59 mmol (13.56 mg) of sodium per vial.

3. LIST OF EXCIPIENTS

--

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous or intramuscular use

For I.M. injection: Add 1ml water for injection. Shake gently to produce an opaque suspension.
For I.V. bolus injection: Dissolve in 2 ml water for injection to produce a clear solution.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

--

8. EXPIRY DATE

EXP:

After Reconstitution: Store at 2 - 8°C for up to 24 hours

9. SPECIAL STORAGE CONDITIONS

This medicinal product does not require any special storage conditions.

Use as directed by the physician
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

The vial is for single use only. Discard any unused portion.

11. NAME AND ADDRESS OF THE MARKETING AUTHORITY OF THE MARKETING AUTHORITY

Orchid Europe Ltd.
Building 3, Chiswick Park, 566, Chiswick High Road,
Chiswick, London, W4 5YA
United Kingdom.

12. MARKETING AUTHORIZATION NUMBER(S)

PL 22805/0023

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
**PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS (Vial)**

**1. NAME OF THE MEDICINAL PRODUCT**

Cefuroxime 750 mg Powder for solution for injection
Cefuroxime

**2. STATEMENT OF ACTIVE SUBSTANCE (S)**

Each vial contains 789 mg of cefuroxime sodium equivalent to 750 mg of cefuroxime. Also contains 1.77 mmol (40.69 mg) of sodium per vial.

**3. LIST OF EXCIPIENTS**

--

**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder for solution for injection

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

For intravenous or intramuscular use
Read the package leaflet before use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

--

**8. EXPIRY DATE**

EXP:
After Reconstitution: Store at 2 - 8°C for up to 24 hours

**9. SPECIAL STORAGE CONDITIONS**

This medicinal product does not require any special storage conditions.
Keep the vial in the outer carton.
Use as directed by the physician.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

The vial is for single use only. Discard any unused portion

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Orchid Europe Ltd.
UK.

12. MARKETING AUTHORISATION NUMBER(S)

PL 22805/0024

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING (Carton)**

<table>
<thead>
<tr>
<th><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefuroxime 750mg Powder for solution for injection</td>
</tr>
<tr>
<td>Cefuroxime</td>
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</table>

<table>
<thead>
<tr>
<th><strong>2. STATEMENT OF ACTIVE SUBSTANCE (S)</strong></th>
</tr>
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<tbody>
<tr>
<td>Each vial contains 789 mg of cefuroxime sodium equivalent to 750mg of cefuroxime.</td>
</tr>
<tr>
<td>Also contains 1.77 mmol (40.69 mg) of sodium per vial.</td>
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<tr>
<th><strong>3. LIST OF EXCIPIENTS</strong></th>
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</table>

<table>
<thead>
<tr>
<th><strong>4. PHARMACEUTICAL FORM AND CONTENTS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Powder for solution for injection</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>5. METHOD AND ROUTE(S) OF ADMINISTRATION</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>For intravenous or intramuscular use</td>
</tr>
<tr>
<td><strong>For I.M. injection:</strong> Add 3 ml water for injection. Shake gently to produce an opaque suspension.</td>
</tr>
<tr>
<td><strong>For I.V. bolus injection:</strong> Dissolve in 6 ml water for injection to produce a clear solution.</td>
</tr>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the reach and sight of children</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>7. OTHER SPECIAL WARNING(S), IF NECESSARY</strong></th>
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<tbody>
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<tr>
<th><strong>8. EXPIRY DATE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP:</td>
</tr>
<tr>
<td>After Reconstitution: Store at 2 - 8°C for up to 24 hours</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>9. SPECIAL STORAGE CONDITIONS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>This medicinal product does not require any special storage conditions.</td>
</tr>
<tr>
<td>Use as directed by the physician</td>
</tr>
</tbody>
</table>


10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

The vial is for single use only. Discard any unused portion.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Orchid Europe Ltd.
Building 3, Chiswick Park, 566, Chiswick High Road,
Chiswick, London, W4 5YA
United Kingdom.

12. MARKETING AUTHORISATION NUMBER(S)

PL 22805/0024

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
(Vial)

1. NAME OF THE MEDICINAL PRODUCT

Cefuroxime 1.5 g Powder for solution for injection/infusion
Cefuroxime

2. STATEMENT OF ACTIVE SUBSTANCE (S)

Each vial contains 1.578g of cefuroxime sodium equivalent to 1.5g of cefuroxime. Also contains 3.54 mmol (81.38 mg) of sodium per vial.

3. LIST OF EXCIPIENTS

--

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection or infusion.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

--

8. EXPIRY DATE

EXP:
After Reconstitution: Store at 2 - 8°C for up to 24 hours.

9. SPECIAL STORAGE CONDITIONS

This medicinal product does not require any special storage conditions. Keep the vial in the outer carton. Use as directed by the physician.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

The vial is for single use only. Discard any unused portion.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Orchid Europe Ltd.
UK.

12. MARKETING AUTHORISATION NUMBER(S)

PL 22805/0025
PL 22805/0026

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE
1. NAME OF THE MEDICINAL PRODUCT

Cefuroxime 1.5 g Powder for solution for injection/infusion

2. STATEMENT OF ACTIVE SUBSTANCE (S)

Each vial contains 1.578g of cefuroxime sodium equivalent to 1.5g of cefuroxime. Also contains 3.54 mmol (81.38 mg) of sodium per vial.

3. LIST OF EXCIPIENTS

--

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection or infusion.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

20 ml vial – For intravenous injection
100 ml vial – For intravenous infusion

For I.V. bolus injection: Dissolve in 15 ml water for injection to produce a clear solution.
For short I.V. infusion: Dissolve in 15 ml water for injection and then add to 50 or 100 ml of any of the compatible infusion solution.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

--

8. EXPIRY DATE

EXP:
After Reconstitution: Store at 2 - 8°C for up to 24 hours.

9. SPECIAL STORAGE CONDITIONS

This medicinal product does not require any special storage conditions.
Use as directed by the physician.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

The vial is for single use only. Discard any unused portion.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Orchid Europe Ltd.
Building 3, Chiswick Park, 566, Chiswick High Road,
Chiswick, London, W4 5YA
United Kingdom.

12. MARKETING AUTHORISATION NUMBER(S)

PL 22805/0025
PL 22805/0026

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Cefuroxime 250 mg Powder for solution for injection, Cefuroxime 750 mg Powder for solution for injection and Cefuroxime 1.5 g Powder for solution for injection/infusion (PL 22805/0023-6; UK/H/1485/001-4/DC) could be approved. These applications were submitted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Belgium, Germany, Spain, Italy, The Netherlands and Poland as Concerned Member States (CMS).

The products are prescription-only medicines (POM) indicated for the treatment of the following infections caused by susceptible organisms:

- lower respiratory tract infections: acute exacerbation of chronic bronchitis, bacterial pneumonia.
- urinary tract infections.
- soft tissue infections.
- bone and joint infections.
- obstetric and gynaecological infections.
- meningitis.
- prophylaxis against infection in abdominal, pelvic, orthopaedic, cardiac, pulmonary, oesophageal and vascular surgery.

These applications made according to Article 10.1 of 2001/83/EC, as amended claiming to be generic medicinal products of Zinacef 250mg, 750mg and 1500mg powder for solution for injection or infusion, which were originally granted licences to Glaxo Operations UK Ltd, UK (trading as GlaxoSmithKline) in April 1978.

Cefuroxime belongs to a group of medicines called second-generation cephalosporins. It is a semi-synthetic derivative of cephalosporanic acid and exerts antibacterial activity by inhibition of bacterial cell wall synthesis in susceptible species. Cefuroxime has good stability to several bacterial beta-lactamase enzymes and, consequently, is active against many penicillin-resistant or ampicillin and amoxicillin-resistant strains of susceptible species.

Cefuroxime binds to cell receptors, called penicillin-binding proteins. After a β-lactam antibiotic has bound to these receptors, the transpeptidation reaction is inhibited and peptidoglycan synthesis is blocked. This results in bacterial lysis.

No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.
The RMS and CMS considered that the applications could be approved with the end of procedure (Day 210) on 01 September 2010. After a subsequent national phase, the licences were granted in the UK on 05 October 2010.
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Cefuroxime 250 mg Powder for solution for injection  
Cefuroxime 750 mg Powder for solution for injection  
Cefuroxime 1.5 g Powder for solution for injection/infusion |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Cefuroxime sodium</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Second generation cephalosporin, (J01DC02)</td>
</tr>
</tbody>
</table>
| Pharmaceutical form and strength(s)              | 250mg and 750mg: Powder for solution for injection  
1.5g: Powder for injection or infusion               |
| Reference numbers for the Mutual Recognition Procedure | UK/H/1485/001-4/DC                                                                                       |
| Reference Member State (RMS)                     | United Kingdom                                                                                             |
| Concerned Member States (CMS)                    | UK/H/1485/001-2 & 004/DC: Belgium, Germany, Spain, Italy, The Netherlands and Poland.  
UK/H/1485/003/DC: Germany, Spain, Italy, The Netherlands and Poland. |
| Marketing Authorisation Number(s)                | PL 22805/0023-6                                                                                            |
| Name and address of the authorisation holder      | Orchid Europe Ltd, Building 3, Chiswick Park, 566 Chiswick High Road, Chiswick, London, W4 5YA, UK        |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Cefuroxime sodium


Structure:

![Structure of Cefuroxime Sodium]

Molecular formula: C_{16}H_{15}N_{4}NaO_{8}S

Molecular mass: 446.4 (cefuroxime sodium)

424.4 (cefuroxime)

Appearance: Cefuroxime sodium is a white or almost white powder, slightly hygroscopic, freely soluble in water, very slightly soluble in alcohol. It does not exhibit polymorphism.

Cefuroxime sodium is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance cefuroxime sodium are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

P. Medicinal Product

Other Ingredients

No other excipients are used in this product.

Pharmaceutical Development

The objective of the development programme was to formulate products that could be considered generic medicinal products of the reference products Zinacef 250mg, 750mg and 1500mg powder for solution for injection or infusion, which were originally granted licences to Glaxo Operations UK Ltd, UK (trading as GlaxoSmithKline) in April 1978.

Details of the pharmaceutical development of the product have been supplied and are satisfactory.

Comparative impurity profiles have been provided for all strengths of proposed and originator products.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of all strengths of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.
Finished Product Specification
The finished product specifications proposed are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Container-Closure System
Each 250mg, 750mg and 1.5g powder for solution for injection strength carton contains:
One 20 ml Type I glass vial with a grey bromo butyl rubber stopper and a coloured flip-off seal (250mg seal is red, 750mg is blue and 1.5g strength is white).

Each 1.5g powder for solution for infusion carton contains:
One 100 ml Type I glass vial with a grey bromo butyl rubber stopper and a white flip-off seal.

The Marketing Authorisation Holder has stated that they do not intend to market all pack sizes of the products in all member states at this present time. However, they have committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years, with no special storage conditions for the dry powder.

When prepared under aseptic condition the reconstituted product has demonstrated chemical and physical stability for 24 hours when stored in a refrigerator at 2-8°C. From a microbiological point of view, once opened, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, when prepared in Water for Injections or any of the injections listed in Section 6.6 of the SmPC.

Bioequivalence/bioavailability
No bioequivalence studies have been submitted and none are required to support applications of this type.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPC, PIL and labels 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, as amended. 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.

The Marketing Authorisation Holder has stated that they do not intend to market all pack sizes of the products in all member states at this present time. However, they have committed
to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
There are no objections to the approval of these products from a pharmaceutical viewpoint.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of cefuroxime sodium are well-known, no new non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment.

There are no objections to the approval of these products from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS
Pharmacokinetics
In accordance with Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), point 5.1.6, a bioequivalence study is not requested if the product is an aqueous intravenous solution containing the same active substance in the same concentration as the currently licensed product.

Efficacy
No new efficacy data were submitted and none were required for these applications.

Safety
No new safety data were submitted and none were required for these applications

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPC, PIL and labels are medically acceptable. The SPCs are consistent with those for the originator products. The PIL is consistent with the SPC and in-line current guidelines. The labelling is in-line with current guidelines.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan
The pharmacovigilance system, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person
responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a risk management plan for these applications.

Conclusion
There are no objections to the approval of these applications from a clinical viewpoint.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The important quality characteristics of Cefuroxime 250 mg Powder for solution for injection, Cefuroxime 750 mg Powder for solution for injection and Cefuroxime 1.5 g Powder for solution for injection/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.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
No new efficacy data were submitted and none were required for these applications.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The SPCs, PIL and labelling are satisfactory and consistent with those for the reference products, where appropriate.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with cefuroxime sodium is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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