Public Assessment Report

Decentralised Procedure

Cefuroxime 250mg powder for solution for injection
Cefuroxime 750mg powder for solution for injection
Cefuroxime 1.5g powder for solution for injection or infusion

Procedure Nos: UK/H/2112/001-3/DC

UK Licence Nos: PL 30306/0160-2

Actavis Group PTC ehf
On 06 September 2010, Denmark, Finland, Ireland, Norway, the Netherlands, Poland, Portugal, Sweden, Estonia, Lithuania, Latvia and the UK agreed to grant Marketing Authorisations to Actavis Group PTC ehf for the medicinal products Cefuroxime 250mg and 750mg powder for solution for injection (PL 30306/0160-1; UK/H/2112/001-2/DC) and Cefuroxime 1.5g powder for solution for injection or infusion (PL 30306/0162; UK/H/2112/003/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 16 November 2010. These are prescription-only medicines (POM) for the treatment of infections, including infections of the chest and kidneys. These medicines may also be given before an operation for the prevention of infection.

Cefuroxime 250mg and 750mg powder for solution for injection, and Cefuroxime 1.5g powder for solution for injection or infusion, contain the active ingredient cefuroxime sodium. Cefuroxime sodium belongs to a group of antibiotics called cephalosporins. Antibiotics are used to kill the bacteria or ‘germs’ that cause infections.

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

<table>
<thead>
<tr>
<th>Module</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Module 1: Information about initial procedure</td>
<td>4</td>
</tr>
<tr>
<td>Module 2: Summary of Product Characteristics</td>
<td>5</td>
</tr>
<tr>
<td>Module 3: Product Information Leaflet</td>
<td>32</td>
</tr>
<tr>
<td>Module 4: Labelling</td>
<td>34</td>
</tr>
<tr>
<td>Module 5: Scientific Discussion</td>
<td>41</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></td>
</tr>
</tbody>
</table>
Module 1
Information about the initial procedure

| Product Names | UK/H/2112/001/DC: Cefuroxime 250mg powder for solution for injection  
UK/H/2112/002/DC: Cefuroxime 750mg powder for solution for injection  
UK/H/2112/003/DC: Cefuroxime 1.5g powder for solution for injection or infusion |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Application</td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td>Active Substances</td>
<td>Cefuroxime sodium</td>
</tr>
</tbody>
</table>
| Form | UK/H/2112/001-2/DC: Powder for Solution for Injection  
UK/H/2112/003DC: Powder for Solution for Injection or Infusion |
| Strength | Powder for solution for injection: 250mg and 750mg  
Powder for solution for injection or infusion: 1.5g |
| MA Holder | Actavis Group PTC ehf  
Reykjavikurvegi 76-78  
220 Hafnarfjordur  
Iceland |
| Reference Member State (RMS) | UK |
| Concerned Member States (CMS) | UK/H/2112/001/DC: Denmark, Finland, Ireland, Norway, the Netherlands, Poland, Portugal, Sweden  
UK/H/2112/002/DC: Denmark, Finland, Ireland, Norway the Netherlands, Poland, Portugal, Sweden, Estonia  
UK/H/2112/003/DC: Denmark, Finland, Ireland, Norway the Netherlands, Poland, Portugal, Sweden, Estonia, Lithuania, Latvia |
| Procedure Number | UK/H/2112/001-3/DC |
| Timetable | Day 210 – 06 September 2010 |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Cefuroxime 250mg Powder for Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains cefuroxime sodium equivalent to 250 mg cefuroxime.
Each vial contains approximately 14 mg sodium.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Powder for solution for injection.
Cefuroxime is white to faintly yellow powder.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Cefuroxime is indicated for the treatment of the following infections when caused by susceptible organisms.
Respiratory tract infections: acute exacerbation of chronic bronchitis, hospital acquired pneumonia, severe community acquired pneumonia.
Upper urinary tract infections: pyelonephritis.
Peri-operative prophylaxis against infection in abdominal, orthopaedic and cardiac surgery.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration
Usual dosage for adolescents (aged 12 years to 17 years), adults and the elderly:
The dosage is 1.5 g/day to 6 g/day. In most infections a sufficient dose is 750 mg every 8 hour. In more severe infections the dose should be increased to 1.5 g every 8 hour by intravenous injection.
If necessary, the dosage frequency can be increased to every 6 hour up to total daily dose of 6g.

Prophylaxis
The usual dose is 1500 mg (1.5 g) intravenously with induction of anaesthesia for abdominal and orthopaedic operations, but may be supplemented with two 750 mg intramuscular doses eight and sixteen hours later. In cardiac operations, the usual dose is 1500 mg (1.5 g) intravenously with induction of anaesthesia continuing with 750 mg intramuscularly three times daily for a further 24 hours to 48 hours.

Dosage in impaired renal function for adolescents, adults and elderly
It is not necessary to reduce the dose if creatinine clearance is more than 20 ml/min. The recommended maintenance dose in impaired renal function is as follows:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Recommended dosage of cefuroxime (mg)</th>
<th>Frequency of dosage (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;20</td>
<td>Normal dose</td>
<td></td>
</tr>
<tr>
<td>10-20</td>
<td>750</td>
<td>12</td>
</tr>
<tr>
<td>&lt;10</td>
<td>750</td>
<td>24</td>
</tr>
<tr>
<td>Patients on continuous arteriovenous haemofiltration/haemodialysis</td>
<td>750</td>
<td>12</td>
</tr>
</tbody>
</table>

Special precautions are required if creatinine clearance is <10 ml/minute and treatment should take place under appropriate expert supervision (see section 4.4).

Serum concentration of cefuroxime should be monitored in patients with severe renal impairment.
For patients on haemodialysis a further 750 mg dose, by intravenous or intramuscular injection, should be given at the end of each session.

For low-flux haemofiltration follow the dosage recommended under impaired renal function.

**Paediatric patients**

*Preterm (born at <36 weeks of gestation) and term newborn infants (age 0–27 days):*

Cefuroxime is not recommended for the use in these age groups due to insufficient data on safety and efficacy. In the first weeks of life the serum half-life of cefuroxime can be three to five times that in adults (see section 5.2).

*Infants, toddlers (age 28 days to 23 months) and children (2 years to 11 years):*

The recommended dosage range is 30 to 100 mg/kg/day given as three or four divided doses. Most infections will respond to a dose of 60 mg/kg/day.

*Infants, toddlers (28 days to 23 months) and children (2 years to 11 years) with impaired renal function:*

There are insufficient data regarding use of cefuroxime in paediatric renal insufficiency and therefore such use is not recommended.

**Route of Administration:**

Cefuroxime 250mg Powder for Solution for Injection may be administered by intramuscular injection or intravenous injection (within 3–5 minutes), see section 6.6.

Intramuscular administration should be limited on special indication and/or exceptional clinical situations after benefit-risk-assessment. Intramuscular administration 3 times a day is not recommended.

Doses above 750 mg of cefuroxime should not be administered intramuscularly.

### 4.3 Contraindications

- Hypersensitivity to cefuroxime or to any of the cephalosporins.
- Previous immediate and/or severe hypersensitivity reaction to penicillin or to any other type of beta-lactam medicinal products.

### 4.4 Special warnings and precautions for use

Special care is indicated in patients who have experienced an allergic reaction to penicillins or beta-lactam antibiotics as cross-reactions may occur (for contraindications due to known hypersensitivity reactions see section 4.3).

If after administration of cefuroxime sodium hypersensitivity reactions occur, the use of cefuroxime sodium should be discontinued immediately and an appropriate treatment measures should be initiated.

Special care should be taken in patients with hepatic dysfunction.

As with other antibiotics, use of cefuroxime sodium may result in the overgrowth of *Candida*. Prolonged use may also result in the overgrowth of other non-susceptible organisms (*e.g.* *Enterococci* and *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. Anti-peristaltics are contra-indicated.

Cefuroxime solution is incompatible with aminoglycoside antibiotics (see section 6.2).

The use of cefuroxime may be accompanied by a false positive Coombs test. This may interfere with the performance of cross matching tests with blood (see section 4.8).

Cefuroxime is excreted via the kidneys. Therefore a dose adjustment is required in patients with impaired renal function (see section 4.2).
Due to an increased risk of cefuroxime accumulation in serum accompanied by an increased risk for undesirable effects patients with a creatinine clearance < 10 ml/min should be treated under expert supervision.

As a precaution, renal function should be monitored if renal function is already impaired.

The sodium content of cefuroxime should be taken into account when prescribed to patients requiring sodium restriction.

There are insufficient data regarding use of cefuroxime in paediatric renal insufficiency and therefore such use is not recommended.

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially ‘sodium-free’.

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, amphotericin and aminoglycosides, as concomitant use increases the risk of nephrotoxicity.

Bacteriostatic antibiotics may interfere with the bactericidal action of cephalosporins. Therefore, 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 of cefuroxime are enhanced.

In common with other antibiotics, cefuroxime may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

Oral contraceptives should be supplemented with non-hormonal contraception measures during treatment with cefuroxime.

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 foetus/newborn child. To date no other relevant epidemiological data are available. Animal studies do not show any harmful effects on embryonal and foetal development (see section 5.3). Cefuroxime reaches the embryo/foetus via the placenta. Due to the limited clinical experience Cefuroxime 250mg Powder for Solution for Injection should only be used during pregnancy after careful risk/benefit, especially during the first trimester.

Lactation

Cefuroxime is excreted in human milk. Cefuroxime 250mg Powder for Solution for Injection 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 sensitisation should be borne in mind.

4.7 Effects on ability to drive and use machines

Cefuroxime may sometimes be associated with side effects, such as dizziness, that may impair the ability to drive a vehicle, operate machinery or to work safely.
4.8 Undesirable effects

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

- Very common \(\geq1/10\)
- Common \(\geq1/100\) to \(<1/10\)
- Uncommon \(\geq1/1,000\) to \(<1/100\)
- Rare \(\geq1/10,000\) to \(<1/1,000\)
- Very rare \(<1/10,000\)
- Not known (cannot be estimated from the available data).

Dependent on the dose and duration of the treatment, approximately 3% of all treated patients are expected to experience one or several of the adverse reactions mentioned below.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Undesirable effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Rare</td>
<td>Pseudomembranous colitis. As with other antibiotics prolonged use may lead to secondary superinfections caused by insusceptible organisms, e.g. <em>Candida</em>, <em>Enterococci</em> and <em>Clostridium difficile</em> (see section 4.4).</td>
</tr>
<tr>
<td>Blood and lymphatic system disorder</td>
<td>Uncommon</td>
<td>Eosinophilia, leucopenia, neutropenia, thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Decreased haemoglobin concentration, agranulocytosis</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Haemolytic anemia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Rare</td>
<td>Serum sickness</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Anaphylaxis (see section 4.4)</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Angioneutrotic oedema</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Uncommon</td>
<td>Headache, dizziness</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Vertigo, restlessness, nervousness, confusion</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Gastrointestinal disturbances such as diarrhoea, nausea and vomiting</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Uncommon</td>
<td>Transient increases of hepatic enzyme levels (AST, ALT and LDH) and serum bilirubin</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Jaundice</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Common</td>
<td>Skin rashes, urticaria, pruritus</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Common</td>
<td>Increased levels of creatinine and urea in serum, especially in patients with impaired renal function (see section 4.2 and 4.4)</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Acute interstitial nephritis. Nephrotoxicity. Acute renal tubular necrosis has followed excessive dosage and has also been associated with its use in older patients or those with pre-existing renal impairment (see section 4.2 and 4.4).</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Common</td>
<td>Pain at the injection site following intramuscular administration, thrombophlebitis and pain following intravenous injection, after rapid intravenous administration heat sensations or nausea may occur</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Drug fever</td>
</tr>
<tr>
<td>Investigations</td>
<td>Not known</td>
<td>The use of cefuroxime may be accompanied by a false positive Coombs test. This may interfere with the performance of cross matching tests with blood.</td>
</tr>
</tbody>
</table>

4.9 Overdose

Overdosage 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
ATC code: J01D C02

Mode of action
All cephalosporins (β-lactam antibiotics) inhibit cell wall production and are selective inhibitors of peptidoglycan synthesis. The initial step in drug action consists of binding of the drug 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, resulting in bacterial lysis.

PK/PD relationship
The efficacy is mainly determined by the length of time, during which the drug level is above the minimal inhibitory concentration of the pathogen

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 depressed 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.

Breakpoints
EUCAST (European Committee on Antimicrobial Susceptibility Testing) breakpoints:

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Susceptible</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae</td>
<td>≤ 8 mg/l</td>
<td>&gt; 8 mg/l</td>
</tr>
<tr>
<td>Staphylococcus spp.</td>
<td>_*</td>
<td>_*</td>
</tr>
<tr>
<td>Streptococcus spp. (A, B, C, G)</td>
<td>≤ 0.5 mg/l</td>
<td>&gt; 0.5 mg/l</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>≤ 0.5 mg/l</td>
<td>&gt; 1 mg/l</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>≤ 1 mg/l</td>
<td>&gt; 2 mg/l</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>≤ 1 mg/l</td>
<td>&gt; 2 mg/l</td>
</tr>
<tr>
<td>Non-species related</td>
<td>≤ 4 mg/l</td>
<td>&gt; 8 mg/l</td>
</tr>
</tbody>
</table>

The breakpoint pertains to a dosage of 1.5 g x 3 and to E.coli and Klebsiella spp only.
* Susceptibility of staphylococci to cefuroxime is inferred from the methicillin susceptibility. Methicillin (Oxacillin)-resistant staphylococci are resistant to cephalosporines.
** Based on serum pharmacokinetic.
Susceptability
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.

**Commonly susceptible species**

<table>
<thead>
<tr>
<th>Gram positive aerobes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus (methicillin-susceptible)</td>
</tr>
<tr>
<td>Staphylococcus saprophyticus*</td>
</tr>
<tr>
<td>Streptococcus agalactiae</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
</tr>
</tbody>
</table>

**Gram negative aerobes**

- Proteus mirabilis

**Species for which acquired resistance may be a problem**

<table>
<thead>
<tr>
<th>Gram positive aerobes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus epidermidis*</td>
</tr>
<tr>
<td>Staphylococcus haemolyticus*</td>
</tr>
<tr>
<td>Staphylococcus hominis*</td>
</tr>
<tr>
<td>Streptococcus pneumoniae*</td>
</tr>
</tbody>
</table>

**Gram negative aerobes**

- Citrobacter freundii
- Citrobacter koseri*
- Enterobacter aerogenes*
- Enterobacter cloacae*
- Escherichia coli
- Haemophilus influenzae
- Klebsiella oxytoca
- Klebsiella pneumoniae*                    |
- Moraxella catarrhalis                     |

**Inherently resistant organisms**

<table>
<thead>
<tr>
<th>Gram positive aerobes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterococcus spp.</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
</tr>
<tr>
<td>Staphylococcus aureus (methicillin-resistant)(1,2)</td>
</tr>
<tr>
<td>Staphylococcus epidermidis (methicillin-resistant)</td>
</tr>
</tbody>
</table>

**Gram negative aerobes**

- Acinetobacter baumannii
- Burkholderia cepacia
- Campylobacter spp.
- Morganella morganii
- Proteus vulgaris
- Pseudomonas aeruginosa
- Serratia spp.
- Stenotrophomonas maltophilia

**Anaerobes**

- Bacteroides spp.
- Clostridium difficile

**Others**

- Chlamydia spp.
- Chlamydophila spp.
- Legionella spp.
- Mycobacterium spp.
- Mycoplasma spp.

---

* Refers to German data (March 2007): At the time of publication of the table no current data were available. In primary literature, standard text books, and treatment recommendations susceptibility is anticipated.
+ Prevalence of bacterial resistance is >50% at least in one European country or region.
(1) Frequency of methicillin resistance is about 30 to 50% for all staphylococci in France and is usually observed in hospital.
(2) Staphylococcus resistant to methicillin are resistant to other beta-lactams.
(3) Streptococcus resistant to penicillin are always resistant to cefuroxime.
5.2 Pharmacokinetic properties

Absorption
Cefuroxime is poorly absorbed from the gastro-intestinal tract and is given by intramuscular or intravenous injection or infusion as the sodium salt. Following intravenous doses of 750 mg and 1,500 mg, serum peak concentrations (Cmax) were approximately 50 µg/ml and 100 µg/ml, respectively, after 15 minutes (tmax).

Peak plasma concentrations of 27 µg per ml have been achieved about 45 minutes after an intramuscular dose of 750 mg with measurable amounts present 8 hours after a dose.

Distribution
Cefuroxime is widely distributed in the body and levels, that exceed the MIC-values of most pathogens, are achieved pleural fluid, sputum, bone, synovial fluid, and aqueous humour, but only achieves therapeutic concentrations in the CSF when the meninges are inflamed. The volume of distribution ranges between 9.3 and 15.8 l/1.73 m² in healthy adults. About 33% to 50% of cefuroxime in the circulation is bound to plasma proteins. It diffuses across the placenta and has been detected in breast milk.

Biotransformation
Cefuroxime is metabolized only to a minor extent (<5%).

Elimination
The elimination half-life ranges between about 70 and 80 min after intramuscular or intravenous administration in healthy adults. Most of the dose of cefuroxime is excreted unchanged in active form. About 50% is excreted by glomerular filtration and about 50% through renal tubular secretion within 24 hours, with the majority being eliminated within 6 hours; high concentrations are achieved in the urine. Small amounts of cefuroxime are excreted in bile. The renal clearance is 136.0 and 169.6 ml/min/1.73 m² after 0.5 and 1 g cefuroxime intravenous and 137.9 and 146.3 ml/min/1.73 m² after 0.750 and 1 g cefuroxime intramuscular, respectively. The elimination is impaired in patients with impaired renal function.

Concomitant administration of oral probenecid slows tubular secretion of cefuroxime and decreases renal clearance by approximately 40%.

Oral probenecid (1 g) prolonged the half-life by 63% and increased the area under the concentration-time curve of intravenous cefuroxime (750 mg) by up to 50%.

Cefuroxime is dialysable and small amounts are removed by peritoneal dialysis.

Linearity/non-linearity
The peak plasma concentration and the area under the concentration curve increase with increasing dose.

Pharmacokinetics in special patient groups
The half-life of cefuroxime is prolonged in patients with renal impairment associated with the risk of accumulation. The serum half-life is 4.2 hours at a creatinine clearance of 23 ml/min and 22.3 hours at a creatinine clearance of 5 ml/min. Therefore dose adjustment is required in patients with impaired renal function (see section 4.2).

The serum half-life is prolonged in preterm and term newborn infants during the first weeks of life (3 to 5 times the value in adults).

5.3 Preclinical safety data
Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. 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. The most prominent treatment-related effect was tissue damage at the injection sites.

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. Cefuroxime has been shown to pass the placenta.

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

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.

6.3 Shelf life
2 years.

Reconstituted product:
Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

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

6.5 Nature and contents of container
20 ml type I glass vials, sealed with grey bromo butyl rubber stopper and coloured flip off seal.

Pack sizes:
1 vial, 5 vials, 10 vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
For single use only. Discard any unused solution.
Any unused product or waste material should be disposed of in accordance with local requirements.

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

Preparation of solution

Intramuscular
Add 1 ml water for injections to 250 mg Cefuroxime Powder for Solution for Injection. Shake gently to produce an opaque suspension.
Dissolve Cefuroxime 250mg Powder for Solution for Injection in water for injections using 2 ml for 250 mg. The reconstituted solution should appear yellowish.

The contents and concentrations of cefuroxime as 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>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>50</td>
<td>51.2</td>
<td>29</td>
</tr>
</tbody>
</table>

Cefuroxime is compatible with most commonly used intravenous fluids and electrolyte solutions. Water for injections is recommended for reconstitution, followed by dilution (prior to intravenous administration) with water for injections, 5% glucose injection or 0.9% sodium chloride injection. Cefuroxime sodium is also compatible with Hartmann's solution and 0.18% sodium chloride + 4% glucose.
1 NAME OF THE MEDICINAL PRODUCT
Cefuroxime 750mg Powder for Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains cefuroxime sodium equivalent to 750 mg cefuroxime.
Each 750 mg vial contains approximately 42 mg sodium.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Powder for solution for injection.
Cefuroxime is white to faintly yellow powder.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Cefuroxime is indicated for the treatment of the following infections when caused by susceptible organisms.

Respiratory tract infections: acute exacerbation of chronic bronchitis, hospital acquired pneumonia,
severe community acquired pneumonia.

Upper urinary tract infections: pyelonephritis.

Peri-operative prophylaxis against infection in abdominal, orthopaedic and cardiac surgery.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration
Usual dosage for adolescents (aged 12 years to 17 years), adults and the elderly:
The dosage is 1.5 g/day to 6 g/day. In most infections a sufficient dose is 750 mg every 8 hour. In more severe infections the dose should be increased to 1.5 g every 8 hour by intravenous injection.

If necessary, the dosage frequency can be increased to every 6 hour up to total daily dose of 6 g.

Prophylaxis
The usual dose is 1500 mg (1.5 g) intravenously with induction of anaesthesia for abdominal and orthopaedic operations, but may be supplemented with two 750 mg intramuscular doses eight and sixteen hours later. In cardiac operations, the usual dose is 1500 mg (1.5 g) intravenously with induction of anaesthesia continuing with 750 mg intramuscularly three times daily for a further 24 hours to 48 hours.

Dosage in impaired renal function for adolescents, adults and elderly
It is not necessary to reduce the dose if creatinine clearance is more than 20 ml/min. The recommended maintenance dose in impaired renal function is as follows:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Recommended dosage of cefuroxime (mg)</th>
<th>Frequency of dosage (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;20</td>
<td>Normal dose</td>
<td></td>
</tr>
<tr>
<td>10-20</td>
<td>750</td>
<td>12</td>
</tr>
<tr>
<td>&lt;10</td>
<td>750</td>
<td>24</td>
</tr>
<tr>
<td>Patients on continuous arteriovenous haemofiltration/haemodialysis</td>
<td>750</td>
<td>12</td>
</tr>
</tbody>
</table>

Special precautions are required if creatinine clearance is <10 ml/minute and treatment should take place under appropriate expert supervision (see section 4.4).

Serum concentration of cefuroxime should be monitored in patients with severe renal impairment.

For patients on haemodialysis a further 750 mg dose, by intravenous or intramuscular injection, should be given at the end of each session.
For low-flux haemofiltration follow the dosage recommended under impaired renal function.
Paediatric patients
Preterm (born at <36 weeks of gestation) and term newborn infants (age 0–27 days):
Cefuroxime is not recommended for the use in these age groups due to insufficient data on safety and
efficacy. In the first weeks of life the serum half-life of cefuroxime can be three to five times that in
adults (see section 5.2).

Infants, toddlers (age 28 days to 23 months) and children (2 years to 11 years):
The recommended dosage range is 30 to 100 mg/kg/day given as three or four divided doses. Most
infections will respond to a dose of 60 mg/kg/day.

Infants, toddlers (28 days to 23 months) and children (2 years to 11 years) with impaired renal
function:
There are insufficient data regarding use of cefuroxime in paediatric renal insufficiency and therefore
such use is not recommended.

Route of Administration:
Cefuroxime 750mg Powder for Solution for Injection may be administered by intramuscular injection
or intravenous injection (within 3–5 minutes), see section 6.6.

Intramuscular administration should be limited on special indication and/or exceptional clinical
situations after benefit-risk-assessment. Intramuscular administration 3 times a day is not
recommended.

Doses above 750 mg of cefuroxime should not be administered intramuscularly.

4.3 Contraindications
- Hypersensitivity to cefuroxime or to any of the cephalosporins.
- Previous immediate and/or severe hypersensitivity reaction to penicillin or to any other type of
  beta-lactam medicinal products.

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

If after administration of cefuroxime sodium hypersensitivity reactions occur, the use of cefuroxime
sodium should be discontinued immediately and an appropriate treatment measures should be initiated.

Special care should be taken in patients with hepatic dysfunction.

As with other antibiotics, use of cefuroxime sodium may result in the overgrowth of Candida.
Prolonged use may also result in the overgrowth of other non-susceptible organisms (e.g. Enterococci
and 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. Anti-peristaltics are contra-indicated.

Cefuroxime solution is incompatible with aminoglycoside antibiotics (see section 6.2).

The use of cefuroxime may be accompanied by a false positive Coombs test. This may interfere with
the performance of cross matching tests with blood (see section 4.8).

Cefuroxime is excreted via the kidneys. Therefore a dose adjustment is required in patients with
impaired renal function (see section 4.2).

Due to an increased risk of cefuroxime accumulation in serum accompanied by an increased risk for
undesirable effects patients with a creatinine clearance < 10 ml/min should be treated under expert
supervision.

As a precaution, renal function should be monitored if renal function is already impaired.
The sodium content of cefuroxime should be taken into account when prescribed to patients requiring sodium restriction.

There are insufficient data regarding use of cefuroxime in paediatric renal insufficiency and therefore such use is not recommended.

This medicinal product contains 1.8 mmol (42 mg) sodium per vial. To be taken into consideration by patients on a controlled sodium 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, amphotericin and aminoglycosides, as concomitant use increases the risk of nephrotoxicity.

Bacteriostatic antibiotics may interfere with the bactericidal action of cephalosporins. Therefore, 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 of cefuroxime are enhanced.

In common with other antibiotics, cefuroxime may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

Oral contraceptives should be supplemented with non-hormonal contraception measures during treatment with cefuroxime.

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 foetus/newborn child. To date no other relevant epidemiological data are available. Animal studies do not show any harmful effects on embryonal and foetal development (see section 5.3). Cefuroxime reaches the embryo/foetus via the placenta. Due to the limited clinical experience Cefuroxime 750mg Powder for Solution for Injection should only be used during pregnancy after careful risk/benefit, especially during the first trimester.

#### Lactation

Cefuroxime is excreted in human milk. Cefuroxime 750mg Powder for Solution for Injection 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 sensitisation should be borne in mind.

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

Cefuroxime may sometimes be associated with side effects, such as dizziness, that may impair the ability to drive a vehicle, operate machinery or to work safely.
4.8 Undesirable effects

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

- Very common: ≥1/10
- Common: ≥1/100 to <1/10
- Uncommon: ≥1/1,000 to <1/100
- Rare: ≥1/10,000 to <1/1,000
- Very rare: <1/10,000, not known (cannot be estimated from the available data).

Dependent on the dose and duration of the treatment approximately 3% of all treated patients are expected to experience one or several of the adverse reactions mentioned below.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Undesirable effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Rare</td>
<td>Pseudomembranous colitis. As with other antibiotics prolonged use may lead to secondary superinfections caused by insusceptible organisms, e.g. <em>Candida</em>, Enterococci and <em>Clostridium difficile</em> (see section 4.4).</td>
</tr>
<tr>
<td>Blood and lymphatic system disorder</td>
<td>Uncommon</td>
<td>Eosinophilia, leucopenia, neutropenia, thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Decreased haemoglobin concentration, agranulocytosis</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Haemolytic anemia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Rare</td>
<td>Serum sickness</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Anaphylaxis (see section 4.4)</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Angioneutrotic oedema</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Uncommon</td>
<td>Headache, dizziness</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Vertigo, restlessness, nervousness, confusion</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Gastrointestinal disturbances such as diarrhoea, nausea and vomiting</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Uncommon</td>
<td>Transient increases of hepatic enzyme levels (AST, ALT and LDH) and serum bilirubin</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Jaundice</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Common</td>
<td>Skin rashes, urticaria, pruritus</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Common</td>
<td>Increased levels of creatinine and urea in serum, especially in patients with impaired renal function (see section 4.2 and 4.4).</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Acute interstitial nephritis. Nephrotoxicity. Acute renal tubular necrosis has followed excessive dosage and has also been associated with its use in older patients or those with pre-existing renal impairment (see section 4.2 and 4.4).</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Common</td>
<td>Pain at the injection site following intramuscular administration, thrombophlebitis and pain following intravenous injection, after rapid intravenous administration heat sensations or nausea may occur</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Drug fever</td>
</tr>
<tr>
<td>Investigations</td>
<td>Not known</td>
<td>The use of cefuroxime may be accompanied by a false positive Coombs test. This may interfere with the performance of cross matching tests with blood.</td>
</tr>
</tbody>
</table>

4.9 Overdose

Overdosage 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
ATC code: J01D C02

Mode of action

All cephalosporins (β-lactam antibiotics) inhibit cell wall production and are selective inhibitors of peptidoglycan synthesis. The initial step in drug action consists of binding of the drug 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, resulting in bacterial lysis.

PK/PD relationship
The efficacy is mainly determined by the length of time, during which the drug level is above the minimal inhibitory concentration of the pathogen.

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 depressed 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.

Breakpoints
EUCAST (European Committee on Antimicrobial Susceptibility Testing) breakpoints:

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Susceptible</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus spp.</td>
<td>≤ 8 mg/l</td>
<td>&gt; 8 mg/l</td>
</tr>
<tr>
<td>Streptococcus spp. (A, B, C, G)</td>
<td>≤ 0.5 mg/l</td>
<td>&gt; 0.5 mg/l</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>≤ 0.5 mg/l</td>
<td>&gt; 1 mg/l</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>≤ 1 mg/l</td>
<td>&gt; 2 mg/l</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>≤ 1 mg/l</td>
<td>&gt; 2 mg/l</td>
</tr>
<tr>
<td>Non-species related</td>
<td>≤ 4 mg/l</td>
<td>&gt; 8 mg/l</td>
</tr>
</tbody>
</table>

* The breakpoint pertains to a dosage of 1.5 g x 3 and to E. coli and Klebsiella spp only.
* Susceptibility of staphylococci to cefuroxime is inferred from the methicillin susceptibility.
Methicillin (Oxacillin)-resistant staphylococci are resistant to cephalosporines.
** Based on serum pharmacokinetic.

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.
## Commonly susceptible species

<table>
<thead>
<tr>
<th>Gram positive aerobes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em> (methicillin-susceptible)</td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus saprophyticus</em></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gram negative aerobes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Proteus mirabilis</em></td>
<td></td>
</tr>
</tbody>
</table>

## Species for which acquired resistance may be a problem

### Gram positive aerobes

|  |
|----------------------|--|
| *Staphylococcus epidermidis* |  |
| *Staphylococcus haemolyticus* |  |
| *Staphylococcus hominis* |  |
| *Streptococcus pneumoniae* |  |

### Gram negative aerobes

|  |
|----------------------|--|
| *Citrobacter freundii* |  |
| *Citrobacter koseri* |  |
| *Enterobacter aerogenes* |  |
| *Enterobacter cloacae* |  |
| *Escherichia coli* |  |
| *Haemophilus influenzae* |  |
| *Klebsiella oxytoca* |  |
| *Klebsiella pneumoniae* |  |
| *Moraxella catarrhalis* |  |

## Inherently resistant organisms

### Gram positive aerobes

|  |
|----------------------|--|
| *Enterococcus* spp. |  |
| *Listeria monocytogenes* |  |
| *Staphylococcus aureus* (methicillin-resistant) |  |
| *Staphylococcus epidermidis* (methicillin-resistant) |  |

### Gram negative aerobes

|  |
|----------------------|--|
| *Acinetobacter baumannii* |  |
| *Burkholderia cepacia* |  |
| *Campylobacter* spp. |  |
| *Morganella morganii* |  |
| *Proteus vulgaris* |  |
| *Pseudomonas aeruginosa* |  |
| *Serratia* spp. |  |
| *Stenotrophomonas maltophilia* |  |

### Anaerobes

|  |
|----------------------|--|
| *Bacteroides* spp. |  |
| *Clostridium difficile* |  |

### Others

|  |
|----------------------|--|
| *Chlamydia* spp. |  |
| *Chlamydophila* spp. |  |
| *Legionella* spp. |  |
| *Mycobacterium* spp. |  |
| *Mycoplasma* spp. |  |

---

* Refers to German data (March 2007): At the time of publication of the table no current data were available. In primary literature, standard text books, and treatment recommendations susceptibility is anticipated.

(+) Prevalence of bacterial resistance is $>50\%$ at least in one European country or region.

(1) Frequency of methicillin resistance is about 30 to 50\% for all staphylococci in France and is usually observed in hospital.

(2) Staphylococcus resistant to methicillin are resistant to other beta-lactams.

(3) Streptococci resistant to penicillin are always resistant to cefuroxime.
5.2 Pharmacokinetic properties

Absorption
Cefuroxime is poorly absorbed from the gastro-intestinal tract and is given by intramuscular or intravenous injection or infusion as the sodium salt. Following intravenous doses of 750 mg and 1,500 mg, serum peak concentrations (C\text{max}) were approximately 50 µg/ml and 100 µg/ml, respectively, after 15 minutes (t\text{max}).

Peak plasma concentrations of 27 µg per ml have been achieved about 45 minutes after an intramuscular dose of 750 mg with measurable amounts present 8 hours after a dose.

Distribution
Cefuroxime is widely distributed in the body and levels, that exceed the MIC-values of most pathogens, are achieved pleural fluid, sputum, bone, synovial fluid, and aqueous humour, but only achieves therapeutic concentrations in the CSF when the meninges are inflamed. The volume of distribution ranges between 9.3 and 15.8 l/1.73 m² in healthy adults. About 33% to 50% of cefuroxime in the circulation is bound to plasma proteins. It diffuses across the placenta and has been detected in breast milk.

Biotransformation
Cefuroxime is metabolized only to a minor extent (<5%).

Elimination
The elimination half-life ranges between about 70 and 80 min after intramuscular or intravenous administration in healthy adults. Most of the dose of cefuroxime is excreted unchanged in active form. About 50% is excreted by glomerular filtration and about 50% through renal tubular secretion within 24 hours, with the majority being eliminated within 6 hours; high concentrations are achieved in the urine. Small amounts of cefuroxime are excreted in bile. The renal clearance is 136.0 and 169.6 ml/min/1.73 m² after 0.5 and 1 g cefuroxime intravenous and 137.9 and 146.3 ml/min/1.73 m² after 0.750 and 1 g cefuroxime intramuscular, respectively. The elimination is impaired in patients with impaired renal function.

Concomitant administration of oral probenecid slows tubular secretion of cefuroxime and decreases renal clearance by approximately 40%.

Oral probenecid (1 g) prolonged the half-life by 63% and increased the area under the concentration-time curve of intravenous cefuroxime (750 mg) by up to 50%.

Cefuroxime is dialysable and small amounts are removed by peritoneal dialysis.

Linearity/non-linearity
The peak plasma concentration and the area under the concentration curve increase with increasing dose.

Pharmacokinetics in special patient groups
The half-life of cefuroxime is prolonged in patients with renal impairment associated with the risk of accumulation. The serum half-life is 4.2 hours at a creatinine clearance of 23 ml/min and 22.3 hours at a creatinine clearance of 5 ml/min. Therefore dose adjustment is required in patients with impaired renal function (see section 4.2).

The serum half-life is prolonged in preterm and term newborn infants during the first weeks of life (3 to 5 times the value in adults).

5.3 Preclinical safety data
Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. 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.

The most prominent treatment-related effect was tissue damage at the injection sites.
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. Cefuroxime has been shown to pass the placenta.

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

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.

6.3 Shelf life
2 years.

Reconstituted product:
Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

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

6.5 Nature and contents of container
20 ml type I glass vials, sealed with grey bromo butyl rubber stopper and coloured flip off seal.

1 vial, 5 vials, 10 vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
For single use only. Discard any unused solution. Any unused product or waste material should be disposed of in accordance with local requirements.

The dilution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.
**Preparation of solution**

**Intramuscular**
Add 3 ml water for injections to 750 mg Cefuroxime Powder for Solution for Injection. Shake gently to produce an opaque suspension.

**Intravenous**
Dissolve Cefuroxime 750mg Powder for Solution for Injection in water for injections using 6 ml for 750 mg.
The reconstituted solution should appear yellowish.

The contents and concentrations of cefuroxime as 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>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>50</td>
<td>51.2</td>
<td>29</td>
</tr>
</tbody>
</table>

Cefuroxime is compatible with most commonly used intravenous fluids and electrolyte solutions. Water for injections is recommended for reconstitution, followed by dilution (prior to intravenous administration) with water for injections, 5% glucose injection or 0.9% sodium chloride injection.

Cefuroxime sodium is also compatible with Hartmann's solution and 0.18% sodium chloride + 4% glucose.

7 **MARKETING AUTHORISATION HOLDER**
Actavis Group PTC ehf
Reykjavikurvegi 76-78
220 Hafnarfjordur
Iceland

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 30306/0161

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
16/11/2010

10 **DATE OF REVISION OF THE TEXT**
16/11/2010
1 NAME OF THE MEDICINAL PRODUCT
Cefuroxime 1.5g Powder for Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains cefuroxime sodium equivalent to 1500 mg cefuroxime.

Each 1500 mg vial contains approximately 84 mg sodium.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Powder for solution for injection/infusion.

Cefuroxime is white to faintly yellow powder.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Cefuroxime is indicated for the treatment of the following infections when caused by susceptible organisms.

Respiratory tract infections: acute exacerbation of chronic bronchitis, hospital acquired pneumonia, severe community acquired pneumonia.

Upper urinary tract infections: pyelonephritis.

Peri-operative prophylaxis against infection in abdominal, orthopaedic and cardiac surgery.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration
Usual dosage for adolescents (aged 12 years to 17 years), adults and the elderly:
The dosage is 1.5 g/day to 6 g/day. In most infections a sufficient dose is 750 mg every 8 hour. In more severe infections the dose should be increased to 1.5 g every 8 hour by intravenous injection.

If necessary, the dosage frequency can be increased to every 6 hour up to total daily dose of 6 g.

Prophylaxis
The usual dose is 1500 mg (1.5 g) intravenously with induction of anaesthesia for abdominal and orthopaedic operations, but may be supplemented with two 750 mg intramuscular doses eight and sixteen hours later. In cardiac operations, the usual dose is 1500 mg (1.5 g) intravenously with induction of anaesthesia continuing with 750 mg intramuscularly three times daily for a further 24 hours to 48 hours.

Dosage in impaired renal function for adolescents, adults and elderly
It is not necessary to reduce the dose if creatinine clearance is more than 20 ml/min. The recommended maintenance dose in impaired renal function is as follows:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Recommended dosage of cefuroxime (mg)</th>
<th>Frequency of dosage (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>Normal dose</td>
<td></td>
</tr>
<tr>
<td>10-20</td>
<td>750</td>
<td>12</td>
</tr>
<tr>
<td>&lt;10</td>
<td>750</td>
<td>24</td>
</tr>
<tr>
<td>Patients on continuous</td>
<td>750</td>
<td>12</td>
</tr>
<tr>
<td>arteriovenous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>haemofiltration/haemodialysis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Special precautions are required if creatinine clearance is <10 ml/minute and treatment should take place under appropriate expert supervision (see section 4.4).

Serum concentration of cefuroxime should be monitored in patients with severe renal impairment.
For patients on haemodialysis a further 750 mg dose, by intravenous or intramuscular injection, should be given at the end of each session.

For low-flux haemofiltration follow the dosage recommended under impaired renal function.

**Paediatric patients**

*Preterm (born at <36 weeks of gestation) and term newborn infants (age 0–27 days):*

Cefuroxime is not recommended for the use in these age groups due to insufficient data on safety and efficacy. In the first weeks of life the serum half-life of cefuroxime can be three to five times that in adults (see section 5.2).

*Infants, toddlers (age 28 days to 23 months) and children (2 years to 11 years):*

The recommended dosage range is 30 to 100 mg/kg/day given as three or four divided doses. Most infections will respond to a dose of 60 mg/kg/day.

*Infants, toddlers (28 days to 23 months) and children (2 years to 11 years) with impaired renal function:*

There are insufficient data regarding use of cefuroxime in paediatric renal insufficiency and therefore such use is not recommended. Cefuroxime 1.5g Powder for Solution for Injection or Infusion may be administered by intravenous injection (within 3–5 minutes) or infusion (up to 30 minutes), see section 6.6. Intramuscular administration should be limited on special indication and/or exceptional clinical situations after benefit-risk-assessment. Intramuscular administration 3 times a day is not recommended.

Doses above 750 mg of cefuroxime should not be administered intramuscularly.

### 4.3 Contraindications

- Hypersensitivity to cefuroxime or to any of the cephalosporins.
- Previous immediate and/or severe hypersensitivity reaction to penicillin or to any other type of beta-lactam medicinal products.

### 4.4 Special warnings and precautions for use

Special care is indicated in patients who have experienced an allergic reaction to penicillins or beta-lactam antibiotics as cross-reactions may occur (for contraindications due to known hypersensitivity reactions see section 4.3).

If after administration of cefuroxime sodium hypersensitivity reactions occur, the use of cefuroxime sodium should be discontinued immediately and an appropriate treatment measures should be initiated.

Special care should be taken in patients with hepatic dysfunction.

As with other antibiotics, use of cefuroxime sodium may result in the overgrowth of *Candida*. Prolonged use may also result in the overgrowth of other non-susceptible organisms (e.g. *Enterococci* and *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. Anti-peristaltics are contra-indicated.

Cefuroxime solution is incompatible with aminoglycoside antibiotics (see section 6.2).

The use of cefuroxime may be accompanied by a false positive Coombs test. This may interfere with the performance of cross matching tests with blood (see section 4.8).

Cefuroxime is excreted via the kidneys. Therefore a dose adjustment is required in patients with impaired renal function (see section 4.2).

Due to an increased risk of cefuroxime accumulation in serum accompanied by an increased risk for undesirable effects patients with a creatinine clearance < 10 ml/min should be treated under expert supervision.
As a precaution, renal function should be monitored if renal function is already impaired. The sodium content of cefuroxime should be taken into account when prescribed to patients requiring sodium restriction.

There are insufficient data regarding use of cefuroxime in paediatric renal insufficiency and therefore such use is not recommended.

This medicinal product contains 3.7 mmol (84 mg) sodium per vial. To be taken into consideration by patients on a controlled sodium 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, amphotericin and aminoglycosides, as concomitant use increases the risk of nephrotoxicity.

Bacteriostatic antibiotics may interfere with the bactericidal action of cephalosporins. Therefore, 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 of cefuroxime are enhanced.

In common with other antibiotics, cefuroxime may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives. Oral contraceptives should be supplemented with non-hormonal contraception measures during treatment with cefuroxime.

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 foetus/newborn child. To date no other relevant epidemiological data are available. Animal studies do not show any harmful effects on embryonal and foetal development (see section 5.3). Cefuroxime reaches the embryo/foetus via the placenta. Due to the limited clinical experience Cefuroxime 1.5g Powder for Solution for Injection or Infusion should only be used during pregnancy after careful risk/benefit, especially during the first trimester.

Lactation

Cefuroxime is excreted in human milk. Cefuroxime 1.5g Powder for Solution for Injection or Infusion 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 sensitisation should be borne in mind.

4.7 Effects on ability to drive and use machines

Cefuroxime may sometimes be associated with side effects, such as dizziness, that may impair the ability to drive a vehicle, operate machinery or to work safely.

4.8 Undesirable effects

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

Very common ≥1/10
Common ≥1/100 to <1/10
Uncommon ≥1/1,000 to <1/100
Rare ≥1/10,000 to <1/1,000
Very rare <1/10,000, not known (cannot be estimated from the available data).
Dependent on the dose and duration of the treatment approximately 3% of all treated patients are expected to experience one or several of the adverse reactions mentioned below.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Undesirable effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Rare</td>
<td>Pseudomembranous colitis. As with other antibiotics prolonged use may lead to secondary superinfections caused by insusceptible organisms, e.g. <em>Candida</em>, Enterococci and <em>Clostridium difficile</em> (see section 4.4).</td>
</tr>
<tr>
<td>Blood and lymphatic system disorder</td>
<td>Uncommon</td>
<td>Eosinophilia, leucopenia, neutropenia, thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Decreased haemoglobin concentration, agranulocytosis</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Haemolytic anemia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Rare</td>
<td>Serum sickness</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Anaphylaxis (see section 4.4)</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Angioneutrotic oedema</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Uncommon</td>
<td>Headache, dizziness</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Vertigo, restlessness, nervousness, confusion</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Gastrointestinal disturbances such as diarrhoea, nausea and vomiting</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Uncommon</td>
<td>Transient increases of hepatic enzyme levels (AST, ALT and LDH) and serum bilirubin</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Jaundice</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Common</td>
<td>Skin rashes, urticaria, pruritus</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Common</td>
<td>Increased levels of creatinine and urea in serum, especially in patients with impaired renal function (see section 4.2 and 4.4)</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Acute interstitial nephritis. Nephrotoxicity. Acute renal tubular necrosis has followed excessive dosage and has also been associated with its use in older patients or those with pre-existing renal impairment (see section 4.2 and 4.4).</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Common</td>
<td>Pain at the injection site following intramuscular administration, thrombophlebitis and pain following intravenous injection, after rapid intravenous administration heat sensations or nausea may occur</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Drug fever</td>
</tr>
<tr>
<td>Investigations</td>
<td>Not known</td>
<td>The use of cefuroxime may be accompanied by a false positive Coombs test. This may interfere with the performance of cross matching tests with blood.</td>
</tr>
</tbody>
</table>

4.9 Overdose
Overdosage 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
ATC code: J01D C02

Mode of action
All cephalosporins (β-lactam antibiotics) inhibit cell wall production and are selective inhibitors of peptidoglycan synthesis. The initial step in drug action consists of binding of the drug 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, resulting in bacterial lysis.

PK/PD relationship
The efficacy is mainly determined by the length of time, during which the drug level is above the minimal inhibitory concentration of the pathogen.
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 depressed 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.

Breakpoints

EUCAST (European Committee on Antimicrobial Susceptibility Testing) breakpoints:

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Susceptible</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Enterobacteriaceae</em></td>
<td>≤ 8 mg/l</td>
<td>&gt; 8 mg/l</td>
</tr>
<tr>
<td><em>Staphylococcus</em> spp.</td>
<td>_*</td>
<td>_*</td>
</tr>
<tr>
<td><em>Streptococcus</em> spp. (A, B, C, G)</td>
<td>≤ 0.5 mg/l</td>
<td>&gt; 0.5 mg/l</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>≤ 0.5 mg/l</td>
<td>&gt; 1 mg/l</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>≤ 1 mg/l</td>
<td>&gt; 2 mg/l</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>≤ 1 mg/l</td>
<td>&gt; 2 mg/l</td>
</tr>
<tr>
<td>Non-species related **</td>
<td>≤ 4 mg/l</td>
<td>&gt; 8 mg/l</td>
</tr>
</tbody>
</table>

* The breakpoint pertains to a dosage of 1.5 g x 3 and to *E.coli* and *Klebsiella* spp only.
* Susceptibility of staphylococci to cefuroxime is inferred from the methicillin susceptibility. Methicillin (Oxacillin)-resistant staphylococci are resistant to cephalosporines.
** Based on serum pharmacokinetic.

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.
**Commonly susceptible species**

<table>
<thead>
<tr>
<th>Gram positive aerobes</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em> (methicillin-susceptible)</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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gram negative aerobes</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Proteus mirabilis</em></td>
</tr>
</tbody>
</table>

**Species for which acquired resistance may be a problem**

<table>
<thead>
<tr>
<th>Gram positive aerobes</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus epidermidis</em></td>
</tr>
<tr>
<td><em>Staphylococcus haemolyticus</em></td>
</tr>
<tr>
<td><em>Staphylococcus hominis</em></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gram negative aerobes</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Citrobacter freundii</em></td>
</tr>
<tr>
<td><em>Citrobacter koseri</em></td>
</tr>
<tr>
<td><em>Enterobacter aerogenes</em></td>
</tr>
<tr>
<td><em>Enterobacter cloacae</em></td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
</tr>
<tr>
<td><em>Klebsiella oxytoca</em></td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
</tr>
</tbody>
</table>

**Inherently resistant organisms**

<table>
<thead>
<tr>
<th>Gram positive aerobes</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Enterococcus</em> spp.</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> (methicillin-resistant)</td>
</tr>
<tr>
<td><em>Staphylococcus epidermidis</em> (methicillin-resistant)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gram negative aerobes</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Acinetobacter baumannii</em></td>
</tr>
<tr>
<td><em>Burkholderia cepacia</em></td>
</tr>
<tr>
<td><em>Campylobacter</em> spp.</td>
</tr>
<tr>
<td><em>Morganella morganii</em></td>
</tr>
<tr>
<td><em>Proteus vulgaris</em></td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td><em>Serratia</em> spp.</td>
</tr>
<tr>
<td><em>Stenotrophomonas maltophilia</em></td>
</tr>
</tbody>
</table>

**Anaerobes**

| Bacteroides* spp.              |
| Closstridium difficile         |

**Others**

| Chlamydia* spp.                |
| Chlamydophila* spp.            |
| Legionella* spp.               |
| Mycobacterium* spp.            |
| Mycoplasma* spp.               |

---

* Refers to German data (March 2007): At the time of publication of the table no current data were available. In primary literature, standard text books, and treatment recommendations susceptibility is anticipated.
  (+) Prevalence of bacterial resistance is >50% at least in one European country or region.
  (1) Frequency of methicillin resistance is about 30 to 50% for all staphylococci in France and is usually observed in hospital.
  (2) Staphylococcus resistant to methicillin are resistant to other beta-lactams.
  (3) Streptococcus resistant to penicillin are always resistant to cefuroxime.
5.2 Pharmacokinetic properties

**Absorption**
Cefuroxime is poorly absorbed from the gastro-intestinal tract and is given by intramuscular or intravenous injection or infusion as the sodium salt. Following intravenous doses of 750 mg and 1,500 mg, serum peak concentrations (Cmax) were approximately 50 µg/ml and 100 µg/ml, respectively, after 15 minutes (tmax).

Peak plasma concentrations of 27 µg per ml have been achieved about 45 minutes after an intramuscular dose of 750 mg with measurable amounts present 8 hours after a dose.

**Distribution**
Cefuroxime is widely distributed in the body and levels, that exceed the MIC-values of most pathogens, are achieved pleural fluid, sputum, bone, synovial fluid, and aqueous humour, but only achieves therapeutic concentrations in the CSF when the meninges are inflamed. The volume of distribution ranges between 9.3 and 15.8 l/1.73 m² in healthy adults. About 33% to 50% of cefuroxime in the circulation is bound to plasma proteins. It diffuses across the placenta and has been detected in breast milk.

**Biotransformation**
Cefuroxime is metabolized only to a minor extent (<5%).

**Elimination**
The elimination half-life ranges between about 70 and 80 min after intramuscular or intravenous administration in healthy adults. Most of the dose of cefuroxime is excreted unchanged in active form. About 50% is excreted by glomerular filtration and about 50% through renal tubular secretion within 24 hours, with the majority being eliminated within 6 hours; high concentrations are achieved in the urine. Small amounts of cefuroxime are excreted in bile. The renal clearance is 136.0 and 169.6 ml/min/1.73 m² after 0.5 and 1 g cefuroxime intravenous and 137.9 and 146.3 ml/min/1.73 m² after 0.750 and 1 g cefuroxime intramuscular, respectively. The elimination is impaired in patients with impaired renal function.

Concomitant administration of oral probenecid slows tubular secretion of cefuroxime and decreases renal clearance by approximately 40%.

Oral probenecid (1 g) prolonged the half-life by 63% and increased the area under the concentration-time curve of intravenous cefuroxime (750 mg) by up to 50%.

Cefuroxime is dialysable and small amounts are removed by peritoneal dialysis.

**Linearity/non-linearity**
The peak plasma concentration and the area under the concentration curve increase with increasing dose.

**Pharmacokinetics in special patient groups**
The half-life of cefuroxime is prolonged in patients with renal impairment associated with the risk of accumulation. The serum half-life is 4.2 hours at a creatinine clearance of 23 ml/min and 22.3 hours at a creatinine clearance of 5 ml/min. Therefore dose adjustment is required in patients with impaired renal function (see section 4.2).

The serum half-life is prolonged in preterm and term newborn infants during the first weeks of life (3 to 5 times the value in adults).

5.3 Preclinical safety data
Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. 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. The most prominent treatment-related effect was tissue damage at the injection sites. 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. Cefuroxime has been shown to pass the placenta.

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

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.

6.3 Shelf life
2 years.

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

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

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

6.5 Nature and contents of container
20 ml type I glass vials (for injection) and 100 ml type I glass vials (for infusion), sealed with grey bromo butyl rubber stopper and coloured flip off seal.

20 ml vials (injection): 1 vial, 5 vials, 10 vials
100 ml vials (infusion): 1 vial, 5 vials, 10 vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
For single use only. Discard any unused solution.
Any unused product or waste material should be disposed of in accordance with local requirements.

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

Preparation of solution
Intravenous
Dissolve Cefuroxime 1.5g Powder for Solution for Injection or Infusion in water for injections using 15 ml for 1500 mg (1.5 g). For short intravenous infusion (e.g. up to 30 minutes), 1500 mg (1.5 g) may be dissolved in 50 ml water for injections. These solutions may be given directly into the vein or introduced into the tubing of the giving set if the patient is receiving parenteral fluids. The reconstituted solution should appear yellowish.
The contents and concentrations of cefuroxime as 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>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></td>
<td>IV Bolus</td>
<td>15</td>
<td>16.2</td>
<td>93</td>
</tr>
<tr>
<td>1500</td>
<td>IV Infusion</td>
<td>50</td>
<td>51.2</td>
<td>29</td>
</tr>
</tbody>
</table>

Cefuroxime is compatible with most commonly used intravenous fluids and electrolyte solutions. Water for injections is recommended for reconstitution, followed by dilution (prior to intravenous administration) with water for injections, 5% glucose injection or 0.9% sodium chloride injection.

Cefuroxime sodium is also compatible with Hartmann's solution and 0.18% sodium chloride + 4% glucose.

7 MARKETING AUTHORISATION HOLDER
Actavis Group PTC ehf
Reykjavikurvegi 76-78
220 Hafnarfjordur
Iceland

8 MARKETING AUTHORISATION NUMBER(S)
PL 30306/0162

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
16/11/2010

10 DATE OF REVISION OF THE TEXT
16/11/2010
Cefuroxime 250mg and 750mg powder for solution for injection, and Cefuroxime 1.5g powder for solution for injection or infusion

Read all of this leaflet carefully before you start receiving 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.

The full name of this medicine is Cefuroxime 250mg Powder for Solution for Injection, Cefuroxime 750mg Powder for Solution for Injection and Cefuroxime 1500mg (1.5g) Powder for Solution for Injection or Infusion. But within the leaflet it will be referred to as Cefuroxime powder.

Before you are given Cefuroxime powder
Do not use Cefuroxime powder if you:
- Are allergic (hypersensitive) to any of the ingredients (see section 6 for a list of the ingredients).
- Are allergic to penicillins or cephalosporins (an allergic reaction may include a rash, itching or breathing difficulties).

- Have special care with Cefuroxime powder if you:
- Have kidney disease or you are on dialysis.
- Have liver problems.
- Have any blood tests. Cefuroxime powder can affect the results.

- Long-term use of Cefuroxime powder can result in infections caused by bacteria that are not sensitive to Cefuroxime.

- Diabetes may develop while you are on antibiotics. If it becomes severe or persistent, please tell your doctor immediately.

- Cefuroxime powder Treatment will have to be stopped immediately, as this can be lethal.

- Do not take medicines that stop or slow down bowel movements.

Important information about some of the ingredients of Cefuroxime powder
- 250mg vial
  - This medicinal product contains less than 1mmol sodium (23mg) per vial, i.e., essentially sodium-free.
- 750mg vial
  - This medicinal product contains 12mmol (424mg) sodium per vial. To be taken into consideration by patients on a controlled sodium diet.
- 1500mg (1.5g) vial
  - This medicinal product contains 35mmol (1210mg) sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

Driving and using machines
In rare cases Cefuroxime powder may cause dizziness, nausaea or confusion. If you feel at all unwell after being given Cefuroxime powder you should not attempt to drive or use machines.

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

1. What Cefuroxime powder is and what it is used for
Cefuroxime belongs to a group of antibiotics called cephalosporins. Antibiotics are used to kill the bacteria or germs that cause infections. Cefuroxime is a powder which is mixed into a solution for injection into a vein or into a muscle.

A doctor may also give it to you before an operation to protect you from infection.

2. Before you are given Cefuroxime powder
Do not use Cefuroxime powder if you:
- Are allergic (hypersensitive) to any of the ingredients (see section 6 for a list of the ingredients).
- Are allergic to penicillins or cephalosporins (an allergic reaction may include a rash, itching or breathing difficulties).

- Have special care with Cefuroxime powder if you:
- Have kidney disease or you are on dialysis.
- Have liver problems.
- Have any blood tests. Cefuroxime powder can affect the results.

- Long-term use of Cefuroxime powder can result in infections caused by bacteria that are not sensitive to Cefuroxime.

- Diabetes may develop while you are on antibiotics. If it becomes severe or persistent, please tell your doctor immediately.

- Cefuroxime powder treatment will have to be stopped immediately, as this can be lethal.

- Do not take medicines that stop or slow down bowel movements.

3. How Cefuroxime powder is given
Your doctor will decide on the dose and the duration of treatment. This medicine will normally be given by injection of a solution into a vein or a muscle. The usual dose is:
- Children (aged 2 months to 12 years):
- Adults and elderly:

4. Possible side effects

- Contraceptive pills
Tell your doctor or pharmacist if you are taking the contraceptive pill. This medicine may stop the oral contraceptive used working properly. As with other antibiotics you may need to take other contraceptive precautions.

- Pregnancy and breast feeding
Ask your doctor or pharmacist for advice before taking any medicine. There is no evidence of harmful effects caused by Cefuroxime powder in pregnancy. But, Cefuroxime powder should only be given during pregnancy after careful consideration of the risks and benefits.

If you are pregnant or think you may be pregnant or you are trying to become pregnant, tell your doctor or pharmacist before taking this medicine.

Cefuroxime powder is excreted in breast milk and should be avoided when breastfeeding. Please tell your doctor if you are breast-feeding.

The following information is intended for medical or healthcare professionals only:

Cefuroxime 250mg Powder for Solution for Injection
Cefuroxime 750mg Powder for Solution for Injection
Cefuroxime 1500mg (1.5g) Powder for Solution for Injection or Infusion
For single use only. Discard any unused solution.
The solution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.

Preparation of solution
Intematocellular
Add 2ml water for injections to 250mg Cefuroxime powder or 3ml water for injections to 750mg Cefuroxime powder. Shake gently to produce an opaque suspension.

Intravenous
Dissolve Cefuroxime powder in water for injections using 2.5ml water for 750mg or 5ml for 1500mg (1.5g). For short intermittent infusion (up to 30 minutes), 1500mg (1.5g) may be dissolved in 50ml water for injections.
Cefuroxime 250mg and 750mg powder for solution for injection, and Cefuroxime 1.5g powder for solution for injection or infusion

UK/II/2112/001-3/DC

If you miss a dose or receive too much of Cefuroxime powder
As this medicine will be given to you whilst you are in hospital, it is unlikely that you will miss a dose or be given too much medicine. However, if you have any concerns discuss this with your doctor or nurse.

While you are receiving Cefuroxime
If you have any further questions on the use of this product, ask your doctor or pharmacist.

Possible side effects
Like all medicines, Cefuroxime powder can cause side effects, although not everybody gets them. It important that you are aware of what these side effects may be.

If you notice any of the following serious side effects, stop Cefuroxime powder and contact a doctor immediately:

- Reddening of the skin, with blisters or peeling. There may be severe blisters and bleeding in the lips, eyes, mouth, nose and genitals. This could be a Stevens-Johnson syndrome or toxic epidermal necrolysis.
- Severe paradoxical reaction, in which the condition worsens, or in which they may have blood or mucus in their mouth, accompanied by stomach pain and fever. This could be pseudoallergic reactions.
- Severe skin reaction, such as a rash or severe swelling of the face, lips, tongue, or throat, which is accompanied by difficulty breathing, or difficulty swallowing and general feeling unwell. Symptoms can take 5 days to appear after the start of treatment.

Very rare side effects affect less than 1 in 10,000 people.

Uncommon side effects:

- Diarrhoea, nausea or vomiting
- Increase in the number of platelets in the blood (neutrophilia) and uric acid (especially in patients with kidney problems)
- Pain or swelling where the needle went into the vein or muscle.

Common side effects:

- Abnormal increase in certain type of white blood cells in blood (eosinophilia). Symptoms include weight loss, night sweats and fever
- Abnormal decrease in some types of white blood cells in blood (leucopenia and neutropenia), which can make you more likely to get infections
- Unusual bleeding or bruising caused by a reduction in the number of platelets in the blood (blood thrombocytopenia)
- Headache, dizziness
- Severe kidney problems (especially in elderly patients and patients with previous kidney disorders)
- Changes to test used to measure functioning of the liver.

Further Information

What Cefuroxime powder contains:
- The active ingredient is Cefuroxime 250mg, 750mg or 1500mg (1.5g) (as sodium salt)
- Other ingredients: None.

What Cefuroxime powder looks like and contents of the pack:
Cefuroxime is white to faintly yellow powder to be prepared for use with water.

250mg, 750mg powder for solution for injection:
20ml type I glass vials, sealed with grey bromo butyl rubber stopper and coloured flip off seal.

1500mg (1.5g) powder for solution for infusion:
20ml type I glass vials (for injection) and 100ml type I glass vials (for infusion), sealed with grey bromo butyl rubber stopper and coloured flip off seal.

Pack sizes:
230mg powder for solution for injection:
5 vials
750mg powder for solution for injection:
1 vial and 10 vials
1500mg (1.5g) powder for solution for injection:
20ml vials (for injection): 1 vial and 10 vials
100ml vials (for infusion): 1 vial and 10 vials

Marketing Authorisation Holder:
Actavis Group PTC eft Reykjavikurvegi 79-78, 220
Hafnarfjörður, Iceland

Manufacturers:
Orchid Europe Limited
Building 2, Cheswick Park, 366 Cheswick High Road, Chesswood, London, W4 5YA
United Kingdom

This leaflet was last revised in October 2010

These solutions may be given directly into the vein or introduced into the tubing of the giving set of the patient is receiving parenteral fluids. The reconstituted solution should appear yellow.

Cefuroxime is compatible with most commonly used intravenous fluids and electrolyte solutions.

Water for injections is recommended for reconstitution, followed by dilution (prior to intravenous administration) with water for injections. 5% glucose injection or 0.9% sodium chloride injection.

Cefuroxime powder is also compatible with Hartmann's solution and 0.18% sodium chloride + 4% glucose.

Reconstituted product:
Chemical and physical in use stability has been demonstrated for 24 hours at 2°C-8°C.

33
Module 4

Cefuroxime 250mg Powder for Solution for Injection

For intravenous or intramuscular use after reconstitution and dilution.

For single use only.

Once reconstituted, store at 2-8°C for up to 24 hours.

Keep out of the reach and sight of children.

Each vial contains cefuroxime sodium equivalent to 250mg cefuroxime.

Read the package leaflet before use.

 batch code

POM

1 x 20ml/30ml

Overprinting Zone for Batch coding details

Cefuroxime 250mg Powder for Solution for Injection

For intravenous or intramuscular use after reconstitution and dilution.

5 x 20ml vials

Cefuroxime 250mg Powder for Solution for Injection

For intravenous or intramuscular use after reconstitution and dilution.

5 x 20ml vials
Cefuroxime 250mg and 750mg powder for solution for injection, and Cefuroxime 1.5g powder for solution for injection or infusion

Overprinting Zone for Batch coding details

For single use only.
- Once reconstituted, store at 2-8°C for up to 24 hours.
- Keep out of the reach and sight of children.
- Each vial contains cefuroxime sodium equivalent to 1500mg cefuroxime.
- Read the package leaflet before use.

PL 30306/0162

For intravenous use after reconstitution and dilution. 1 x 20ml vial

UK/H/2112/001-3/DC

37
Cefuroxime 250mg and 750mg powder for solution for injection, and Cefuroxime 1.5g powder for solution for injection or infusion

Cefuroxime 1.5g Powder for Solution for Injection or Infusion
For intravenous use after reconstitution and dilution.

For single use only.

Pack of 10 vials of 20 ml of Cefuroxime 1.5 g for injection or infusion. Each vial contains a sterile ready to use solution for injection or infusion.

Store at 2-8°C.

Contains sodium.

For full details see the Summary of Product Characteristics (SmPC) and the Package Leaflet (PL)

For use in hospitals only

For use in hospitals only

Overprinting Zone for Batch coding details
Cefuroxime 250mg and 750mg powder for solution for injection, and Cefuroxime 1.5g powder for solution for injection or infusion

For intravenous use after reconstitution and dilution.

For single use only.

Once reconstituted, store at 2-8°C for up to 24 hours.

Keep out of the reach and sight of children.

Each vial contains cefuroxime sodium equivalent to 1500mg cefuroxime.

Read the package leaflet before use.

PL 30306/0162

1x 100ml vial

Overprinting Zone for Batch coding details
Cefuroxime 250mg and 750mg powder for solution for injection, and Cefuroxime 1.5g powder for solution for injection or infusion

UK/H/2112/001-3/DC
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 250mg and 750mg powder for solution for injection (PL 30306/0160-1; UK/H/2112/001-2/DC), and Cefuroxime 1.5g powder for solution for injection or infusion (PL 30306/0162; UK/H/2112/003/DC), could be approved. The products are prescription-only medicines (POM) for the treatment of the following infections when caused by susceptible organisms:

- Upper urinary tract infections: pyelonephritis.

Cefuroxime 250mg and 750mg powder for solution for injection, and Cefuroxime 1.5g powder for solution for injection or infusion, may also be used in peri-operative prophylaxis against infection in abdominal, orthopaedic and cardiac surgery. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Denmark, Finland, Ireland, Norway, the Netherlands, Poland, Portugal, Sweden, Estonia, Lithuania and Latvia as Concerned Member States (CMS). The applications were submitted under Article 10.1 of 2001/83/EC, as amended, claiming to be generic medicinal products of Zinnat 250mg and 750mg poudre pour solution injectable (GlaxoSmithKline, France), and Zinnat 1.5g poudre pour solution pour perfusion (GlaxoSmithKline, France), which have been licensed since 21 March 1983. The corresponding reference products in the UK are Zinacef 250mg and 750mg powder for solution for injection and Zinacef 1.5g powder for solution for injection or infusion (Glaxo Operations UK Limited), which were first authorised on 07 April 1978.

The active ingredient cefuroxime (as cefuroxime sodium) is a second-generation cephalosporin antibiotic that is resistant to most beta-lactamases and is active against a wide range of Gram-positive and Gram-negative organisms. It binds to cell receptors called penicillin-binding proteins, inhibiting the transpeptidation reaction and blocking peptidoglycan synthesis, resulting in bacterial lysis. Cefuroxime is active against H. influenzae type B (including beta-lactamase producing strains), pneumococci, Streptococcus pyogenes, and Staphylococcus aureus.

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

No new clinical data have been submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years. A bioequivalence study was not necessary to support these applications for parenteral products.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product. For manufacturing sites outside the Community, the RMS has accepted copies of
current GMP Certificates, satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the applications could be approved at the end of procedure (Day 210) on 06 September 2010. After a subsequent national phase, licences were granted in the UK on 16 November 2010.
## II. ABOUT THE PRODUCT

| Names of the products in the Reference Member State | UK/H/2112/001/DC: Cefuroxime 250mg powder for solution for injection  
UK/H/2112/002/DC: Cefuroxime 750mg powder for solution for injection  
UK/H/2112/003/DC: Cefuroxime 1.5g powder for solution for injection or 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) | UK/H/2112/001-2/DC: Powder for solution for injection, 250mg and 750mg  
UK/H/2112/003/DC: Powder for solution for injection or infusion, 1.5g |
| Reference numbers for the Decentralised Procedure | UK/H/2112/001-3/DC |
| Reference Member State (RMS) | United Kingdom |
| Concerned Member States (CMS) | UK/H/2112/001/DC: Denmark, Finland, Ireland, Norway, the Netherlands, Poland, Portugal, Sweden  
UK/H/2112/002/DC: Denmark, Finland, Ireland, Norway, the Netherlands, Poland, Portugal, Sweden, Estonia  
UK/H/2112/003/DC: Denmark, Finland, Ireland, Norway, the Netherlands, Poland, Portugal, Sweden, Estonia, Lithuania, Latvia |
| Marketing Authorisation Number(s) | PL 30306/0160-2 |
| Name and address of the authorisation holder | Actavis Group PTC ehf  
Reykjavikurvegi 76-78,  
220 Hafnarfjordur,  
Iceland |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

INN: Cefuroxime sodium

Chemical name: Sodium (6R,7R)-3-[carbamoyloxy)methyl]-7-[(Z)-(furan-2-yl)(methoxyimino)acet-yl] amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate

Structure:

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.

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.

MEDICINAL PRODUCT

Other Ingredients

There are no pharmaceutical excipients in these products. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, stable products that could be considered generic medicinal products of the UK reference products Zinacef 250mg, 750mg powder for solution for injection, and Zinacef 1.5g powder for solution for injection or infusion (Glaxo Operations UK Limited).

Suitable pharmaceutical development data have been provided for these applications.

Comparative impurity profiles have been provided for these products and the UK reference products Zinacef 250mg, 750mg powder for solution for injection, and Zinacef 1.5g powder for solution for injection or infusion (Glaxo Operations UK Limited).
Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the products, together 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
The finished products are supplied in 20ml (250mg, 750mg and 1.5g injectable) and 100ml (1.5g infusion) Type I glass vials with grey bromobutyl rubber stoppers and coloured flip-off seals (red for the 250mg strength, blue for the 750mg and white for the 1.5g strength).

The products are available in pack sizes of 1, 5 and 10 vials. Not all pack sizes may be marketed. However, the Marketing Authorisation Holder has 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 for all packaging material have been provided. These are satisfactory. All primary packaging complies with guidelines concerning materials in contact with parenteral products.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years has been proposed, with no special storage instructions for the products when stored in the vial.

For the reconstituted products, chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C.

From a microbiological point of view, the reconstituted 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°C to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Bioequivalence/Bioavailability
A bioequivalence study was not necessary to support these applications for parenteral products.

Summaries of Product Characteristics (SmPCs), Product Information Leaflet (PIL), Labels
The SmPCs, 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.

**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 aspects of the dossiers.

**Conclusion**
The grant of marketing authorisations is recommended.
III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of cefuroxime sodium are well-known, no new non-clinical data have been submitted and none are required.

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

A suitable justification has been provided for non-submission of an environmental risk assessment. As these products are intended for generic substitution with products that are already marketed, thus no increase in environmental burden is anticipated, the justification for non-submission of an Environmental Risk Assessment is accepted.

The grant of marketing authorisations is recommended.
III.3 CLINICAL ASPECTS

Clinical Pharmacology
No new clinical pharmacology data have been submitted and none are required for applications of this type. A bioequivalence study was not necessary to support these applications for parenteral products.

Efficacy
No new efficacy data have been submitted and none are required for applications of this type.

Safety
No new safety data have been submitted with these applications and none are required. No new or unexpected safety concerns arose from these applications.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL), Labels
The SmPCs, PIL and labels are clinically acceptable. The SmPCs are consistent with those for the originator products. The PIL is consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with the 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 dossiers.

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.

Suitable justification has been provided for not submitting a risk management plan for these products.

Conclusion
The grant of marketing authorisations is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Cefuroxime 250mg and 750mg powder for solution for injection (PL 30306/0160-1; UK/H/2112/001-2/DC), and Cefuroxime 1.5g powder for solution for injection or infusion (PL 30306/0162; UK/H/2112/003/DC), 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 clinical data were submitted for these applications. No bioequivalence studies were submitted or required for these applications.

SAFETY
No new safety data were submitted for these applications.

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

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant’s products and the originator products are interchangeable. 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

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>