Public Assessment Report
Decentralised Procedure

Cefuroxime 125 mg Film-coated Tablets
Cefuroxime 250 mg Film-coated Tablets
Cefuroxime 500 mg Film-coated Tablets

PL 00289/1185
PL 00289/1186
PL 00289/1187

UK/H/1699/01-03/DC

TEVA UK Limited
Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted TEVA UK Limited Marketing Authorisations (licences) for the medicinal products Cefuroxime 125 mg, 250 mg and 500 mg Film-coated Tablets (Product Licence numbers: PL 00289/1185-7). These medicines are available on prescription only.

Cefuroxime 125 mg, 250 mg and 500 mg Film-coated Tablets are antibiotics that belong to a class of medicines called cephalosporins. They are used to treat certain types of infections and work by killing certain types of bacteria.

Cefuroxime 125 mg, 250 mg and 500 mg Film-coated Tablets may be used to treat the following infections:

- Upper respiratory tract infections (including infections occurring in the ears, sinuses, tonsils and throat)
- Chest infections such as bronchitis
- Bladder infections (water infections)
- Skin infections (recurring boils, ulcers and impetigo)
- Early Lyme disease (a rare infection caused by tick bites)

The data submitted in support of these applications for Cefuroxime 125 mg, 250 mg and 500 mg Film-coated Tablets raised no clinically significant safety concerns and it was therefore judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.
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1 Introduction
2 Quality aspects
3 Non-clinical aspects
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5 Overall conclusions
## Module 1

### Information about decentralised procedure

| Name of the product in the Reference Member State | Cefuroxime 125mg Film-coated Tablets  
Cefuroxime 250mg Film-coated Tablets  
Cefuroxime 500mg Film-coated Tablets |
|-----------------------------------------------|-----------------------------------------------------------------------------------|
| Type of application (Eudratrack details)       | Level 1  
Abridged  
Level 2  
Initial  
Level 3  
10.1  
Level 4  
Chemical substance  
Level 5  
Prescription only |
| Name of the active substance (INN)             | Cefuroxime axetil |
| Pharmacotherapeutic classification (ATC code)  | Second-generation cephalosporins (J01DC02) |
| Pharmaceutical form and strength              | Film-coated Tablet, 125mg, 250mg and 500mg |
| Reference numbers for the decentralised Procedure | UK/H/1699/01-03/DC |
| Reference Member State                        | United Kingdom |
| Member States concerned                       | CZ, DE, ES, IE, IT, PL, PT, SK |
| Date of start of the procedure                | 7 July 2009 |
| End date of decentralised procedure           | 22 December 2009 |
| Marketing Authorisation Number                | PL 00289/1185-87 |
| Name and address of the authorisation holder  | TEVA UK Limited  
Brampton Road,  
Hampden Park,  
Eastbourne,  
East Sussex BN22 9AG  
UNITED KINGDOM |
Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Cefuroxime 125 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 125 mg film-coated tablet contains 125 mg cefuroxime (as cefuroxime axetil)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

White to off white coloured film-coated tablets engraved with “125” on one side and “P124” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Cefuroxime is indicated for the treatment of the following mild to moderately severe infections caused by micro-organisms susceptible to cefuroxime:
- upper respiratory tract infections: acute otitis media, sinusitis, tonsillitis and pharyngitis
- acute bacterial bronchitis, acute exacerbations of chronic bronchitis
- lower uncomplicated urinary tract infections: cystitis
- skin and soft tissue infections: furunculosis, pyoderma and impetigo
- treatment of early stage Lyme disease (stadium I) and subsequent prevention of late complications in adults and children above 12 years of age.

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

4.2 Posology and method of administration
Cefuroxime tablets are coated to mask their taste: they should not be chewed.

The usual duration of therapy is 7 days (ranging from 5 to 10 days). For treatment of pharyngotonsillitis caused by Streptococcus pyogenes a therapy duration of at least 10 days is indicated. The duration of treatment of early Lyme disease should be 20 days. In order to achieve optimum absorption Cefuroxime Film-coated Tablets should be taken shortly after meals.

The dosage depends on the severity of the infection. For severe infections parenteral forms of cefuroxime are recommended. Where appropriate
Cefuroxime is effective when used following initial parenteral cefuroxime sodium in the treatment of pneumonia and acute exacerbations of chronic bronchitis. The dose may need to be revised when switching from parenteral to oral treatment.

*Dosage schedule for tablets:*

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</tr>
<tr>
<td>Lower respiratory tract infections</td>
<td>500 mg twice daily</td>
</tr>
<tr>
<td>Lower uncomplicated urinary tract infections</td>
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<td>Early Lyme disease</td>
<td>500 mg twice daily during 20 days</td>
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<th></th>
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</tr>
<tr>
<td>Acute otitis media</td>
<td>250 mg twice daily</td>
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</table>

*Children under 5 years of age:*

Cefuroxime Film-coated Tablets are not suitable for use in children under the age of 5. For patients in this age group it is advised to use an oral suspension. There is no experience in children under 3 months of age.

*Dosage regimen in renal impairment, in dialysis patients and elderly:*

No special precautions are necessary in patients with renal impairment, or in elderly patients if the daily dosage does not exceed 1 gram. In patients with renal impairment and creatinine clearance below 20 ml/min Cefuroxime Film-coated Tablets should be dosed carefully. Patients undergoing haemodialysis will require a supplementary dose of cefuroxime at the end of each dialysis treatment.

4.3 **Contraindications**

Hypersensitivity to cefuroxime, other cephalosporins or to any of the excipients.

Previous immediate and /or severe hypersensitivity reaction to a penicillin or to any other type of betalactam medicinal products.
4.4 Special warnings and precautions for use
If after administration of Cefuroxime sensitivity reactions occur, the use should be discontinued immediately and an appropriate treatment should be established.
Special care is indicated in patients who have experienced an allergic reaction to penicillins or other beta-lactams.

As with other broad spectrum antibiotics, prolonged use of cefuroxime axetil may result in the overgrowth of non-susceptible organisms (e.g. candida, enterococci and clostridium difficile), which may require interruption of treatment.
In patients who develop severe diarrhoea during or after use of Cefuroxime, the risk of life threatening pseudomembranous colitis should be taken into account. The use of Cefuroxime should be discontinued and the appropriate treatment established. The use of preparations inhibiting the intestinal peristalsis is contra-indicated (see section 4.8).
A 20-day treatment of Lyme disease may cause the frequency of developing diarrhoea to increase.

Long term use of Cefuroxime may lead to an excess of pathogens resistant to cefuroxime axetil.
It is of high importance that the patient is carefully checked. If a superinfection occurs during treatment, appropriate measures should be taken (see section 4.8).

The use of Cefuroxime is not recommended in patients with severe intestinal tract disorders accompanied by vomiting and diarrhoea, since in these situations a sufficient absorption cannot be guaranteed. Administration of a parenteral formulation of cefuroxime should be considered.

The Jarisch-Herxheimer reaction has been reported following cefuroxime axetil treatment of Lyme disease. The reaction results directly from the bactericidal activity of cefuroxime axetil on the spirochaete Borrelia burgdorferi. Patients should be informed of this common and usually self-limiting reaction being a consequence of antibiotic treatment of Lyme disease.
Simultaneous use of medicines enhancing the pH of the stomach is not recommended (see section 4.5).

There is no clinical experience with the use of cefuroxime axetil in children under the age of 3 months. With respect to the treatment of early Lyme disease there is only clinical experience with children from the age of 12 and with adults.

Either the glucose oxidase or the hexokinase methods are recommended to determine the blood and plasma glucose levels in patients receiving Cefuroxime. Cefuroxime does not interfere in the alkaline picrate assay for creatinine (see section 4.5).
Please refer to section 4.5 for information on the use of cefuroxime axetil in combination with oral contraceptives.

During the treatment with cefuroxime sodium, some children have experienced slight to moderate hearing loss.

4.5 Interaction with other medicinal products and other forms of interaction

Simultaneous use of medicines enhancing the pH of the stomach decreases the bioavailability of Cefuroxime. It is recommended to avoid this combination (see section 4.4).

Since bacteriostatic drugs may interfere with the bactericidal action of cephalosporins, it is advisable to avoid giving tetracyclines, macrolides, or chloramphenicol in conjunction with Cefuroxime.

The concomitant administration of probenecid can produce higher and sustained concentrations of cefuroxime in the serum and in the bile.

Cefuroxime may interfere with the determination of glucose in urine with copper containing reagentia (Benedict- or Fehling-solution, Clinitest). For the determination of blood and plasma sugar levels in patients receiving Cefuroxime, the glucose-oxidase- or hexokinase method is recommended (see section 4.4).

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).

Cephalosporin antibiotics at high dosage should be given with caution to patients receiving potent diuretics, aminoglycosides, or amphotericin as these combinations increase the risk of nephrotoxicity.

The reliability of the contraceptive effect of oral contraceptives is in doubt when using cefuroxime axetil at the same time. For this reason, other non-hormonal contraceptive means should be used in addition to oral contraceptives during treatment with Cefuroxime.

Please refer to section 4.4 for information on other interactions.

4.6 Pregnancy and lactation

Pregnancy

There are not sufficient data on the use of cefuroxime axetil during pregnancy to assess its possible harmfulness. Animal studies do not show any harmful effects on embryonal and fetal development (see section 5.3). Cefuroxime crosses the placenta. Cefuroxime should not be used during pregnancy unless considered essential by the physician.

Lactation

Cefuroxime is excreted to a small degree in human milk; breast feeding should be avoided in women using Cefuroxime.
4.7 Effects on ability to drive and use machines
There are no studies of the effect of cefuroxime axetil on the ability to drive and to handle machines. However, any effects are not to be expected.

4.8 Undesirable effects
Common ($\geq 1/100$ to $<1/10$)
Uncommon ($\geq 1/1,000$ to $<1/100$)
Rare ($\geq 1/10,000$ to $<1/1,000$)
Very rare ($<1/10,000$)

Infections and infestations
Rare
Pseudomembranous colitis
As with other antibiotics prolonged use may lead to secondary superinfections caused by insusceptible organisms, e.g. Candida, Enterococci and Clostridium difficile (see section 4.4)

Blood and the lymphatic system disorders
Rare
Decreased haemoglobin concentration, eosinophilia, leucopenia, neutropenia and thrombocytopenia
Very rare
Haemolytic anaemia

Immune system disorders
Common
Jarisch-Herxheimer reaction following cefuroxime axetil treatment of Lyme disease (see section 4.4)
Rare
Serum sickness
Very rare
Anaphylaxis

Nervous system disorders
Uncommon
Headache, dizziness
Very rare
Restlessness, nervousness, confusion

Gastrointestinal disorders
Common
Diarrhoea, nausea and vomiting. The frequency of diarrhoea is related to the administered dose and may range up to 10% with tablets. The incidence is even higher (approx. 13%) after prolonged treatment of early Lyme disease for 20 days

Hepato-biliary disorders
Rare
Transient increases of hepatic enzyme levels (AST, ALT and LDH) and serum bilirubin

*Very rare*

Jaundice

**Skin and subcutaneous tissue disorders**

*Common*

Skin rashes, urticaria, pruritus

*Very rare*

Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis

**Renal and urinary disorders**

*Common*

Increased levels of creatinine and urea in serum, especially in patients with impaired renal function

*Uncommon*

Acute interstitial nephritis

**General disorders and administration site conditions**

*Rare*

Drug fever

**Investigations**

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 4.5. Interactions).

**4.9 Overdose**

Overdose of cephalosporins may cause cerebral irritancy leading to convulsions. In case of overdose cefuroxime serum levels can be reduced by haemodialysis and peritoneal dialysis.

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: second-generation cephalosporins

ATC-Code: J01DC02

**Mode of action**

Cefuroxime axetil owes its *in vivo* bactericidal activity to the parent compound cefuroxime. 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. Bacterial lysis is the end result.

**PK/PD relationship**
For cephalosporins, the most important pharmacokinetic-pharmacodynamic index correlating with in vivo efficacy has been shown to be the duration that the unbound drug concentration remains above the minimum inhibitory concentration (MIC) as a percentage of the dosing interval (%T>MIC).

**Mechanism of resistance**

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

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

Methicillin-resistant staphylococci (MRS) are resistant to all currently available beta-lactam antibiotics including cefuroxime. Penicillin-resistant *Streptococcus pneumoniae* are cross-resistant to cephalosporins such as cefuroxime through alteration of penicillin binding proteins. Beta-lactamase negative, ampicillin resistant (BLNAR) strains of *H. influenzae* should be considered resistant to cefuroxime despite apparent in vitro susceptibility. Strains of Enterobacteriaceae, in particular *Klebsiella* spp. and *Escherichia coli* that produce ESBLs (extended spectrum beta-lactamase) may be clinically resistant to therapy with cephalosporins despite apparent in vitro susceptibility and should be considered as resistant.

According to the EUCAST 2006 v1.1 the following breakpoints have been defined for cefuroxime axetil:

<table>
<thead>
<tr>
<th>BACTERIA SPECIES</th>
<th>MIC breakpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>S ≤ / R &gt; (mg/L)</strong></td>
</tr>
<tr>
<td><em>Enterobacteriaceae</em></td>
<td>8.0/8.01</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>0.12/1.0</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>0.12/2.0</td>
</tr>
<tr>
<td><em>Staphylococcus spp</em></td>
<td>Note²</td>
</tr>
<tr>
<td><em>Streptococcus A,B,C,G</em></td>
<td>Note³</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>0.25/0.5</td>
</tr>
</tbody>
</table>

1 For uncomplicated urinary tract infections only.

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

3 The susceptibility of streptococcus groups A, B, C and G can be inferred from their susceptibility to benzylpenicillin.
**Susceptibility:**
The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. 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.

<table>
<thead>
<tr>
<th>Commonly susceptible species</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aerobes, Gram positive:</strong></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> (methicillin-susceptible)</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci (methicillin susceptible)</td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em></td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
</tr>
</tbody>
</table>

| **Aerobes, Gram negative:** |
| *Haemophilus influenzae* |
| *Moraxella catarrhalis* |
| *Proteus mirabilis* |

| **Anaerobes:** |
| *Peptococcus* species |
| *Peptostreptococcus* species |

| **Other organisms:** |
| *Borrelia burgdorferi* |

| **Species for which acquired resistance may be a problem** |
| *Acinetobacter* species |
| *Citrobacter* species |
| *Enterobacter* species |
| *Escherichia coli* |
| *Klebsiella* species |
| *Providencia rettgeri* |
| *Streptococcus pneumoniae* |

| **Inherently resistant organisms** |
| *Bacteroides fragilis* |
| *Clostridium difficile* |
| *Enterococcus* spp |
| *Listeria monocytogenes* |
| *Morganella morganii* |
| *Proteus vulgaris* |
| *Pseudomonas aeruginosa* |
| *Serratia* species |
| **Others:** |
| *Legionella* spp. |
| *Clamydophila pneumoniae* |
5.2 Pharmacokinetic properties

Absorption: After oral administration cefuroxime axetil is absorbed from the gastrointestinal tract and rapidly hydrolysed in the intestinal mucosa and blood causing the release of the active compound cefuroxime into the circulation. Optimum absorption occurs when cefuroxime axetil is taken shortly after a meal (50-60%). Under these circumstances maximum serum concentration is achieved after 2-3 hours.

Distribution: Cefuroxime is widely distributed in the body including pleural fluid, sputum, bone, synovial fluid, and aqueous humour, but only achieves therapeutic concentrations in the CSF when the meninges are inflamed. About 50% of cefuroxime in the circulation is bound to plasma proteins. It diffuses across the placenta and has been detected in breast milk.

Metabolism: Cefuroxime is not metabolised.

Elimination: Most of the dose of cefuroxime is excreted unchanged. 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. Probenecid competes with cefuroxime for renal tubular secretion resulting in higher and more prolonged plasma concentrations of cefuroxime. The plasma half-life ranges between 60 and 90 minutes and is prolonged in patients with renal impairment and in neonates.

Dialysis causes the decrease of cefuroxime serum levels.

5.3 Preclinical safety data

Cefuroxime sodium has a very low order of toxicity as demonstrated by acute toxicity studies. Investigations of chronic toxicity in several animal species (rat, dog and monkey) yielded no indications of drug related toxicological effects. The most prominent treatment-related effect was tissue damage at the injection sites.

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

A cefuroxime ester did not show clinically relevant effects when tested in vitro and in vivo for genotoxic potential.

No long-term investigations for determination of 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

Core:
Pregelatinized starch
Crocarmellose sodium
Sodium laurilsulfate
Microcrystalline cellulose
Colloidal anhydrous silica
Hydrogenated vegetable oil (Type I)

Coat:
Hypermellose (E464)
Titanium dioxide (E 171)
Propylene glycol (E 1520)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

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

6.5 Nature and contents of container
PVC/PCTFE Aluminium blister packaging

Pack sizes: 10, 12, 14 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
TEVA UK Limited
Brampton Road,
Hampden Park,
Eastbourne,
East Sussex BN22 9AG
UNITED KINGDOM
1 NAME OF THE MEDICINAL PRODUCT
Cefuroxime 250 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 250 mg film-coated tablet contains 250 mg cefuroxime (as cefuroxime axetil)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

Light blue coloured film-coated tablets engraved with “250” on one side and “P125” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Cefuroxime is indicated for the treatment of the following mild to moderately severe infections caused by micro-organisms susceptible to cefuroxime:
- upper respiratory tract infections: acute otitis media, sinusitis, tonsillitis and pharyngitis
- acute bacterial bronchitis, acute exacerbations of chronic bronchitis
- lower uncomplicated urinary tract infections: cystitis
- skin and soft tissue infections: furunculosis, pyoderma and impetigo
- treatment of early stage Lyme disease (stage I) and subsequent prevention of late complications in adults and children above 12 years of age.

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

4.2 Posology and method of administration
Cefuroxime tablets are coated to mask their taste: they should not be chewed.
The usual duration of therapy is 7 days (ranging from 5 to 10 days). For treatment of pharyngotonsillitis caused by *Streptococcus pyogenes* a therapy duration of at least 10 days is indicated. The duration of treatment of early Lyme disease should be 20 days. In order to achieve optimum absorption Cefuroxime Film-coated Tablets should be taken shortly after meals.

The dosage depends on the severity of the infection. For severe infections parenteral forms of cefuroxime are recommended. Where appropriate Cefuroxime is effective when used following initial parenteral cefuroxime sodium in the treatment of pneumonia and acute exacerbations of chronic bronchitis. The dose may need to be revised when switching from parenteral to oral treatment.

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Children under 5 years of age:
Cefuroxime Film-coated Tablets are not suitable for use in children under the age of 5. For patients in this age group it is advised to use an oral suspension. There is no experience in children under 3 months of age.

Dosage regimen in renal impairment, in dialysis patients and elderly:
No special precautions are necessary in patients with renal impairment, or in elderly patients if the daily dosage does not exceed 1 gram. In patients with renal impairment and creatinine clearance below 20 ml/min Cefuroxime Film-coated Tablets should be dosed carefully. Patients undergoing haemodialysis will require a supplementary dose of cefuroxime at the end of each dialysis treatment.
4.3 **Contraindications**

Hypersensitivity to cefuroxime, other cephalosporins or to any of the excipients.

Previous immediate and/or severe hypersensitivity reaction to a penicillin or to any other type of betalactam medicinal products.

4.4 **Special warnings and precautions for use**

If after administration of Cefuroxime sensitivity reactions occur, the use should be discontinued immediately and an appropriate treatment should be established.

Special care is indicated in patients who have experienced an allergic reaction to penicillins or other beta-lactams.

As with other broad spectrum antibiotics, prolonged use of cefuroxime axetil may result in the overgrowth of non-susceptible organisms (e.g. candida, enterococci and clostridium difficile), which may require interruption of treatment.

In patients who develop severe diarrhoea during or after use of Cefuroxime, the risk of life threatening pseudomembranous colitis should be taken into account. The use of Cefuroxime should be discontinued and the appropriate treatment established. The use of preparations inhibiting the intestinal peristaltism is contra-indicated (see section 4.8).

A 20-day treatment of Lyme disease may cause the frequency of developing diarrhoea to increase.

Long term use of Cefuroxime may lead to an excess of pathogens resistant to cefuroxime axetil.

It is of high importance that the patient is carefully checked. If a superinfection occurs during treatment, appropriate measures should be taken (see section 4.8).

The use of Cefuroxime is not recommended in patients with severe intestinal tract disorders accompanied by vomiting and diarrhoea, since in these situations a sufficient absorption cannot be guaranteed. Administration of a parenteral formulation of cefuroxime should be considered.

The Jarisch-Herxheimer reaction has been reported following cefuroxime axetil treatment of Lyme disease. The reaction results directly from the bactericidal activity of cefuroxime axetil on the spirochaete *Borrelia burgdorferi*. Patients should be informed of this common and usually self-limiting reaction being a consequence of antibiotic treatment of Lyme disease.

Simultaneous use of medicines enhancing the pH of the stomach is not recommended (see section 4.5).

There is no clinical experience with the use of cefuroxime axetil in children under the age of 3 months. With respect to the treatment of early Lyme disease...
there is only clinical experience with children from the age of 12 and with adults.

Either the glucose oxidase or the hexokinase methods are recommended to determine the blood and plasma glucose levels in patients receiving Cefuroxime. Cefuroxime does not interfere in the alkaline picrate assay for creatinine (see section 4.5).

Please refer to section 4.5 for information on the use of cefuroxime axetil in combination with oral contraceptives.

During the treatment with cefuroxime sodium, some children have experienced slight to moderate hearing loss.

4.5 Interaction with other medicinal products and other forms of interaction

Simultaneous use of medicines enhancing the pH of the stomach decreases the bioavailability of Cefuroxime. It is recommended to avoid this combination (see section 4.4).

Since bacteriostatic drugs may interfere with the bactericidal action of cephalosporins, it is advisable to avoid giving tetracyclines, macrolides, or chloramphenicol in conjunction with Cefuroxime.

The concomitant administration of probenecid can produce higher and sustained concentrations of cefuroxime in the serum and in the bile.

Cefuroxime may interfere with the determination of glucose in urine with copper containing reagentia (Benedict- or Fehling-solution, Clinitest). For the determination of blood and plasma sugar levels in patients receiving Cefuroxime, the glucose-oxidase- or hexokinase method is recommended (see section 4.4).

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).

Cephalosporin antibiotics at high dosage should be given with caution to patients receiving potent diuretics, aminoglycosides, or amphotericin as these combinations increase the risk of nephrotoxicity.

The reliability of the contraceptive effect of oral contraceptives is in doubt when using cefuroxime axetil at the same time. For this reason, other non-hormonal contraceptive means should be used in addition to oral contraceptives during treatment with Cefuroxime.

Please refer to section 4.4 for information on other interactions.

4.6 Pregnancy and lactation

Pregnancy
There are not sufficient data on the use of cefuroxime axetil during pregnancy to assess its possible harmfulness. Animal studies do not show any harmful effects on embryonal and fetal development (see section 5.3). Cefuroxime crosses the placenta. Cefuroxime should not be used during pregnancy unless considered essential by the physician.

*Lactation*
Cefuroxime is excreted to a small degree in human milk; breast feeding should be avoided in women using Cefuroxime.

### 4.7 Effects on ability to drive and use machines
There are no studies of the effect of cefuroxime axetil on the ability to drive and to handle machines. However, any effects are not to be expected.

### 4.8 Undesirable effects

#### 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)

**Infections and infestations**

*Rare*

Pseudomembranous colitis

As with other antibiotics prolonged use may lead to secondary superinfections caused by insusceptible organisms, e.g. *Candida, Enterococci* and *Clostridium difficile* (see section 4.4)

**Blood and the lymphatic system disorders**

*Rare*

Decreased haemoglobin concentration, eosinophilia, leucopenia, neutropenia and thrombocytopenia

*Very rare*

Haemolytic anaemia

**Immune system disorders**

*Common*

Jarisch-Herxheimer reaction following cefuroxime axetil treatment of Lyme disease (see section 4.4)

*Rare*

Serum sickness

*Very rare*

Anaphylaxis

**Nervous system disorders**

*Uncommon*

Headache, dizziness

*Very rare*

Restlessness, nervousness, confusion

**Gastrointestinal disorders**
Common
Diarrhoea, nausea and vomiting. The frequency of diarrhoea is related to the administered dose and may range up to 10% with tablets. The incidence is even higher (approx. 13%) after prolonged treatment of early Lyme disease for 20 days.

Hepato-biliary disorders
Rare
Transient increases of hepatic enzyme levels (AST, ALT and LDH) and serum bilirubin
Very rare
Jaundice

Skin and subcutaneous tissue disorders
Common
Skin rashes, urticaria, pruritus
Very rare
Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis

Renal and urinary disorders
Common
Increased levels of creatinine and urea in serum, especially in patients with impaired renal function
Uncommon
Acute interstitial nephritis

General disorders and administration site conditions
Rare
Drug fever

Investigations
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 4.5. Interactions).

4.9 Overdose
Overdose of cephalosporins may cause cerebral irritancy leading to convulsions. In case of overdose cefuroxime serum levels can be reduced by haemodialysis and peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: second-generation cephalosporins
ATC-Code: J01DC02

Mode of action
Cefuroxime axetil owes its *in vivo* bactericidal activity to the parent compound cefuroxime. 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. Bacterial lysis is the end result.

**PK/PD relationship**

For cephalosporins, the most important pharmacokinetic-pharmacodynamic index correlating with in vivo efficacy has been shown to be the duration that the unbound drug concentration remains above the minimum inhibitory concentration (MIC) as a percentage of the dosing interval (%T>MIC).

**Mechanism of resistance**

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

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

Methicillin-resistant staphylococci (MRS) are resistant to all currently available β-lactam antibiotics including cefuroxime. Penicillin-resistant *Streptococcus pneumoniae* are cross-resistant to cephalosporins such as cefuroxime through alteration of penicillin binding proteins. Beta-lactamase negative, ampicillin resistant (BLNAR) strains of *H. influenzae* should be considered resistant to cefuroxime despite apparent in vitro susceptibility. Strains of Enterobacteriaceae, in particular *Klebsiella* spp. and *Escherichia coli* that produce ESBLs (extended spectrum β-lactamase) may be clinically resistant to therapy with cephalosporins despite apparent in vitro susceptibility and should be considered as resistant.

According to the EUCAST 2006 v1.1 the following breakpoints have been defined for cefuroxime axetil:

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</tr>
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2 Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility

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

**Susceptibility:**

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. 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.

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<tr>
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<tr>
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<tr>
<td><em>Peptostreptococcus</em> species</td>
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<tr>
<td><strong>Other organisms:</strong></td>
</tr>
<tr>
<td><em>Borrelia burgdorferi</em></td>
</tr>
<tr>
<td><strong>Species for which acquired resistance may be a problem:</strong></td>
</tr>
<tr>
<td><em>Acinetobacter</em> species</td>
</tr>
<tr>
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</tr>
<tr>
<td><em>Enterobacter</em> species</td>
</tr>
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<tbody>
<tr>
<td><em>Bacteroides fragilis</em></td>
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</table>
### 5.2 Pharmacokinetic properties

**Absorption:** After oral administration cefuroxime axetil is absorbed from the gastrointestinal tract and rapidly hydrolysed in the intestinal mucosa and blood causing the release of the active compound cefuroxime into the circulation. Optimum absorption occurs when cefuroxim axetil is taken shortly after a meal (50-60%). Under these circumstances maximum serum concentration is achieved after 2-3 hours.

**Distribution:** Cefuroxime is widely distributed in the body including pleural fluid, sputum, bone, synovial fluid, and aqueous humour, but only achieves therapeutic concentrations in the CSF when the meninges are inflamed. About 50% of cefuroxime in the circulation is bound to plasma proteins. It diffuses across the placenta and has been detected in breast milk.

**Metabolism:** Cefuroxime is not metabolised.

**Elimination:** Most of the dose of cefuroxime is excreted unchanged. 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. Probenecid competes with cefuroxime for renal tubular secretion resulting in higher and more prolonged plasma concentrations of cefuroxime. The plasma half-life ranges between 60 and 90 minutes and is prolonged in patients with renal impairment and in neonates.

Dialysis causes the decrease of cefuroxime serum levels.

### 5.3 Preclinical safety data

Cefuroxime sodium has a very low order of toxicity as demonstrated by acute toxicity studies. Investigations of chronic toxicity in several animal species (rat, dog and monkey) yielded no indications of drug related toxicological effects. The most prominent treatment-related effect was tissue damage at the injection sites.
Preclinical nephrotoxicity studies showed the product can cause renal damage in some species when administered in very high doses. Its nephrotoxicity increases when administered in combination with glycerol and furosemide. A cefuroxime ester did not show clinically relevant effects when tested in vitro and in vivo for genotoxic potential. No long-term investigations for determination of 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

Core:
Pregelatinized starch
Croscarmellose sodium
Sodium laurilsulfate
Microcrystalline cellulose
Colloidal anhydrous silica
Hydrogenated vegetable oil (Type I)

Coat:
Hypermellose (E464)
Titanium dioxide (E171)
Propylene glycol (E 1520)
Brilliant Blue FCF aluminium lake (E133)
Indigo Carmine Aluminium Lake (E132)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

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

6.5 Nature and contents of container
PVC/PCTFE Aluminium blister packaging

Pack sizes: 8, 10, 12, 14, 16, 20, 24 tablets

Not all pack sizes may be marketed.
6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
TEVA UK Limited
Brampton Road,
Hampden Park,
Eastbourne,
East Sussex BN22 9AG
UNITED KINGDOM

8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/1186

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
22/12/2009

10 DATE OF REVISION OF THE TEXT
22/12/2009

1 NAME OF THE MEDICINAL PRODUCT
Cefuroxime 500 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 500 mg film-coated tablet contains 500 mg cefuroxime (as cefuroxime axetil)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

Light blue coloured film-coated tablets engraved with “500” on one side and “P126” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Cefuroxime is indicated for the treatment of the following mild to moderately severe infections caused by micro-organisms susceptible to cefuroxime:
- upper respiratory tract infections: acute otitis media, sinusitis, tonsillitis and pharyngitis
- acute bacterial bronchitis, acute exacerbations of chronic bronchitis
- lower uncomplicated urinary tract infections: cystitis
- skin and soft tissue infections: furunculosis, pyoderma and impetigo
- treatment of early stage Lyme disease (stadium I) and subsequent prevention of late complications in adults and children above 12 years of age.

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

4.2 **Posology and method of administration**

Cefuroxime tablets are coated to mask their taste: they should not be chewed.

The usual duration of therapy is 7 days (ranging from 5 to 10 days). For treatment of pharyngotonsillitis caused by *Streptococcus pyogenes* a therapy duration of at least 10 days is indicated. The duration of treatment of early Lyme disease should be 20 days. In order to achieve optimum absorption Cefuroxime Film-coated Tablets should be taken shortly after meals.

The dosage depends on the severity of the infection. For severe infections parenteral forms of cefuroxime are recommended. Where appropriate Cefuroxime is effective when used following initial parenteral cefuroxime sodium in the treatment of pneumonia and acute exacerbations of chronic bronchitis. The dose may need to be revised when switching from parenteral to oral treatment.

**Dosage schedule for tablets:**

<table>
<thead>
<tr>
<th>Adults and children over 12 years of age</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infections</td>
<td>250 (– 500) mg twice daily</td>
</tr>
<tr>
<td>Lower respiratory tract infections</td>
<td>500 mg twice daily</td>
</tr>
<tr>
<td>Lower uncomplicated urinary tract infections</td>
<td>125 – 250 mg twice daily</td>
</tr>
<tr>
<td>Skin and soft tissue infections</td>
<td>250 – 500 mg twice daily</td>
</tr>
<tr>
<td>Early Lyme disease</td>
<td>500 mg twice daily during 20 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Children from 5 to 12 years of age</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Above-mentioned indications, if relevant for this group of children</td>
<td>125 – 250 mg twice daily</td>
</tr>
<tr>
<td>Acute otitis media</td>
<td>250 mg twice daily</td>
</tr>
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</table>

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</table>
Cefuroxime Film-coated Tablets are not suitable for use in children under the age of 5. For patients in this age group it is advised to use an oral suspension. There is no experience in children under 3 months of age.

**Dosage regimen in renal impairment, in dialysis patients and elderly:**
No special precautions are necessary in patients with renal impairment, or in elderly patients if the daily dosage does not exceed 1 gram. In patients with renal impairment and creatinine clearance below 20 ml/min Cefuroxime Film-coated Tablets should be dosed carefully. Patients undergoing haemodialysis will require a supplementary dose of cefuroxime at the end of each dialysis treatment.

4.3 **Contraindications**
Hypersensitivity to cefuroxime, other cephalosporins or to any of the excipients.

Previous immediate and/or severe hypersensitivity reaction to a penicillin or to any other type of betalactam medicinal products.

4.4 **Special warnings and precautions for use**
If after administration of Cefuroxime sensitivity reactions occur, the use should be discontinued immediately and an appropriate treatment should be established.

Special care is indicated in patients who have experienced an allergic reaction to penicillins or other beta-lactams.

As with other broad spectrum antibiotics, prolonged use of cefuroxime axetil may result in the overgrowth of non-susceptible organisms (e.g. candida, enterococci and clostridium difficile), which may require interruption of treatment.

In patients who develop severe diarrhoea during or after use of Cefuroxime, the risk of life threatening pseudomembranous colitis should be taken into account. The use of Cefuroxime should be discontinued and the appropriate treatment established. The use of preparations inhibiting the intestinal peristaltism is contra-indicated (see section 4.8).

A 20-day treatment of Lyme disease may cause the frequency of developing diarrhoea to increase.

Long term use of Cefuroxime may lead to an excess of pathogens resistant to cefuroxime axetil.

It is of high importance that the patient is carefully checked. If a superinfection occurs during treatment, appropriate measures should be taken (see section 4.8).

The use of Cefuroxime is not recommended in patients with severe intestinal tract disorders accompanied by vomiting and diarrhoea, since in these situations a sufficient absorption cannot be guaranteed. Administration of a parenteral formulation of cefuroxime should be considered.
The Jarisch-Herxheimer reaction has been reported following cefuroxime axetil treatment of Lyme disease. The reaction results directly from the bactericidal activity of cefuroxime axetil on the spirochaete *Borrelia burgdorferi*. Patients should be informed of this common and usually self-limiting reaction being a consequence of antibiotic treatment of Lyme disease.

Simultaneous use of medicines enhancing the pH of the stomach is not recommended (see section 4.5).

There is no clinical experience with the use of cefuroxime axetil in children under the age of 3 months. With respect to the treatment of early Lyme disease there is only clinical experience with children from the age of 12 and with adults.

Either the glucose oxidase or the hexokinase methods are recommended to determine the blood and plasma glucose levels in patients receiving Cefuroxime. Cefuroxime does not interfere in the alkaline picrate assay for creatinine (see section 4.5).

Please refer to section 4.5 for information on the use of cefuroxime axetil in combination with oral contraceptives.

During the treatment with cefuroxime sodium, some children have experienced slight to moderate hearing loss.

4.5 Interaction with other medicinal products and other forms of interaction

Simultaneous use of medicines enhancing the pH of the stomach decreases the bioavailability of Cefuroxime. It is recommended to avoid this combination (see section 4.4).

Since bacteriostatic drugs may interfere with the bactericidal action of cephalosporins, it is advisable to avoid giving tetracyclines, macrolides, or chloramphenicol in conjunction with Cefuroxime.

The concomitant administration of probenecid can produce higher and sustained concentrations of cefuroxime in the serum and in the bile.

Cefuroxime may interfere with the determination of glucose in urine with copper containing reagentia (Benedict- or Fehling-solution, Clinitest). For the determination of blood and plasma sugar levels in patients receiving Cefuroxime, the glucose-oxidase- or hexokinase method is recommended (see section 4.4).

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Please refer to section 4.4 for information on other interactions.

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Pregnancy
There are not sufficient data on the use of cefuroxime axetil during pregnancy to assess its possible harmfulness. Animal studies do not show any harmful effects on embryonal and fetal development (see section 5.3). Cefuroxime crosses the placenta. Cefuroxime should not be used during pregnancy unless considered essential by the physician.

Lactation
Cefuroxime is excreted to a small degree in human milk; breast feeding should be avoided in women using Cefuroxime.

4.7 Effects on ability to drive and use machines
There are no studies of the effect of cefuroxime axetil on the ability to drive and to handle machines. However, any effects are not to be expected.

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Common (≥1/100 to <1/10)
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| Aerobes, Gram negative:     |
| *Haemophilus influenzae*    |
| *Moraxella catarrhalis*     |
| *Proteus mirabilis*         |

| Anaerobes:                  |
| *Peptococcus* species       |
| *Peptostreptococcus* species|

| Other organisms:            |
| *Borrelia burgdorferi*      |

<table>
<thead>
<tr>
<th>Species for which acquired resistance may be a problem</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Acinetobacter</em> species</td>
</tr>
<tr>
<td><em>Citrobacter</em> species</td>
</tr>
</tbody>
</table>
### 5.2 Pharmacokinetic properties

**Absorption:** After oral administration cefuroxime axetil is absorbed from the gastrointestinal tract and rapidly hydrolysed in the intestinal mucosa and blood causing the release of the active compound cefuroxime into the circulation. Optimum absorption occurs when cefuroxime axetil is taken shortly after a meal (50-60%). Under these circumstances maximum serum concentration is achieved after 2-3 hours.

**Distribution:** Cefuroxime is widely distributed in the body including pleural fluid, sputum, bone, synovial fluid, and aqueous humour, but only achieves therapeutic concentrations in the CSF when the meninges are inflamed. About 50% of cefuroxime in the circulation is bound to plasma proteins. It diffuses across the placenta and has been detected in breast milk.

**Metabolism:** Cefuroxime is not metabolised.

**Elimination:** Most of the dose of cefuroxime is excreted unchanged. 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. Probenecid competes with cefuroxime for renal tubular secretion resulting in higher and more prolonged plasma concentrations of cefuroxime. The plasma half-life ranges between 60 and 90 minutes and is prolonged in patients with renal impairment and in neonates.

Dialysis causes the decrease of cefuroxime serum levels.

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<table>
<thead>
<tr>
<th>Enterobacter species</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
</tr>
<tr>
<td><em>Klebsiella species</em></td>
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<tr>
<td><em>Providencia rettgeri</em></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
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</table>

<table>
<thead>
<tr>
<th>Inherently resistant organisms</th>
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</thead>
<tbody>
<tr>
<td><em>Bacteroides fragilis</em></td>
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<td><em>Clostridium difficile</em></td>
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<tr>
<td><em>Enterococcus spp</em></td>
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<tr>
<td><em>Listeria monocytogenes</em></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> species</td>
</tr>
<tr>
<td>Others:</td>
</tr>
<tr>
<td><em>Legionella</em> spp.</td>
</tr>
<tr>
<td><em>Clamydophila pneumoniae</em></td>
</tr>
<tr>
<td><em>Mycoplasma pneumoniae</em></td>
</tr>
</tbody>
</table>

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MHRA PAR; CEFUROXIME 125 MG, 250 MG AND 500 MG FILM-COATED TABLETS, PL 00289/1185-7
5.3 Preclinical safety data
Cefuroxime sodium has a very low order of toxicity as demonstrated by acute toxicity studies. Investigations of chronic toxicity in several animal species (rat, dog and monkey) yielded no indications of drug related toxicological effects. The most prominent treatment-related effect was tissue damage at the injection sites.
Preclinical nephrotoxicity studies showed the product can cause renal damage in some species when administered in very high doses. Its nephrotoxicity increases when administered in combination with glycerol and furosemide.
A cefuroxime ester did not show clinically relevant effects when tested in vitro and in vivo for genotoxic potential.
No long-term investigations for determination of 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
Core:
Pregelatinized starch
Croskarmellose sodium
Sodium laurilsulfate
Microcrystalline cellulose
Colloidal anhydrous silica
Hydrogenated vegetable oil (Type I)

Coat:
Hypropmellese (E464)
Titanium dioxide (E171)
Propylene glycol (E 1520)
Brilliant Blue FCF aluminium lake (E133)
Indigo Carmine Aluminium Lake (E132)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

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

6.5 Nature and contents of container
PVC/PCTFE Aluminium blister packaging
Pack sizes: 6, 8, 10, 12, 14, 16, 20, 24 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
TEVA UK Limited
Brampton Road,
Hampden Park,
Eastbourne,
East Sussex BN22 9AG
UNITED KINGDOM

8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/1187

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
22/12/2009

10 DATE OF REVISION OF THE TEXT
22/12/2009
Module 3

Product Information Leaflet
PACKAGE LEAFLET: INFORMATION FOR THE USER

CEFROXIME 125 MG, 250 MG AND 500 MG FILM-COATED TABLETS

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

IN THIS LEAFLET:
1. What Cefuroxime Film-coated Tablets are and what they are used for
2. Before you take Cefuroxime Film-coated Tablets
3. How to take Cefuroxime Film-coated Tablets
4. Possible side effects
5. How to store Cefuroxime Film-coated Tablets
6. Further information

1. WHAT CEFROXIME FILM-COATED TABLETS ARE AND WHAT THEY ARE USED FOR

The name of your medicine is Cefuroxime Film-coated Tablets. It is an antibiotic and belongs to a class of medicines called “cephalosporins.” It is used to treat certain types of infections and works by killing certain types of bacteria.

Your doctor may have prescribed Cefuroxime Film-coated Tablets to treat one of the following infections:
- Upper respiratory tract infections (including infections occurring in the ears, sinuses, tonsils and throat).
- Chest infections such as bronchitis.
- Bladder infections (water infections).
- Skin infections (recurring boils, ulcers and impetigo).
- Early ‘Lyme disease’ (rare infection spread by tick bites) and prevention of complications in adults and children above 12 years of age.

2. BEFORE YOU TAKE CEFROXIME FILM-COATED TABLETS

Do NOT take Cefuroxime Film-coated Tablets:
- If you are allergic (hypersensitive) to cefuroxime or to any other antibiotics in the same class (cephalosporins).
- If you are allergic (hypersensitive) to any of the other ingredients included in Cefuroxime Film-coated Tablets.
- If you allergic to penicillin or other similar antibiotics. Not all people who are allergic to penicillin are allergic to cefuroxime. However, if you have previously suffered from a severe allergic reaction then you should not take this medicine. Tell your doctor if you have had an allergic reaction to penicillin in the past and he/she will decide whether it is appropriate for you to take Cefuroxime Film-coated Tablets.

If you are not sure whether any of the above apply to you speak to your doctor or pharmacist before taking this medicine.

UK/1/1699/01-03/DC

MHRA PAR; CEFROXIME 125 MG, 250 MG AND 500 MG FILM-COATED TABLETS, PL 00289/1185-7
Take special care with Cefuroxime Film-coated Tablets

Tell your doctor before you start to take this medicine if:

- You have previously suffered from an allergic reaction to penicillins or other beta-lactam antibiotics.
- You suffer from any other condition which causes vomiting (sickness) and diarrhoea as this could stop your medicine from being absorbed properly. In this case your doctor may recommend an injection of cefuroxime.
- You are taking other medicines which decrease stomach acidity (such as medicines used to treat indigestion, heartburn or stomach ulcers). In this case your medicine may not be absorbed properly (see the “Using other medicines” section below).

If, after starting treatment, you begin to experience symptoms of an allergic reaction (see “Possible side effects” section for details of potentially serious symptoms) stop taking your medicine and contact your doctor immediately.

If, during treatment, you develop sickness and diarrhoea then contact your doctor as this could stop your medicine from being absorbed properly.

If you develop severe diarrhoea while using or after using Cefuroxime Film-coated Tablets you should contact your doctor straight away as this could indicate that you are suffering from a serious condition called “pseudomembranous colitis”. In this case, do not take medicines to slow down bowel movements for treatment of diarrhoea.

Your medicine may cause overgrowth of other microorganisms which occur naturally in your body. This can lead to other conditions such as vaginal thrush and stomach upsets.

If you have Lyme disease you may experience fever, chills, headache and weakness after starting treatment with Cefuroxime Film-coated Tablets. This is quite common and you should not worry. However, if any of the symptoms become serious then contact your doctor.

During treatment with Cefuroxime Film-coated Tablets some children may experience slight to moderate hearing loss.

Taking other medicines

Talk to your doctor if you are taking any of the following:

- The oral contraceptive Pill. Your medicine may stop your Pill from working properly and other non-hormonal methods of contraception (e.g. condoms) should be used. Speak to your doctor or pharmacist for further advice.
- Medicines which slow down contractions of your intestines (such as medicines used to stop diarrhoea).
- Medicines which decrease stomach acidity (such as medicines used to treat indigestion, heartburn or stomach ulcers). These could stop your medicine from being absorbed properly.
- Other antibiotics including tetracyclines (e.g. tetracycline, doxycycline and minocycline), macrolides (e.g. erythromycin, azithromycin and clarithromycin) and chloramphenicol. This could prevent your medicine from working properly.
- Probenecid (used in the treatment of gout). This could lead to higher concentrations of cefuroxime in your body increasing the risk of side-effects.
- Certain diuretics (water tablets) such as furosemide as this could lead to kidney damage.
- Aminoglycoside antibiotics (e.g. gentamycin, neomycin and tobramycin) and amphotericin (used to treat fungal infections) as this could lead to kidney damage.

Taking Cefuroxime Film-coated Tablets can interfere with certain medical tests including those used to determine levels of glucose (sugar) in your blood. If you are due to have a medical test make sure that your
doctor knows that you are taking Cefuroxime Film-coated Tablets before the test. If you monitor the levels of glucose in your blood or urine yourself (e.g. diabetic patients) speak to your doctor or pharmacist to see if your medicine could affect the results of your test.

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

**Taking Cefuroxime Film-coated Tablets with food and drink**

To ensure that your medicine is absorbed properly it should be taken shortly after meals.

**Pregnancy and breast-feeding**

If you are pregnant you should only take Cefuroxime Film-coated Tablets if your doctor considers it to be absolutely necessary. The risks to your baby are not fully understood.

Cefuroxime passes into the breast milk. You should not breast feed your baby if you are taking Cefuroxime Film-coated Tablets.

Ask your doctor or pharmacist for advice before taking any medicine.

**Driving and using machines**

Taking Cefuroxime Film-coated Tablets does not affect your ability to drive or operate heavy machinery.

3. **HOW TO TAKE CEFUROXIME FILM-COATED TABLETS**

Always take Cefuroxime Film-coated Tablets exactly as your doctor has told you to. You should check with your doctor or pharmacist if you are not sure.

The dose of Cefuroxime Film-coated Tablets that you take, how often you should take it and the length of your treatment will depend on the type and severity of infection that you have. Your doctor will tell you precisely how to take your medicine. Further advice will also be included on the dispensing label prepared by your pharmacist. Make sure that you read this carefully before starting treatment.

You should always complete the full course of your medicine even if you start to feel better.

You should take your tablets after meals to ensure that they are absorbed properly.

The usual dose is included below:

**Adults and children over 12 years of age:**

- **Upper respiratory tract infection (ears, sinuses, tonsils and throat)**
  250 mg to 500 mg twice daily for 5 to 10 days
- **Chest infections such as bronchitis**
  500 mg twice daily for 5 to 10 days
- **Bladder infections (water infections)**
  125 mg to 250 mg twice daily for 5 to 10 days
- **Skin infections (recurring boils, ulcers and impetigo)**
  250 mg to 500 mg twice daily for 5 to 10 days
- **Treatment of early Lyme disease**
  500 mg twice daily for 20 days
Children from 5 to 12 years of age:

- *Ear infections*
  250 mg twice daily for 5 to 10 days
- *All other infections listed above*
  125 mg to 250 mg twice daily for 5 to 10 days

Children under 5 years of age:

- **Cefuroxime Film-coated Tablets** is not suitable for use in children under the age of 5.

If you have severe kidney disease your doctor will monitor your dose carefully during treatment and may decide to change it. If you have kidney problems and are being treated with haemodialysis then you may need to take an additional dose after each dialysis session. Speak to your doctor for further advice.

**If you take more Cefuroxime Film-coated Tablets than you should**

If you (or someone else) swallow a lot of the tablets all together or if you think a child has swallowed any of the tablets, contact your nearest hospital casualty department or your doctor immediately. An overdose is likely to cause fitting (convulsions). Please take this leaflet, any remaining tablets and the container with you to the hospital or doctor so that they know which tablets were consumed.

**If you forget to take Cefuroxime Film-coated Tablets**

If you forgot to take a dose of your medicine then take it as soon as you remember. However, if it is nearly time for your next dose then skip the missed dose and take the next dose at the normal time. Do not take a double dose to make up for a forgotten tablet.

**If you stop taking Cefuroxime Film-coated Tablets**

Do not stop taking your medicine unless under the advise of your doctor. Your doctor will tell you how many days you need to take Cefuroxime Film-coated Tablets for. It is important to complete the whole course of treatment, even if you start to feel better.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Cefuroxime Film-coated Tablets can cause side effects, although not everybody gets them.

Some of the side effects of Cefuroxime Film-coated Tablets can be serious. If you suffer from any of the following symptoms you should contact your doctor straight away:

- Sudden wheeziness or chest tightness, breathing difficulties, swelling of eyelids, face or lips or collapse (fainting) as these may be symptoms of an acute allergic reaction to your medicine
- Severe diarrhoea (this could indicate that you are suffering from a condition called “Pseudomembranous colitis”).
- Blistering of the skin, mouth, eyes and genital organs which could indicate a severe adverse reaction.

The following side effects have been reported at the approximate frequencies shown:
Common (affecting fewer than one person in 10 but more than one person in 100):
- Combination of fever, chills, headache and weakness in patients being treated for Lyme disease
- Diarrhoea, nausea and vomiting. If you are taking a long course of Cefuroxime Film-coated Tablets for the treatment of Lyme disease, diarrhoea occurs in up to 13% of patients (13 patients out of every 100 undergoing treatment).
- Rash, skin eruptions and itchiness.
- Renal and urinary problems. If your kidneys do not work very well, worsening of kidney function may occur (higher levels of creatinine and urea in your blood which may be detected by blood tests).

Uncommon (affecting fewer than one person in 100 but more than one person in 1,000):
- Headache and dizziness.
- Inflammation of the kidneys leading to fever, pain in the side, and blood in the urine.

Rare (affecting fewer than one person in 1,000 but more than one person in 10,000):
- A serious condition called “Pseudomembranous colitis” which results in severe diarrhoea.
- Other infections caused by overgrowth of microorganisms which occur naturally in your body.
- Decreases in levels of haemoglobin (a chemical in your blood which carries oxygen around your body).
- Blood disorders which result in a decrease in the number of white blood cells in your blood making your body more susceptible to infections. If levels of white blood cells fall too low you may develop fever or chills, a sore throat or ulcers in your mouth or throat.
- A reduction in blood platelets, which increases the risk of bleeding or bruising.
- A condition called “serum sickness” which results in an itchy rash, joint pain, fever and enlarged lymph nodes (glands).
- Changes in levels of certain chemicals in your liver which may be detected by blood tests.
- Fever.

Very rare (affecting fewer than one person in 10,000):
- Reduction in red blood cells which can make the skin pale or yellow and cause weakness or breathlessness.
- Serious allergic reaction which causes difficulty in breathing or dizziness.
- Restlessness, nervousness and confusion.
- Jaundice (yellowing of the skin or whites of the eyes).
- Serious allergic reaction which leads to flu-like symptoms, blistering of the skin, mouth, eyes and genital organs.

Cefuroxime Film-coated Tablets can also interfere with certain medical tests. Please refer to the “Take special care with Cefuroxime Film-coated Tablets” and “Taking other medicines” section of the leaflet for further information.

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

5. HOW TO STORE CEFUROXIME FILM-COATED TABLETS

Keep out of the reach and sight of children.

Do not use Cefuroxime Film-coated Tablets after the expiry date that is stated on the blister or outer packaging. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Cefuroxime Film-coated Tablets contains:

- The active ingredient is cefuroxime (as cefuroxime axetil).
- The other ingredients in the tablet core are pregelatinised starch, croscarmellose sodium, sodium laurilsulfate, microcrystalline cellulose, anhydrous colloidal silica and hydrogenated vegetable oil.
- The other ingredients in the tablet coating are as follows:

  **Cefuroxime 125 mg Film-coated Tablets:**
  Hypromellose (E464), titanium dioxide (E171), propylene glycol (E1520).

  **Cefuroxime 250 mg and 500 mg Film-coated Tablets:**
  Hypromellose (E464), titanium dioxide (E171), propylene glycol (E1520), Brilliant Blue FCF aluminium lake (E133), Indigo Carmine Aluminium Lake (E132).

What Cefuroxime Film-coated Tablets looks like and contents of the pack:

Cefuroxime 125mg Film-coated Tablets are white to off-white coloured film-coated tablets engraved with “125” on one side and “P124” on the other side.

Cefuroxime 250 mg Film-coated Tablets are light blue coloured film-coated tablets engraved with “250” on one side and “P125” on the other side.

Cefuroxime 500 mg Film-coated Tablets are light blue coloured film-coated tablets engraved with “500” on one side and “P126” on the other side.

Your medicine is provided in blister packs. Pack sizes are as follows:

- Cefuroxime 125 mg Film-coated Tablets: 10, 12 and 14 tablets.
- Cefuroxime 250 mg Film-coated Tablets: 8, 10, 12, 14, 16, 20 and 24 tablets.
- Cefuroxime 500 mg Film-coated Tablets: 6, 8, 10, 12, 14, 16, 20 and 24 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Teva UK Limited, Eastbourne, BN22 9AG.

This leaflet was last revised: November 2009

PL 00289/1185-1187
Module 4

Labelling
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton (10, 12, 14 tablets in PVC/PCTFE Aluminium blisters. Not all pack sizes may be marketed)

1. NAME OF THE MEDICINAL PRODUCT

Cefuroxime 125 mg Film-coated Tablets
Cefuroxime (as cefuroxime axetil)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 125 mg cefuroxime (as cefuroxime axetil)

3. LIST OF EXCIPIENTS

[Not applicable]

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
10 tablets
12 tablets
14 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Please read the enclosed package leaflet before use

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

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

[Not applicable]

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

There are no special storage conditions
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

[Not applicable]

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

TEVA UK Limited, Eastbourne, BN22 9AG

12. MARKETING AUTHORISATION NUMBER(S)

PL 00289/1185

13. BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by the doctor

16. INFORMATION IN BRAILLE

Cefuroxime 125mg Film-coated Tablets
### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

<p>| | |</p>
<table>
<thead>
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<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></td>
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<td><strong>3. EXPIRY DATE</strong></td>
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<td><strong>4. BATCH NUMBER</strong></td>
<td>LOT:</td>
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<tr>
<td><strong>5. OTHER</strong></td>
<td>[Not applicable]</td>
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</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton (8, 10, 12, 14, 16, 20, 24 tablets in PVC/PCTFE Aluminium blisters. Not all pack sizes may be marketed)

1. **NAME OF THE MEDICINAL PRODUCT**
   Cefuroxime 250 mg Film-coated Tablets
   Cefuroxime (as cefuroxime axetil)

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**
   Each tablet contains 250 mg cefuroxime (as cefuroxime axetil)

3. **LIST OF EXCIPIENTS**
   [Not applicable]

4. **PHARMACEUTICAL FORM AND CONTENTS**
   Film-coated tablets
   8 tablets
   10 tablets
   12 tablets
   14 tablets
   16 tablets
   20 tablets
   24 tablets

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**
   Oral use
   Please read the enclosed package leaflet before use

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**
   Keep out of the reach and sight of children

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**
   [Not applicable]

8. **EXPIRY DATE**
   EXP:

9. **SPECIAL STORAGE CONDITIONS**
There are no special storage conditions

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

[Not applicable]

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

TEVA UK Limited, Eastbourne, BN22 9AG

12. MARKETING AUTHORISATION NUMBER(S)

PL 00289/1186

13. BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by the doctor

16. INFORMATION IN BRAILLE

Cefuroxime 250mg Film-coated Tablets
### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

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<td>LOT:</td>
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<tr>
<td><strong>5. OTHER</strong></td>
<td>[Not applicable]</td>
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PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton (6, 8, 10, 12, 14, 16, 20, 24 tablets in PVC/PCTFE Aluminium blisters. Not all pack sizes may be marketed)

1. NAME OF THE MEDICINAL PRODUCT
Cefuroxime 500 mg Film-coated Tablets
Cefuroxime (as cefuroxime axetil)

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each tablet contains 500 mg cefuroxime (as cefuroxime axetil)

3. LIST OF EXCIPIENTS
[Not applicable]

4. PHARMACEUTICAL FORM AND CONTENTS
Film-coated tablets
6 tablets
8 tablets
10 tablets
12 tablets
14 tablets
16 tablets
20 tablets
24 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION
Oral use
Please read the enclosed package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN
Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY
[Not applicable]

8. EXPIRY DATE
EXP:

9. SPECIAL STORAGE CONDITIONS
There are no special storage conditions

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

[Not applicable]

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

TEVA UK Limited, Eastbourne, BN22 9AG

**12. MARKETING AUTHORISATION NUMBER(S)**

PL 00289/1187

**13. BATCH NUMBER**

LOT:

**14. GENERAL CLASSIFICATION FOR SUPPLY**

POM

**15. INSTRUCTIONS ON USE**

Use as directed by the doctor

**16. INFORMATION IN BRAILLE**

Cefuroxime 500mg Film-coated Tablets
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<tr>
<td>5. OTHER</td>
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Module 5

Scientific discussion during initial procedure

RECOMMENDATION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) considers that the applications for Cefuroxime 125 mg, 250 mg and 500 mg Film-coated Tablets in the treatment of bacterial infections due to susceptible organisms are approvable.

EXECUTIVE SUMMARY
About the product
Cefuroxime axetil owes its \textit{in vivo} bactericidal activity to the parent compound cefuroxime. 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. Bacterial lysis is the end result.

General comments on the submitted dossier
This is a Decentralised Procedure with the United Kingdom acting as the Reference Member State. These applications are submitted under article 10.1 of Directive 2001/83/EC, as amended, cross-referring to Zinnat® 125mg Tablets (PL 10949/0095, granted 3 September 1987), Zinnat® 250mg Tablets (PL 10949/0096, granted 3 September 1987) and Zinnat® 500mg Tablets (PL 10949/0019, granted 18 August 1987).

With UK as the Reference Member State in this Decentralized Procedure, Teva Pharma B.V., The Netherlands is applying for a Marketing Authorisations for Cefuroxime 125 mg, 250 mg and 500 mg Film-coated Tablets in the Czech Republic, Germany, Spain, Ireland, Italy, Poland, Portugal, and the Slovak Republic.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles.
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites located outside the Community, the RMS has accepted a copy of the current GMP certificate of satisfactory inspection issued by the inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS has been reassured that the submitted studies have been carried out in accordance with GCP, and agreed ethical principles.
SCIENTIFIC OVERVIEW AND DISCUSSION

QUALITY ASPECTS

Drug substance
The chemical-pharmaceutical documentation and Expert Report in relation to Cefuroxime 125 mg, 250 mg and 500 mg Film-coated Tablets are of sufficient quality in view of the present European regulatory requirements. The active substance, cefuroxime axetil, which is the subject of a Ph. Eur. monograph, is controlled by current Certificates of Suitability. The drug substance specifications for the drug substances are acceptable. Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. An adequate re-test period has been defined based on conducted stability studies.

Drug Product
The development of the products has been described, the choice of excipients is justified and their functions explained. The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. The batch analysis results show that the finished products meet the specifications proposed. The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug products are adequately drawn up. The proposed shelf-life of 3 years is acceptable. This medicinal product does not require any special storage conditions.

NON CLINICAL ASPECTS
The pharmacodynamic, pharmacokinetic and toxicological properties of cefuroxime axetil are well known. Therefore, no further studies are required and the applicant provides none.

The lack of an environmental risk assessment is justified since the products are generic versions of an already approved one and it is not likely to change the total market of cefuroxime.

CLINICAL ASPECTS

PHARMACOKINETICS

Pharmacokinetics of active ingredient
Absorption: After oral administration cefuroxime axetil is absorbed from the gastrointestinal tract and rapidly hydrolysed in the intestinal mucosa and blood causing the release of the active compound cefuroxime into the circulation. Optimum absorption occurs when cefuroxime axetil is taken shortly after a meal (50-60%). Under these circumstances maximum serum concentration is achieved after 2-3 hours.

Distribution: Cefuroxime is widely distributed in the body including pleural fluid, sputum, bone, synovial fluid, and aqueous humour, but only achieves therapeutic concentrations in the CSF when the meninges are inflamed. About 50% of cefuroxime in the circulation is bound to plasma proteins. It diffuses across the placenta and has been detected in breast milk.
Metabolism: Cefuroxime is not metabolised.
Elimination: Most of the dose of cefuroxime is excreted unchanged. 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. Probenecid competes with cefuroxime for renal tubular secretion resulting in higher and more prolonged plasma concentrations of cefuroxime. The plasma half-life ranges between 60 and 90 minutes and is prolonged in patients with renal impairment and in neonates.

Bioequivalence studies
The applicant claims Cefuroxime 125 mg, 250 mg and 500 mg Film-coated Tablets are generic versions of the reference drug product, Zinnat tablets.

To support the application, the applicant has submitted two single dose bioequivalence studies (fasting and fed), comparing the proposed 500 mg tablet to Zinnat 500mg Tablets. The relative rate and extent of absorption of cefuroxime axetil from test and reference formulations were determined.

Study 1

Study design
A randomized, single dose, open-label, two-treatment, two-period, two-sequence, crossover comparative bioequivalence study in healthy subjects under fasting conditions.

The investigator states that the study was performed in compliance with Good Clinical Practice (GCP).

Population(s) studied and clinical part of the study
36 (+ 2 standby) healthy adult male volunteers with age range from 18 to 39 years were entered in the study. Acceptable inclusion and exclusion criteria were presented. Thirty four volunteers completed both study periods. Four subjects were withdrawn, three due to adverse events during the study and one who was found positive for drugs of abuse at period II check in.
Study drug was administered with 240ml water after an overnight fast. Twenty blood samples were collected from pre-dose (0.0 hr) to 10.0 hours post-dose after administration of each product with a washout period of 7 days between study drug administrations.

There were six adverse events reported in four subjects. All were considered as possibly related to the study medication. None were serious.
Eight subjects were found to have abnormal blood results during the post study safety assessment.

Analytical methods
Appropriate analytical methods were used to study the samples.

Pharmacokinetic Variables and Statistical methods
The pre-specified acceptance range for bioequivalence was 80-125% for the difference of means of Cmax, AUC0-t and AUC0-∞.
Pharmacokinetic parameters Cmax, AUC0-t, AUC0-∞, Tmax, T1/2 and Ke are determined using WinNonlin Version 5.0 software. The analysis of variance (ANOVA) was performed for log-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ and 90% confidence intervals were calculated (Test-Reference) for the log-transformed pharmacokinetic parameters.

The ratio of AUCt/AUC∞ was within the acceptance range (>80%) for all subjects. The ANOVA model includes sequence, subject nested within the sequence, period and formulation as factors.

Results

**Summary statistics of pharmacokinetic parameters of cefuroxime axetil under fasting conditions** [veda clinical research (2006a)]

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>Reference Product (R)</th>
<th>Test Product (T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tmax (h)</td>
<td>2.374 ± 0.7984</td>
<td>2.019 ± 0.7337</td>
</tr>
<tr>
<td>Cmax (µg/ml)</td>
<td>6.554 ± 1.3565</td>
<td>6.946 ± 1.7171</td>
</tr>
<tr>
<td>AUC0-t (µg.h/ml)</td>
<td>23.226 ± 5.4094</td>
<td>23.971 ± 6.9437</td>
</tr>
<tr>
<td>AUC0-∞ (µg.h/ml)</td>
<td>23.836 ± 5.5265</td>
<td>24.557 ± 7.0488</td>
</tr>
<tr>
<td>Kd (t/h)</td>
<td>0.4759 ± 0.06740</td>
<td>0.4701 ± 0.06113</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>1.485 ± 0.2076</td>
<td>1.499 ± 0.1990</td>
</tr>
<tr>
<td>AUC % Extrapolated (%)</td>
<td>2.589 ± 0.7380</td>
<td>2.513 ± 1.1512</td>
</tr>
</tbody>
</table>

90% confidence intervals for the difference of least square means of in-transformed parameters Cmax, AUC0-t and AUC0-∞ for cefuroxime [veda clinical research (2006a)]

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Lower limit</th>
<th>Upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (µg/ml)</td>
<td>93.70</td>
<td>109.13</td>
</tr>
<tr>
<td>AUC0-t (µg.h/ml)</td>
<td>93.83</td>
<td>108.82</td>
</tr>
</tbody>
</table>

**Conclusion on single dose fasted study**
The study design was adequate to address the BE of an immediate release oral formulation with the pharmacokinetic parameters of cefuroxime. None of the pre-dose samples contained detectable levels of cefuroxime, the length of the washout period was adequate. The blood collection time of 10 hours was sufficient, AUC extrapolated area was <10% of AUC0-inf for all of the individuals after both treatments. The analytical part of the study adhered to the GLP requirements. The analytical methods were appropriate. Pharmacokinetic and statistical methods applied were adequate.

Study 2

**Study design**
A randomized, single dose, open-label, two-treatment, two-period, two-sequence, crossover bioequivalence study in healthy subjects under fed conditions.
The investigator states that the study was performed in compliance with Good Clinical Practice (GCP).

Population(s) studied and clinical part of the study
Thirty-six (+ two standby) healthy male volunteers with an age range from 20-43 years were entered in the study. Acceptable inclusion and exclusion criteria were presented. Thirty-four volunteers completed both study periods. Two subjects were withdrawn, both before the start of period II. One subject was withdrawn due to nausea and vomiting, one subject experienced fever and received medication.

The study drug was administered 30 min after the start of a high fat breakfast (800-1000kcal) after an overnight fast of 10h with 240 ml water. Twenty blood samples were collected from pre-dose (0.0h) to 10.0 hours post-dose after administration of each product with a washout period of 7 days between study drug administrations.

There were three adverse events reported in three subjects. One subject suffered with fever, one subject had vomiting, one subject had fever and a sore throat. Two of these received concomitant medication and were withdrawn. All events were considered as possibly related to the study medication. None were serious. Nine subjects were found to have abnormal blood results during the post study safety assessment.

Analytical methods
Appropriate analytical methods were used to study the samples.

Pharmacokinetic Variables and Statistical methods
The prespecified acceptance range for bioequivalence was 80-125% for the difference of means of Cmax, AUC0-t and AUC0-∞.
Pharmacokinetic parameters Cmax, AUC0-t, AUC0-∞, Tmax, T 1/2 and Kel were determined. (using WinNonlin Version 5.0 software).
The analysis of variance (ANOVA) was performed for log-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ and 90% confidence intervals were calculated for the log-transformed pharmacokinetic parameters. The ANOVA model includes sequence, subject nested within the sequence, period and formulation as factors.
The ratio of AUCt/AUC∞ was within the acceptance range (<80%) for all subjects.

Results

<table>
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<tr>
<th>Parameters (Units)</th>
<th>Reference Product (R)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>T_{max} (h)</td>
<td>2.769 ± 0.9657</td>
<td>2.821 ± 0.8101</td>
</tr>
<tr>
<td>C_{max} (μg/ml)</td>
<td>10.172 ± 1.5953</td>
<td>10.077 ± 1.6778</td>
</tr>
<tr>
<td>AUC_{0-t} (μg.h/ml)</td>
<td>37.043 ± 5.2209</td>
<td>37.896 ± 5.7993</td>
</tr>
<tr>
<td>AUC_{0-∞} (μg.h/ml)</td>
<td>38.069 ± 5.6875</td>
<td>38.872 ± 6.2825</td>
</tr>
<tr>
<td>K_{a} (1/h)</td>
<td>0.4741 ± 0.05724</td>
<td>0.4827 ± 0.04344</td>
</tr>
<tr>
<td>t_{1/2} (h)</td>
<td>1.484 ± 0.1893</td>
<td>1.448 ± 0.1409</td>
</tr>
<tr>
<td>AUC_{%Extrapolated} (%)</td>
<td>2.575 ± 1.4365</td>
<td>2.393 ± 1.3136</td>
</tr>
</tbody>
</table>
Conclusion on single dose fed study
The study design was adequate to address the BE of an immediate release oral formulation with pharmacokinetic parameters of cefuroxime. None of the pre-dose samples contained detectable levels of cefuroxime, the length of the washout period was adequate. The blood collection time of 10h was sufficient, AUC extrapolated area was <10% of AUC0-inf for all of the individuals after both treatments.
The analytical part of the study adhered to the GLP requirements. The analytical method was validated except for the long term stability of cefuroxime in plasma. Pharmacokinetic and statistical methods applied were adequate.

Overall bioequivalence conclusion
The bioequivalence studies submitted by the applicant were performed according to the respective NfG and GCP requirements. Single dose studies are appropriate as the pharmacokinetics of cefuroxime is neither time nor dose dependent. Both fed and fasting studies were conducted as there is a known food effect on the bioavailability of cefuroxime. The dose used for testing was the highest dose, which is appropriate. The 90% confidence intervals for the ratio of the AUC and Cmax lie within the acceptance criteria of 80-125%.

Therefore, bioequivalence with the reference product was demonstrated after single dose (500mg) fasting and fed administration of the test product. Absorption is enhanced in the presence of food for both test and reference product. This is reflected in the recommendations on how to take the medication in the SPC.

Pharmacokinetic conclusion
The submitted bioequivalence study has confirmed that the applicant’s medicinal product is bioequivalent to the reference product with respect to the rate and extent of absorption.

Clinical efficacy
No new efficacy data have been submitted and none are required for this application.

Clinical safety
No new safety data have been submitted and none are required for this application.

Pharmacovigilance system
The RMS considers that 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.

Risk Management Plan
MHRA PAR; CEFUROXIME 125 MG, 250 MG AND 500 MG FILM-COATED TABLETS, PL 00289/1185-7
Cefuroxime 125 mg, 250 mg and 500 mg Film-coated Tablets are generic products. As with the reference medicinal product, no special important risks or potential risks have been identified which require additional risk minimization activities other than the global pharmacovigilance system.

**Product literature**
All product literature (SPC, PIL and labelling) is satisfactory. The package leaflet was submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that they contain.

**BENEFIT RISK ASSESSMENT**
Bioequivalence to the originator has been established. Approval is recommended.