Public Assessment Report

Decentralised Procedure

Cefixime 400 mg Film-coated Tablets

PL 22805/0032
PL 22805/0033

UK/H/1532/001/DC
UK/H/3965/001/DC

Orchid Europe Ltd.
Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Orchid Europe Ltd. Marketing Authorisations (licences) for the medicinal product Cefixime 400 mg Film-coated Tablets (product licence numbers: PL 22805/0032 and PL 22805/0033) on 16 December 2010. This medicine is available on prescription only.

Cefixime belongs to a group of medicines called cephalosporins, which are used for treating infections. Cefixime 400 mg Film-coated Tablets are used to treat:

- Infection of the middle ear
- Sinus infection
- Throat infection
- Infection causing sudden worsening of long-standing bronchitis
- Lung infections (pneumonia) acquired outside hospital
- Infections in the urinary tract including some infections of the kidneys

The data submitted in support of these applications for Cefixime 400 mg Film-coated Tablets raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using this product outweigh the risks; hence Marketing Authorisations have been granted.
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**Module 1**

**Information about Decentralised Procedures**

<table>
<thead>
<tr>
<th>Name of the products in the Reference Member State</th>
<th>Cefixime 400 mg Film-coated Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of applications</td>
<td>Generic (Article 10.1)</td>
</tr>
<tr>
<td>Name of the active substance (INN)</td>
<td>Cefixime</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Third-generation cephalosporins (J01DD08)</td>
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<tr>
<td>Pharmaceutical form and strength</td>
<td>Film-coated tablet, 400mg</td>
</tr>
<tr>
<td>Reference number for the Decentralised Procedures</td>
<td>UK/H/1532/001/DC UK/H/3965/001/DC</td>
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<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>UK/H/1532/01/DC: AT and DE UK/H/3965/01/DC: AT and IT</td>
</tr>
<tr>
<td>Start of Decentralised Procedures</td>
<td>24 August 2009</td>
</tr>
<tr>
<td>End date of Decentralised Procedures</td>
<td>10 November 2010</td>
</tr>
<tr>
<td>Marketing Authorisation numbers</td>
<td>PL 22805/0032 PL 22805/0033</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Orchid Europe Ltd. Building 3, Chiswick Park, 566 Chiswick High Road, Chiswick, London, W4 5YA, United Kingdom</td>
</tr>
</tbody>
</table>
Module 2

Summaries of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Cefixime 400 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 447.63 mg Cefixime trihydrate, equivalent to 400 mg Cefixime anhydrous

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet

White to off white, film-coated, rectangular shaped tablet having partial break line on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Cefixime is indicated for the treatment of the following infections when caused by susceptible organisms (see section 5.1):

- Acute exacerbations of chronic bronchitis
- Community-acquired Pneumonia
- Uncomplicated lower urinary tract infections
- Uncomplicated pyelonephritis

In the treatment of:
- Otitis media
- Sinusitis
- Pharyngitis

The use of cefixime should be reserved for infections in which the causative organism is known or suspected to be resistant to other commonly used antibacterial agents or when treatment failure may carry significant risk.

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

4.2 Posology and method of administration
Adults
The recommended dose for adults is 400 mg daily taken as a single dose (see section 4.4 and 5.1).
The usual course of treatment is 7 days. This may be continued for up to 14 days if required.

**Elderly patients**
Elderly patients may be given the same dose as recommended for adults. Renal function should be assessed and dosage should be adjusted in severe renal impairment (See above and section 4.4).

**Adolescents ≥ 12 years of age**
Adolescents ≥ 12 years of age may be given the same dose as recommended for adults.

**Children from 6 months to 11 years of age**
It is recommended that Children from 6 months to 11 years of age be given cefixime as an oral suspension. The recommended dosage for children is 8 mg / kg body weight / day administered as a single dose or in two divided doses.

**Children less than 6 months of age**
The safety and efficacy of cefixime has not been established in children less than 6 months of age.

**Renal insufficiency**
Cefixime may be administered in the presence of impaired renal function. Normal dose and schedule may be given in patients with creatinine clearances of 20 ml/min or greater. In patients whose creatinine clearance is less than 20 ml/min, it is recommended that a dose of 200 mg once daily should not be exceeded. The dose and regimen for patients who are maintained on chronic ambulatory peritoneal dialysis or haemodialysis should follow the same recommendation as that for patients with creatinine clearances of less than 20 ml/min.

There are insufficient data regarding use of cefixime in the pediatric and adolescent age group in the presence of renal insufficiency. Therefore, the use of cefixime in these patient-groups is not recommended.

**Method of administration**
Cefixime tablets are for oral administration only. Cefixime tablets should be taken with a sufficient amount of water.
Cefixime may be taken with or without food (see section 5.2).

### 4.3 Contraindications
Hypersensitivity to cefixime, other cephalosporin antibiotics or to any of the excipients.

Previous, immediate and/or severe hypersensitivity reaction to penicillin or any beta-lactam antibiotic.
4.4 Special warnings and precautions for use

Cefixime should be given with caution to patients who have shown hypersensitivity to other drugs. Cephalosporins should be given with caution to penicillin-sensitive patients, as there is some evidence of partial cross-allergenicity between the penicillins and cephalosporins.

Patients have had severe reactions (including anaphylaxis) to both classes of drugs. Special care is indicated in patients who have experienced any allergic reaction to penicillins or any other beta-lactam antibiotics as cross-reactions may occur (for contraindications due to known hypersensitivity reactions see section 4.3).

If severe hypersensitivity reactions or anaphylactic reactions occur after administration of cefixime, the use of cefixime should be discontinued immediately and appropriate emergency measures should be initiated.

Renal insufficiency

Cefixime should be administered with caution in patients with creatinine clearance < 20 ml / min (see sections 4.2 and 5.2). There are insufficient data regarding use of cefixime in the pediatric and adolescent age group in the presence of renal insufficiency. Therefore, the use of cefixime in these patient-groups is not recommended.

Renal function is to be monitored under a combination therapy with cefixime preparations and aminoglycoside antibiotics, polymyxin B, colistin or high-dose loop diuretics (e.g. furosemide) because of the probability of additional renal impairment. This applies particularly for patients with already restricted renal function (see section 4.5).

Treatment with cefixime at the recommended (400mg) dose can significantly alter the normal flora of the colon and lead to overgrowth of clostridia. Studies indicate that a toxin produced by Clostridium difficile is a primary cause of antibiotic-associated diarrhoea.

In patients who develop severe persistent diarrhoea during or after use of cefixime, the risk of life threatening pseudomembranous colitis should be taken into account. The use of cefixime should be discontinued and appropriate treatment measures should be established. Management of pseudomembranous colitis should include sigmoidoscopy, appropriate bacteriologic studies, fluids, electrolytes and protein supplementation. If the colitis does not improve after the drug has been discontinued, or if the symptoms are severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be excluded. The use of medicinal products inhibiting the intestinal peristalsis is contraindicated.

Influence on laboratory diagnostic tests:

A false positive reaction for glucose in the urine may occur with Benedict's or Fehling's solutions or with copper sulphate test tablets, but not with tests based on enzymatic glucose oxidase reactions.
A false positive direct Coombs’ test has been reported during treatment with cephalosporin antibiotics, therefore it should be recognised that a positive Coombs’ test may be due to the drug.

4.5 Interaction with other medicinal products and other forms of interaction
Concomitant intake with potentially nephrotoxic substances (such as aminoglycoside antibiotics, colistin, polymyxin and viomycin) and strong-acting diuretics (e.g. ethacrynic acid or furosemide) induce an increased risk of impairment of renal function (see section 4.4).

Nifedipine, a calcium channel blocker, may increase bioavailability of cefixime up to 70%.

In common with other cephalosporins, increases in prothrombin time have been noted in a few patients. Care should therefore be taken in patients receiving anticoagulation therapy.

Administration of cefixime may reduce the efficacy of oral contraceptives. It is therefore recommended to take supplemental non-hormonal contraceptive measures.

4.6 Pregnancy and lactation

Pregnancy
There are no adequate data from the use of Cefixime in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Cefixime should not be used in pregnant mothers unless considered essential by the physician.

Lactation
It is unknown whether cefixime is excreted in human breast milk. Animal studies have shown excretion of cefixime in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with cefixime should be made taking into account the benefit of breast-feeding to the child and the benefit of cefixime therapy to the woman. However, until further clinical experience is available, cefixime should not be prescribed to breast-feeding mothers.

4.7 Effects on ability to drive and use machines
Cefixime has no known influence on the ability to drive and use machines. However, side effects may occur (See also section 4.8), which may influence the ability to drive and use machines.

4.8 Undesirable effects
In this section, the following convention has been used for the classification of undesirable effects in terms of frequency:

- Common: ≥1/100 to <1/10,
- Uncommon: ≥1/1,000 to <1/100,
- Rare: $\geq 1/10,000$ to $< 1/1,000$ and
- Very rare: $< 1/10,000$

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Drug Reaction</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Superinfection bacterial, superinfection fungal</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Antibiotic-associated colitis</td>
<td>Very rare</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Eosinophilia</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Leucopenia, agranulocytosis, pancytopenia, thrombocytopenia, haemolytic anaemia</td>
<td>Very rare</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Anaphylactic shock, serum sickness</td>
<td>Very rare</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia</td>
<td>Rare</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Vertigo</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Psychomotor hyperactivity</td>
<td>Very rare</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhoea</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain, nausea, vomiting</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Flatulence</td>
<td>Rare</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Hepatitis, cholestatic jaundice</td>
<td>Very rare</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Angioneurotic oedema, pruritus</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Stevens-Johnson syndrome, toxic epidermal necrolysis</td>
<td>Very rare</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Interstitial nephritis</td>
<td>Very rare</td>
</tr>
<tr>
<td>General disorders and administration site</td>
<td>Mucosal inflammation, pyrexia</td>
<td>Rare</td>
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<tr>
<td>conditions</td>
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</tr>
<tr>
<td>System Organ Class</td>
<td>Adverse Drug Reaction</td>
<td>Frequency</td>
</tr>
<tr>
<td>--------------------</td>
<td>-----------------------------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Investigations</td>
<td>Hepatic enzyme increased (transaminase, alkaline phosphatase)</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>blood urea increased</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>blood creatinine increased</td>
<td>Very rare</td>
</tr>
</tbody>
</table>

4.9 Overdose
There is no experience with overdoses with Cefixime.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: ATC code: J01DD08

Mode of Action
Cefixime is an antibacterial agent of the cephalosporin class. Like other cephalosporins, cefixime exerts antibacterial activity by binding to and inhibiting the action of penicillin-binding proteins involved in the synthesis of bacterial cell walls. This leads to bacterial cell lysis and cell death.

PK/PD relationship
The time that the plasma concentration of cefixime exceeds the MIC of the infecting organism has been shown to best correlate with efficacy in PK/PD studies.

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

- Hydrolysis by extended-spectrum beta-lactamases and / or by chromosomally-encoded (AmpC) enzymes that may be induced or derepressed in certain aerobic gram-negative bacterial species
- Reduced affinity of penicillin-binding proteins
- Reduced permeability of the outer membrane of certain gram-negative organisms restricting access to penicillin-binding proteins
- Drug efflux pumps

More than one of these mechanisms of resistance may co-exist in a single bacterial cell. Depending on the mechanism(s) present, bacteria may express cross-resistance to several or all other beta-lactams and / or antibacterial drugs of other classes.

Breakpoints
Clinical minimum inhibitory concentration (MIC) breakpoints established by EUCAST (May 2009) for cefixime are:

- *H. influenzae*: sensitive $\leq 0.12$ mg/L, resistant $> 0.12$ mg/L
- *M. catarrhalis*: sensitive $\leq 0.5$ mg/L, resistant $> 1.0$ mg/L
- *Neisseria gonorrhoeae*: sensitive $\leq 0.12$ mg/L, resistant $> 0.12$ mg/L
- *Enterobacteriaceae*: sensitive $\leq 1.0$ mg/L, resistant $> 1.0$ mg/L (for uncomplicated urinary tract infections only). The breakpoints for *Enterobacteriaceae* will detect reduced susceptibility mediated by most clinically important beta-lactamases in *Enterobacteriaceae*. Occasional ESBL-producing strains will be reported susceptible. For purposes of infection control, epidemiology and surveillance, laboratories may wish to use specific tests to screen for and confirm ESBL-production.
- Non-species related breakpoints: insufficient data.

**Susceptibility**

The prevalence of resistance may vary geographically and over 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>Streptococcus pyogenes</em></td>
</tr>
</tbody>
</table>

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

| Species for which resistance may be a problem   |
| *Streptococcus pneumoniae*                     |
| *Citrobacter freundii* $\$                    |
| *Enterobacter cloacae* $\$                     |
| *Escherichia coli* % &                         |
| *Klebsiella oxytoca* %                         |
| *Klebsiella pneumoniae* %                      |
| *Morganella morganii* $\$                     |
| *Serratia marcescens* $\circ$                 |

| Resistant species                              |

MHRA PAR; CEFIXIME 400 MG FILM-COATED TABLETS, PL 22805/0032-3 11
Chlamydia spp.
Chlamyphila spp.
Clostridium difficile
Bacteroides fragilis
Enterococci
Legionella pneumophila
Mycoplasma spp.
Pseudomonas species
Staphylococcus aureus+
Streptococcus pneumoniae (Penicillin-intermediate and -resistant)

+Cefixime has poor activity against staphylococci (regardless of susceptibility to methicillin)
$ Natural intermediate susceptibility.
% Extended spectrum beta-laktamase (ESBL) producing strains are always resistant.
& Resistance rate <10% in isolates of female patients with uncomplicated cystitis, otherwise ≥10%.

5.2 Pharmacokinetic properties
Absorption
The absolute oral bioavailability of cefixime is in the range of 22-54%.
Absorption is not significantly modified by the presence of food. Cefixime may therefore be given without regard to meals.

Distribution
Serum protein binding is well characterised for human and animal sera; cefixime is almost exclusively bound to the albumin fraction, the mean free fraction being approximately 30%. Protein binding of cefixime is only concentration dependent in human serum at very high concentrations, which are not seen following clinical dosing.

From in vitro studies, serum or urine concentrations of 1 mg/L or greater were considered to be adequate for most common pathogens against which cefixime is active. Typically, the peak serum levels following the recommended adult or paediatric doses are between 1.5 and 3 mg/L. Little or no accumulation of cefixime occurs following multiple dosing.

Metabolism and Elimination
The pharmacokinetics of cefixime in healthy elderly (age > 64 years) and young volunteers (11-35) compared the administration of 400 mg doses once daily for 5 days. Mean $C_{\text{max}}$ and AUC values were slightly greater in the elderly. Elderly patients may be given the same dose as the general population.

Cefixime is predominantly eliminated as unchanged drug in the urine. Glomerular filtration is considered the predominant mechanism. Metabolites of cefixime have not been isolated from human serum or urine.
Transfer of $^{14}$C-labelled cefixime from lactating rats to their nursing offspring through breast milk was quantitatively small (approximately 1.5% of the mothers' body content of cefixime in the pup). No data are available on secretion of cefixime in human breast milk. Placental transfer of cefixime was small in pregnant rats dosed with labelled cefixime.

5.3 Preclinical safety data

There are no findings from chronic toxicity investigations suggesting that any side effects unknown to date could occur in humans. Furthermore, in vivo and in vitro studies did not yield any indication of a potential to cause mutagenicity. Long-term studies on carcinogenicity have not been conducted. Reproduction studies have been performed in mice and rats at doses up to 400 times the human dose and have revealed no evidence of impaired fertility or harm to the foetus due to cefixime. In the rabbit, at doses up to 4 times the human dose, there was no evidence of a teratogenic effect; there was a high incidence of abortion and maternal death, which is an expected consequence of the known sensitivity of rabbits to antibiotic-induced changes in the population of the microflora of the intestine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Pre-gelatinised starch
Calcium hydrogen phosphate
Magnesium stearate.
Silica Colloidal Anhydrous
Opadry White Y-1-7000
Purified water.

Opadry White Y-1-7000 contains:
HPMC 2910/Hypromellose 5 cP (E 464)
Titanium Dioxide (E 171)
Macrogol / PEG 400 (E 1520)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions. Keep blister in the outer carton.

6.5 Nature and contents of container
PVC/ PVdC/ Aluminium blister pack: 3s, 5s, 7s, 10s & 100s.

PVC/Aclar/ Aluminium blister pack: 3s, 5s, 7s, 10s & 100s.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
Not applicable.

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

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

8 MARKETING AUTHORISATION NUMBER(S)
PL 22805/0032

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
16/12/2010

10 DATE OF REVISION OF THE TEXT
16/12/2010

1 NAME OF THE MEDICINAL PRODUCT
Cefixime 400 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 447.63 mg Cefixime trihydrate, equivalent to 400 mg Cefixime anhydrous

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet

White to off white, film-coated, rectangular shaped tablet having partial break line on both sides.
4 CLINICAL PARTICULARS

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Cefixime is indicated for the treatment of the following infections when caused by susceptible organisms (see section 5.1):

- Acute exacerbations of chronic bronchitis
- Community-acquired Pneumonia
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- Uncomplicated pyelonephritis

In the treatment of:
- Otitis media
- Sinusitis
- Pharyngitis

The use of cefixime should be reserved for infections in which the causative organism is known or suspected to be resistant to other commonly used antibacterial agents or when treatment failure may carry significant risk.

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

4.2 Posology and method of administration

Adults
The recommended dose for adults is 400 mg daily taken as a single dose (see section 4.4 and 5.1).

The usual course of treatment is 7 days. This may be continued for up to 14 days if required.

Elderly patients
Elderly patients may be given the same dose as recommended for adults. Renal function should be assessed and dosage should be adjusted in severe renal impairment (See above and section 4.4).

Adolescents ≥ 12 years of age
Adolescents ≥ 12 years of age may be given the same dose as recommended for adults.

Children from 6 months to 11 years of age
It is recommended that Children from 6 months to 11 years of age be given cefixime as an oral suspension. The recommended dosage for children is 8 mg / kg body weight / day administered as a single dose or in two divided doses.

Children less than 6 months of age
The safety and efficacy of cefixime has not been established in children less than 6 months of age.

Renal insufficiency
Cefixime may be administered in the presence of impaired renal function. Normal dose and schedule may be given in patients with creatinine clearances of 20 ml/min or greater. In patients whose creatinine clearance is less than 20 ml/min, it is recommended that a dose of 200 mg once daily should not be exceeded. The dose and regimen for patients who are maintained on chronic ambulatory peritoneal dialysis or haemodialysis should follow the same recommendation as that for patients with creatinine clearances of less than 20 ml/min.

There are insufficient data regarding use of cefixime in the pediatric and adolescent age group in the presence of renal insufficiency. Therefore, the use of cefixime in these patient-groups is not recommended.

**Method of administration**
Cefixime tablets are for oral administration only. Cefixime tablets should be taken with a sufficient amount of water. Cefixime may be taken with or without food (see section 5.2).

### 4.3 Contraindications
Hypersensitivity to cefixime, other cephalosporin antibiotics or to any of the excipients.

Previous, immediate and/or severe hypersensitivity reaction to penicillin or any beta-lactam antibiotic.

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Patients have had severe reactions (including anaphylaxis) to both classes of drugs. Special care is indicated in patients who have experienced any allergic reaction to penicillins or any other beta-lactam antibiotics as cross-reactions may occur (for contraindications due to known hypersensitivity reactions see section 4.3).

If severe hypersensitivity reactions or anaphylactic reactions occur after administration of cefixime, the use of cefixime should be discontinued immediately and appropriate emergency measures should be initiated.

Renal insufficiency
Cefixime should be administered with caution in patients with creatinine clearance < 20 ml / min (see sections 4.2 and 5.2). There are insufficient data regarding use of cefixime in the pediatric and adolescent age group in the presence of renal insufficiency. Therefore, the use of cefixime in these patient-groups is not recommended.

Renal function is to be monitored under a combination therapy with cefixime preparations and aminoglycoside antibiotics, polymyxin B, colistin or high-
dose loop diuretics (e.g. furosemide) because of the probability of additional renal impairment. This applies particularly for patients with already restricted renal function (see section 4.5).

Treatment with cefixime at the recommended (400mg) dose can significantly alter the normal flora of the colon and lead to overgrowth of clostridia. Studies indicate that a toxin produced by Clostridium difficile is a primary cause of antibiotic-associated diarrhoea.

In patients who develop severe persistent diarrhoea during or after use of cefixime, the risk of life threatening pseudomembranous colitis should be taken into account. The use of cefixime should be discontinued and appropriate treatment measures should be established. Management of pseudomembranous colitis should include sigmoidoscopy, appropriate bacteriologic studies, fluids, electrolytes and protein supplementation. If the colitis does not improve after the drug has been discontinued, or if the symptoms are severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be excluded. The use of medicinal products inhibiting the intestinal peristalsis is contraindicated.

Influence on laboratory diagnostic tests:
A false positive reaction for glucose in the urine may occur with Benedict's or Fehling's solutions or with copper sulphate test tablets, but not with tests based on enzymatic glucose oxidase reactions.

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In common with other cephalosporins, increases in prothrombin time have been noted in a few patients. Care should therefore be taken in patients receiving anticoagulation therapy.

Administration of cefixime may reduce the efficacy of oral contraceptives. It is therefore recommended to take supplemental non-hormonal contraceptive measures.

### 4.6 Pregnancy and lactation

*Pregnancy*
There are no adequate data from the use of Cefixime in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Cefixime should not be used in pregnant mothers unless considered essential by the physician.

**Lactation**

It is unknown whether cefixime is excreted in human breast milk. Animal studies have shown excretion of cefixime in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with cefixime should be made taking into account the benefit of breast-feeding to the child and the benefit of cefixime therapy to the woman. However, until further clinical experience is available, cefixime should not be prescribed to breast-feeding mothers.

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

Cefixime has no known influence on the ability to drive and use machines. However, side effects may occur (See also section 4.8), which may influence the ability to drive and use machines.

**4.8 Undesirable effects**

In this section, the following convention has been used for the classification of undesirable effects in terms of frequency:

- **Common:** ≥1/100 to <1/10,
- **Uncommon:** ≥1/1,000 to <1/100,
- **Rare:** ≥1/10,000 to <1/1,000 and
- **Very rare:** <1/10,000

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Drug Reaction</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Superinfection bacterial, superinfection fungal</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Antibiotic-associated colitis</td>
<td>Very rare</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Eosinophilia</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Leucopenia, agranulocytosis, pancytopenia, thrombocytopenia, haemolytic anaemia</td>
<td>Very rare</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Anaphylactic shock, serum sickness</td>
<td>Very rare</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia</td>
<td>Rare</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Vertigo</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Psychomotor hyperactivity</td>
<td>Very rare</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhoea</td>
<td>Common</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Adverse Drug Reaction</td>
<td>Frequency</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>---------------------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Abdominal pain, nausea, vomiting</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Flatulence</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Hepatitis, cholestatic jaundice</td>
<td>Very rare</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Angioneurotic oedema, pruritus</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Stevens-Johnson syndrome, toxic epidermal necrolysis</td>
<td>Very rare</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Interstitial nephritis</td>
<td>Very rare</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Mucosal inflammation, pyrexia</td>
<td>Rare</td>
</tr>
<tr>
<td>Investigations</td>
<td>Hepatic enzyme increased (transaminase, alkaline phosphatase)</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>blood urea increased</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>blood creatinine increased</td>
<td>Very rare</td>
</tr>
</tbody>
</table>

4.9 Overdose
There is no experience with overdoses with Cefixime.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: ATC code: J01DD08

Mode of Action
Cefixime is an antibacterial agent of the cephalosporin class. Like other cephalosporins, cefixime exerts antibacterial activity by binding to and inhibiting the action of penicillin-binding proteins involved in the synthesis of bacterial cell walls. This leads to bacterial cell lysis and cell death.

PK/PD relationship
The time that the plasma concentration of cefixime exceeds the MIC of the infecting organism has been shown to best correlate with efficacy in PK/PD studies.

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

- Hydrolysis by extended-spectrum beta-lactamases and / or by chromosomally-encoded (AmpC) enzymes that may be induced or derepressed in certain aerobic gram-negative bacterial species
- Reduced affinity of penicillin-binding proteins
Reduced permeability of the outer membrane of certain gram-negative organisms restricting access to penicillin-binding proteins

Drug efflux pumps

More than one of these mechanisms of resistance may co-exist in a single bacterial cell. Depending on the mechanism(s) present, bacteria may express cross-resistance to several or all other beta-lactams and/or antibacterial drugs of other classes.

**Breakpoints**
Clinical minimum inhibitory concentration (MIC) breakpoints established by EUCAST (May 2009) for cefixime are:

- *H. influenzae*: sensitive \(\leq 0.12\) mg/L, resistant \(> 0.12\) mg/L
- *M. catarrhalis*: sensitive \(\leq 0.5\) mg/L, resistant \(> 1.0\) mg/L
- *Neisseria gonorrhoeae*: sensitive \(\leq 0.12\) mg/L, resistant \(> 0.12\) mg/L
- *Enterobacteriaceae*: sensitive \(\leq 1.0\) mg/L, resistant \(> 1.0\) mg/L (for uncomplicated urinary tract infections only). The breakpoints for *Enterobacteriaceae* will detect reduced susceptibility mediated by most clinically important beta-lactamases in *Enterobacteriaceae*. Occasional ESBL-producing strains will be reported susceptible. For purposes of infection control, epidemiology and surveillance, laboratories may wish to use specific tests to screen for and confirm ESBL-production.
- Non-species related breakpoints: insufficient data.

**Susceptibility**
The prevalence of resistance may vary geographically and over 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>Streptococcus pyogenes</em></td>
</tr>
</tbody>
</table>

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

| Species for which resistance may be a problem |
"Streptococcus pneumoniae
Citrobacter freundii $
Enterobacter cloacae $
Escherichia coli % &
Klebsiella oxytoca %
Klebsiella pneumoniae %
Morganella morganii $
Serratia marcescens $^°

Resistant species

Chlamydia spp.
Chlamydophila spp.
Clostridium difficile
Bacteroides fragilis
Enterococci
Legionella pneumophila
Mycoplasma spp.
Pseudomonas species
Staphyloccocus aureus$
Streptococcus pneumoniae (Penicillin-intermediate and -resistant)

Cefixime has poor activity against staphylococci (regardless of susceptibility to methicillin)
$ Natural intermediate susceptibility.
% Extended spectrum beta-laktamase (ESBL) producing strains are always resistant.
& Resistance rate <10% in isolates of female patients with uncomplicated cystitis, otherwise ≥10%.

5.2 Pharmacokinetic properties
Absorption
The absolute oral bioavailability of cefixime is in the range of 22-54%.
Absorption is not significantly modified by the presence of food. Cefixime may therefore be given without regard to meals.

Distribution
Serum protein binding is well characterised for human and animal sera; cefixime is almost exclusively bound to the albumin fraction, the mean free fraction being approximately 30%. Protein binding of cefixime is only concentration dependent in human serum at very high concentrations, which are not seen following clinical dosing.

From in vitro studies, serum or urine concentrations of 1 mg/L or greater were considered to be adequate for most common pathogens against which cefixime is active. Typically, the peak serum levels following the recommended adult or paediatric doses are between 1.5 and 3 mg/L. Little or no accumulation of cefixime occurs following multiple dosing.
Metabolism and Elimination
The pharmacokinetics of cefixime in healthy elderly (age > 64 years) and young volunteers (11-35) compared the administration of 400 mg doses once daily for 5 days. Mean $C_{\text{max}}$ and AUC values were slightly greater in the elderly. Elderly patients may be given the same dose as the general population.

Cefixime is predominantly eliminated as unchanged drug in the urine. Glomerular filtration is considered the predominant mechanism. Metabolites of cefixime have not been isolated from human serum or urine.

Transfer of $^{14}$C-labelled cefixime from lactating rats to their nursing offspring through breast milk was quantitatively small (approximately 1.5% of the mothers' body content of cefixime in the pup). No data are available on secretion of cefixime in human breast milk. Placental transfer of cefixime was small in pregnant rats dosed with labelled cefixime.

5.3 Preclinical safety data
There are no findings from chronic toxicity investigations suggesting that any side effects unknown to date could occur in humans. Furthermore, in vivo and in vitro studies did not yield any indication of a potential to cause mutagenicity. Long-term studies on carcinogenicity have not been conducted. Reproduction studies have been performed in mice and rats at doses up to 400 times the human dose and have revealed no evidence of impaired fertility or harm to the foetus due to cefixime. In the rabbit, at doses up to 4 times the human dose, there was no evidence of a teratogenic effect; there was a high incidence of abortion and maternal death, which is an expected consequence of the known sensitivity of rabbits to antibiotic-induced changes in the population of the microflora of the intestine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Microcrystalline cellulose
Pre-gelatinised starch
Calcium hydrogen phosphate
Magnesium stearate.
Silica Colloidal Anhydrous
Opadry White Y-1-7000
Purified water.

Opadry White Y-1-7000 contains:
HPMC 2910/Hypromellose 5 cP (E 464)
Titanium Dioxide (E 171)
Macrogol / PEG 400 (E 1520)

6.2 Incompatibilities
Not applicable.
6.3 Shelf life
24 months.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.
Keep blister in the outer carton

6.5 Nature and contents of container
PVC/ PVdC/ Aluminium blister pack: 3s, 5s, 7s, 10s & 100s.

PVC/Aclar/ Aluminium blister pack: 3s, 5s, 7s, 10s & 100s.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
Not applicable.

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

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

8 MARKETING AUTHORISATION NUMBER(S)
PL 22805/0033

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
16/12/2010

10 DATE OF REVISION OF THE TEXT
16/12/2010
Module 3

Product Information Leaflets

PL 22805/0032:
PACKAGE LEAFLET: INFORMATION FOR THE USER

CeFlixime 400 mg Film-coated Tablets
(Cefixime)

The name of your medicine is CeFlixime 400 mg Film-coated Tablets and will be referred to as CeFlixime throughout the rest of this document.

Read all of this leaflet carefully before you start taking this medicine

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

In this leaflet:
1. WHAT CeFlixime IS AND WHAT IT IS USED FOR
2. BEFORE YOU TAKE CeFlixime
3. HOW TO TAKE CeFlixime
4. POSSIBLE SIDE EFFECTS
5. HOW TO STORE CeFlixime
6. FURTHER INFORMATION

1. WHAT CeFlixime IS AND WHAT IT IS USED FOR

CeFlixime belongs to a group of medicines called Cephalosporins, which are used for treating infections.

CeFlixime is used to treat:
- infection of the middle ear
- sinus infection
- throat infection
- infection causing mild to moderate worsening of chronic respiratory tract infections
- lung infections (pneumonia) acquired outside of hospital
- infections in the urinary tract including some infections of the kidneys.

2. BEFORE YOU TAKE CeFlixime

Do not take CeFlixime if you
- are allergic to a penicillin antibiotic or to any other beta-lactam type of antibiotic.
- have ever had a severe allergic reaction to penicillin antibiotic or to any other beta-lactam type of antibiotic.

Take special care with CeFlixime

CeFlixime is not suitable for everyone. Before you take CeFlixime you should tell your doctor if you:

- are allergic to paracetamol or to any of the ingredients in the tablet (see section 6).
- are allergic to any of the ingredients in the tablet (see section 6).
- are allergic to penicillin antibiotics or to any other beta-lactam type of antibiotic.
- have ever had a severe allergic reaction to penicillin antibiotic or to any other beta-lactam type of antibiotic.

In patients who develop severe allergic reaction or anaphylaxis (serious allergic reaction which causes difficulty in breathing or swelling of the face, lips, throat or tongue) after administration of CeFlixime, the medicine should be withdrawn and appropriate treatment should be given.

- have ever been told that your kidneys do not work very well. Also, if you are taking any sort of treatment (like dialysis) for kidney failure. You may take CeFlixime but you may need a lower dose.
- are taking other medicines which are known to be harmful to your kidneys. Also inform your doctor if you have any kidney problems. Your doctor may perform certain tests regularly to measure how well your kidneys are working during the treatment.
- have severe or persistent diarrhoea with stomach pain or cramps during or shortly after treatment with CeFlixime, stop taking this medicine and contact your doctor immediately. Medicines which may slow or stop bowel movements must not be taken.

Having a course of CeFlixime can temporarily increase the chance that you can get infections caused by other sorts of germs on which CeFlixime does not act. For example, thrush (infection caused by a yeast germ called Candida) may occur.

Effect on laboratory tests

If you are to undertake any blood or urine tests, inform your doctor that you are taking CeFlixime, as CeFlixime may alter the results of some of these tests.

CeFlixime can alter the results of some urine tests for drugs (e.g. nortriptyline, noradrenaline and methyldopa) and tests used to measure the level of uric acid in the urine.

Taking other medicines

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

In particular, tell your doctor or pharmacist if you are taking:

- medicines which are known to be harmful to your kidneys like:
- antibiotics (e.g. amoxicillin, ciprofloxacin).
- medicines that increase the amount of urine (e.g. diuretics such as ethacrynic acid or frusemide).
- rifampicin, a medicine used for the treatment of tuberculosis and other infections.
- non-steroidal anti-inflammatory drugs (NSAIDs)
- oral contraceptives (the birth control pill).

Taking CeFlixime with food and drink

CeFlixime may be taken with or without food. The tablet should be swallowed with a glass of water.

3. HOW TO TAKE CeFlixime

Dosage

Always take CeFlixime exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. This dose of CeFlixime presumes depends on the type of infection and how bad the infection is. It also depends on how well the kidneys are working. Your doctor or pharmacist will explain this to you.

The usual dose is

Adults

The usual adult dose is one tablet taken once daily. The medicine should always be taken at the same time each day.

Patients with kidney problems

In patients with kidney problems, the dosage of CeFlixime may need to be reduced. Your doctor will calculate the right dose for you according to the results of blood or urine tests that measure how well your kidneys are working.

There are insufficient data regarding the use of CeFlixime in children and adolescents with kidney problems. CeFlixime is therefore not recommended for use in these patients.

Elderly

No change in dose is needed for elderly patients, provided the kidneys are normal.

Adolescents 12 years of age and older

Adolescents 12 years of age and older may be given the same dose as adults.
Children older than 6 months and up to 11 years of age.
Children older than 6 months and up to 11 years should be given Cefixime as an oral suspension (liquid to be taken by mouth) rather than as a tablet.

Children less than 6 months of age
Cefixime is not recommended for use in children less than 6 months of age.

If you take more Cefixime than you should
If you or your child have taken more of this medicine than you should, talk to your doctor or contact your nearest hospital emergency department immediately.

If you forget to take Cefixime
If you forget to take a tablet, take one as soon as you remember. However, if the next dose is due in less than 6 hours, skip the missed dose and go back to your regular closing schedule. Do not take double doses.

If you stop taking Cefixime
It is important that you take this medicine until you finish the prescribed course. You should not stop the medicine just because you feel better. If you stop too soon, the infection may start up again. If the person being treated still feels unwell at the end of the prescribed course of treatment, or feels worse during treatment, tell your doctor.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Cefixime can cause side effects, although not everybody gets them. The following side effects are important and will require immediate action if you experience them. You should stop taking Cefixime and see your doctor immediately if the following symptoms occur:

Very rare side effects (affect less than 1 in 10,000 patients) include:
- watery and severe diarrhoea that may also be bloody
- sudden severe allergic reactions (anaphylactic shock) such as skin rash or hives, itching, swelling of the face, lips, tongue or other parts of the body, tightness of the chest, wheezing and collapse
- severe skin illness with blistering of the skin, mouth, eyes and genitals (Steven Johnson syndrome, toxic epidermal necrolysis)

Common side effects (affect less than 1 in 10 patients) include:
- diarrhoea

Uncommon side effects (affect less than 1 in 100 patients) include:
- headache
- nausea
- vomiting
- abdominal (tummy) pain
- changes in blood tests that check how your liver is working
- skin rash

Rare side effects (affect less than 1 in 1000 patients) include:
- an increased chance that you can get infections caused by germs that Cefixime does not act on. For example, thrush
- increase in the numbers of white blood cells called eosinophils
- allergic reaction
- loss of appetite
- dizziness
- flatulence (wind)
- itchy skin
- inflammation of mucus (select) linings such as the mouth and / or other internal surfaces
- fever
- changes in blood tests that check how your kidneys are working

Very rare side effects (affect less than 1 in 10,000 patients) include:
- fall in the number of different cells in the blood (symptoms can include tiredness, new infections and easy bruising or bleeding)
- allergic reaction characterised by skin rashes, fever, joint pains and enlarged organs
- restlessness and increased activity
- liver problems including jaundice (yellowing of the skin or whites of the eyes)
- inflammation of the kidney

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

5. HOW TO STORE CEFIXIME

This medicinal product does not require any special storage conditions.

Keep out of the reach and sight of children.

Keep blister in the outer carton.

Do not take Cefixime after the expiry date which is stated on the blister and carton after "EXP/".

The expiry date refers to the last day of that month.

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 Cefixime contains
The active substance is Cefixime. Each film-coated tablet contains 447.6mg Cefixime trihydrate equivalent to 400mg Cefixime (antimicrobial).

The other ingredients are microcrystalline cellulose, Pre-gelatinised starch, calcium hydrogen phosphate, magnesium stearate, silica colloidal anhydrus, opadry white (Y-1-7000).

Opadry White (Y-1-7000) contains hydron propyl methyl cellulose (E 464), titanium dioxide (E 171), macrogol / PEG 400 (E 1520).

What Cefixime looks like and contents of the pack
White to off white, film-coated, rectangular shaped tablet having partial break line on both sides.

The product is available in:
PVC/PVDC/Aluminium blister pack: 3s, 6s, 7s, 10s & 100s.
PVC/Aluminium/Aluminium blister pack: 3s, 6s, 7s, 10s & 100s.

Not all pack sizes may be marketed.

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

United Kingdom

This medicinal product is authorised in the Member states of the EEA under the following names:

United Kingdom - Cefixim 400 mg Film-coated Tablets

Austria - Cefixim Orchid 400 mg Filmtabletten

Germany - Cefixim Orchid 400 mg Filmtabletten

This leaflet was last approved in 12/2010.
PL 22805/0033:
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, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

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

1. WHAT CEFIXIME IS AND WHAT IT IS USED FOR

Cefixime belongs to a group of medicines called Cephalosporins, which are used for treating infections.

Cefixime is used to treat:
- infection of the middle ear
- sinus infection
- throat infection
- infection causing sudden worsening of long-standing bronchitis
- lung infections (pneumonia) acquired outside of hospital
- infections in the urinary tract including some infections of the kidneys

2. BEFORE YOU TAKE CEFIXIME

Do not take cefixime if you:
- are allergic (hypersensitive) to cefixime or any of the ingredients in the tablet (see section 4). An allergic reaction may include rash, itching, difficulty breathing or swelling of the face, lips, throat or tongue.
- are allergic (hypersensitive) to any other cephalosporin type of antibiotic.
- have ever had a severe allergic reaction to penicillin antibiotic or to any other beta-lactam type of antibiotic.

Take special care with Cefixime
Cefixime is not suitable for everyone. Before you take Cefixime you should tell your doctor if you:
- are allergic to penicillin antibiotics or to any other beta-lactam type of antibiotics.
- Not all people who are allergic to penicillin are also allergic to cephalosporins. However, you should not take this medicine if you ever had a severe allergic reaction to any penicillin. This is because you might also be allergic to this medicine.

In patients who develop severe allergic reaction or anaphylaxis (serious allergic reaction which causes difficulty in breathing or dizziness) after administration of Cefixime, the medicine should be withdrawn and appropriate treatment should be given.
- Have ever been told that your kidneys do not work very well. Also, if you are taking any sort of treatment (like dialysis) for kidney failure. You may take Cefixime but you may need a lower dose.
- are taking other medicines which are known to be harmful to your kidneys. Also inform your doctor if you have any kidney problems. Your doctor may perform certain test regularly to measure how well your kidneys are working during the treatment.
- have severe or persistent diarrhoea with stomach pain or cramps during or shortly after treatment with Cefixime, stop taking this medicine and contact your doctor immediately. Medicines which may slow or stop bowel movements must not be taken.

Having a course of Cefixime can temporarily increase the chance that you can get infections caused by other sort of germs on which Cefixime does not act. For example, thrush (infection caused by a yeast germ called Candida) may occur.

Effect on laboratory tests
If you are to undertake any blood or urine tests, inform your doctor that you are taking Cefixime, as cefixime can alter the results of some of these tests.
Cefixime can alter the results of some urine tests for sugar (such as Benedict's or Fehling's tests). If you have diabetes and routinely test your urine, tell your doctor. This is because other tests may have to be used to monitor your diabetes while you are having this medicine. Cefixime may alter the results of a blood test for antibodies called the direct Coombs test.

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

In particular, tell your doctor or pharmacist if you are taking:
- medicines which are known to be harmful to your kidneys like:
  - antibiotics include amoxicillin, ciprofloxacin, trimethoprim and sulfasalazine.
  - medicines that increase the amount of urine your body produces (diuretics) such as ethacrynic acid or frusemide.
  - anticoagulants (blood thinning medicines) such as warfarin. In some patients, Cefixime causes problems with blood clotting and may increase the time taken for the blood to clot.
  - oral contraceptives (the birth control pill)

Taking Cefixime with food and drink
Cefixime may be taken with or without food. The tablet should be swallowed with a glass of water.

Pregnancy and breastfeeding
If you are pregnant, likely to become pregnant or breastfeeding, you must tell your doctor before taking this medicine. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Cefixime does not usually affect your ability to drive or use machines. However, if you feel light-headed or dizzy, do not drive or use machines.

3. HOW TO TAKE CEFIXIME

Dosage
Always take cefixime exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The dose your doctor prescribes depends on the type of infection and how bad the infection is. It also depends on how well the kidneys are working. Your doctor or pharmacist will explain this to you.

The usual dose is
- Adults
  - The usual adult dose is one tablet taken once daily. The medicine should always be taken at the same time each day.

Patients with kidney problems
In patients with kidney problems, the dosage of Cefixime may need to be reduced. Your
doctor will calculate the right dose for you according to the results of blood or urine tests that measure how well your kidneys are working.

There are insufficient data regarding the use of Cefixime in children and adolescents with kidney problems. Cefixime is therefore not recommended for use in these patients.

**Elderly**

No change in dose is needed for elderly patients, provided the kidneys are normal.

**Adolescents 12 years of age and older**

Adolescents 12 years of age and older may be given the same dose as adults.

**Children older than 6 months and up to 11 years of age**

Children older than 6 months and up to 11 years of age should be given Cefixime as an oral suspension (liquid to be taken by mouth) rather than as a tablet.

**Children less than 6 months of age**

Cefixime is not recommended for use in children less than 6 months of age.

If you take more Cefixime than you should

If you or your child have taken more of this medicine than you should, talk to your doctor or contact your nearest hospital emergency department immediately.

If you forget to take Cefixime

If you forget to take a tablet, take one as soon as you remember. However, if the next dose is due in less than 6 hours, skip the missed dose and go back to your regular dosing schedule. Do not take double doses.

If you stop taking Cefixime

It is important that you take this medicine until you finish the prescribed course. You should not stop the medicine just because you feel better. If you stop too soon, the infection may start up again. If the person being treated still feels unwell at the end of the prescribed course of treatment, or feels worse during treatment, tell your doctor.

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

## 4. POSSIBLE SIDE EFFECTS

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

The following side effects are important and will require immediate action if you experience them. You should stop taking Cefixime and see your doctor immediately if the following symptoms occur:

### Very rare side effects (affect less than 1 in 10,000 patients)

- watery and severe diarrhoea that may also be bloody
- sudden severe allergic reactions (anaphylactic shock) such as skin rash or hives, redness, swelling of the face, lips, tongue or other parts of the body, tightness of the chest, wheezing and collapse
- severe skin illness with blistering of the skin, mouth, eyes and genitalia (Stevens Johnson syndrome, toxic epidermal necrolysis)

### Common side effects (affect less than 1 in 10 patients)

- diarrhoea

### Uncommon side effects (affect less than 1 in 100 patients)

- headache
- nausea
- vomiting
- abdominal (tummy) pain
- changes in blood tests that check how your liver is working
- skin rash

### Rare side effects (affect less than 1 in 1000 patients)

- an increased chance that you can get infections caused by germs that Cefixime does not act on. For example, thrush
- increase in the numbers of white blood cells called eosinophils
- allergic reaction
- loss of appetite
- dizziness
- flatulence (wind)
- itchy skin
- inflammation of mucus (mLastly) lining such as the mouth and / or other internal surfaces
- fever
- changes in blood tests that check how your kidneys are working

### Very rare side effects (affect less than 1 in 10,000 patients)

- fall in the number of different cells in the blood (symptoms can include tiredness, new infections and easy bruising or bleeding)
- allergic reaction characterised by skin rashes, fever, joint pains and enlarged organs
- malaise and increased activity
- liver problems including jaundice (yellowing of the skin or whites of the eyes)
- inflammation of the kidney

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

## 5. HOW TO STORE CEFIXIME

This medicinal product does not require any special storage conditions.

Keep out of the reach and sight of children.

Keep blister in the outer carton. Do not Cefixime after the expiry date which is stated on the blister and carton after “EXP”.

The expiry date refers to the last day of that month.

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 Cefixime contains**

The active substance is Cefixime. Each film-coated tablet contains 447.6mg Cefixime trihydrate equivalent to 400mg Cefixime (anhydrous).

The other ingredients are microcrystalline cellulose, Pre-gelatinised starch, calcium hydrogen phosphate, magnesium stearate, silica colloidal anhydrous, opadry white (Y-1-7000).

Opadry White (Y-1-7000) contains hydroxyl propyl methyl cellulose (E 464), titanium dioxide (E 171), macrogol 400 (E 1520).

**What Cefixime looks like and contents of the pack**

White to off-white, film-coated, rectangular shaped tablet having partial break line on both sides.

The product is available in:

- PVC/Aluminium blister pack: 3s, 5s, 7s, 10s & 100s.
- PVC/Pearl Aluminium blister pack: 3s, 5s, 7s, 10s & 100s.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

Orobi Europe Ltd.
Building 3, Chiswick Park, Chiswick High Road, Chiswick, London, W4 5YA

**United Kingdom**

This medicinal product is authorised in the Member states of the EEA under the following names:

- **United Kingdom** - Cefixime 400mg film-coated Tablets
- **Austria** - Cefixime Arcana 400 mg Filmtabletten
- **Italy** - Cefixima Mylan 400 mg Compressa rivestita con film

This leaflet was last approved in 12/2010.
Module 4

Labelling

PL 22805/0032:

Blisters:

3 tablets

<table>
<thead>
<tr>
<th>Lot</th>
<th>CeFIXime 400 mg Film-coated Tablets</th>
<th>CeFIXime 400 mg Film-coated Tablets</th>
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5 tablets

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<th>CeFIXime 400 mg Film-coated Tablets</th>
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CeFIXime 400 mg
Film-coated Tablets

CeFIXime
400 mg
Film-coated Tablets
Cefixime (as trihydrate)

Oral use
1 Blister strip of 3 Tablets

CeFIXime 400 mg
Film-coated Tablets
PL 22805/0032

Each film-coated tablet contains 447.63 mg Cefixime trihydrate, equivalent to 400 mg of Cefixime.
See leaflet for further information.
Read the package leaflet before use.
This medicinal product does not require any special storage conditions.
Keep the blister in the outer carton.
Use as directed by your doctor.
Keep out of the reach and sight of children.
M.L.No. TN00002768

Affix pharmacy dispensing label here

MHRA PAR; CEFIXIME 400 MG FILM-COATED TABLETS, PL 22805/0032-3 32
CeFIXime 400 mg Film-coated Tablets

Cefixime (as trihydrate)

Oral use

1 Blister strip of
5 Tablets

CeFIXime 400 mg Film-coated Tablets

Each film-coated tablet contains 447.83 mg Cefixime trihydrate, equivalent to 400 mg of Cefixime. See leaflet for further information. Read the package leaflet before use. This medicinal product does not require any special storage conditions. Keep the blister in the outer carton. Use as directed by your doctor. Keep out of the reach and sight of children.

M.I. No. TN00002768

MA Holder: Orchid Europe Ltd, Building 1, Sinnamon Park, 86-88 Chiswick High Road, Chiswick, London W4 5AL, United Kingdom

Affix pharmacy dispensing label here
CeFIXime 400 mg
Film-coated Tablets

CeFIXime (as trihydrate)

Oral use

1 Blister strip of 7 Tablets

CeFIXime 400 mg
Film-coated Tablets

Each film-coated tablet contains 447.63 mg Cefixime trihydrate, equivalent to 400 mg of Cefixime.

See leaflet for further information.

Read the package leaflet before use.

This medicinal product does not require any special storage conditions.

Keep the blister in the outer carton.

Use as directed by your doctor.

Keep out of the reach and sight of children.

M.L. No. TN00027688

MA Holder: Orchid Europe Ltd.
Building 3, Chevick Park
500 Chevick High Road, Chiswick,
London W4 5TA, United Kingdom
CeFIXime 400 mg
Film-coated Tablets

CeFIXime (as trihydrate)

Oral use

1 Blister strip of
10 Tablets

CeFIXime 400 mg
Film-coated Tablets

PL 22805/0032

Each film-coated tablet contains 447.63 mg Cefoxime trihydrate, equivalent to 400 mg of Cefoxime.

See leaflet for further information.

Read the package leaflet before use.

This medicinal product does not require any special storage conditions.

Keep the blister in the outer carton.

Use as directed by your doctor.

Keep out of the reach and sight of children.

MA Holder:
Orchid Europe Ltd.
Building 3, Glaxo Park,
500 Chiswick High Road, Chiswick,
London W4 5JG, United Kingdom

M.L. No. TN00002768
PL 22805/0033:

Blister:

3 tablets

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5 tablets

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### 7 tablets

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M.L.No. TN00002768

### 10 tablets

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M.L.No. TN00002768

### 10 tablets

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M.L.No. TN00002768
CeFIXime 400 mg
Film-coated Tablets
Cefixime (as trihydrate)
Oral use
1 Blister strip of 3 Tablets

Each film-coated tablet contains 447.63 mg Cefixime trihydrate, equivalent to 400 mg of Cefixime.
See leaflet for further information.
Read the package leaflet before use.
This medicinal product does not require any special storage conditions.
Keep the blister in the outer carton.
Use as directed by your doctor.
Keep out of the reach and sight of children.
M.L.No. TN00002768
Module 5
Scientific Discussion

I. INTRODUCTION

Recommendation
Based on the review of the data on quality, safety and efficacy, the RMS considers that the applications for Cefixime 400 mg Film-coated Tablets in the treatment of bacterial infections could be approved.

Problem statement
These Decentralised applications were submitted under Article 10.1 of Directive 2001/83/EC, as amended. The applicant claims that the proposed product is a generic version of the product Suprax 400 mg film-coated tablets, licensed in the EEA to Astellas Pharma GmbH since 13 November 1997. The reference product has, therefore, been authorised in the EEA for at least 10 years and the legal basis of these applications is acceptable.

The reference product in the UK is Suprax Tablets 200 mg, which was first licensed to Cyanamid of Great Britain Limited (PL 00095/0212) on 24 April 1990. Following a change of ownership on 12 August 1998 these tablets are currently licensed to May & Baker Limited (PL 00012/0316). Only the 200 mg strength Suprax Tablets are marketed in the UK, following cancellation of the Marketing Authorisation for Suprax Tablets 400 mg (PL 00012/0317) on 28 February 2005.

With the UK as the Reference Member State in this Decentralised Procedure, Orchid Europe Ltd. is applying for Marketing Authorisations for Cefixime 400 mg Film-coated Tablets in Austria (UK/H/1532/01/DC and UK/H/3965/01/DC), Germany (UK/H/1532/01/DC), Italy (UK/H/3965/01/DC) and the UK (UK/H/1532/01/DC and UK/H/3965/01/DC).

About the product
Cefixime is an orally active semi-synthetic, third generation cephalosporin antibiotic of the aminothiazole group. It acts by interfering with bacterial cell-wall synthesis, leading to lysis of the infectious organism. Cefixime exhibits a broad spectrum of antibacterial activity with minimum inhibitory concentrations similar to or less than those for other oral cephalosporins against many Gram-negative and Gram-positive microorganisms. It is approved for the treatment of upper and lower respiratory tract infections and urinary tract infections.

General comments on the submitted dossier
The submitted documentation in relation to the proposed type of product is considered to be of sufficient quality and is consistent with the current EU regulatory requirements. Satisfactory overall summaries of the dossier regarding the quality, preclinical and clinical parts have been submitted.
General comments on compliance with GMP, GLP, GCP and agreed ethical principles

GMP
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 outside the Community, the RMS has accepted copies of current GMP certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GLP
No new preclinical studies were submitted in support of these applications, and none are needed for an application of this type.

GCP
Statements have been provided confirming that the submitted bioequivalence study was conducted in compliance with Good Clinical Practices (GCP), as referenced in the ICH guidelines (ICH E6), local regulatory requirements, and the principles enunciated in the Declaration of Helsinki.

II. QUALITY ASPECTS

Drug substance

INN name: Cefixime

Chemical name: (6R,7R)-7-[(2Z)-(2-amino-4-thiazolyl) [(carboxymethoxy) imino] acetyl] amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid

Structure:

Molecular formula: C_{16}H_{15}O_{7}S_{2}3H_{2}O
Molecular weight: 507.5
Physical properties: A white or almost white powder, slightly hygroscopic, soluble in methanol, slightly soluble in water and ethanol and practically insoluble in ethyl acetate.

The drug substance holds a valid certificate of suitability. The quality of the substance is suitably controlled by the current edition of the Ph. Eur. monograph.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificate of analysis for all working standards have been provided.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and certificates of analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

Medicinal product
Cefixime 400 mg Film-coated Tablets contain the pharmaceutical excipients cellulose microcrystalline, pre-gelatinised starch, calcium hydrogen phosphate anhydrous, magnesium stearate, silica colloidal anhydrous, opadry white Y-1-7000 [containing HPMC 2910/hypromellose 5 cP (E 464), titanium dioxide (E 171) and macrogol/PEG 400 (E 1520)] and purified water.

All excipients comply with their respective European Pharmacopoeial monograph, with the exception of opadry white Y-1-7000, in the absence of a European Pharmacopoeial monograph for this excipient, this is acceptable. Satisfactory certificates of analysis have been provided for all excipients. Suitable declarations issued by suppliers of the excipients to confirm compliance with the requirements of the relevant guideline and Directives with regard to TSE are provided.

Pharmaceutical development
The objective of the development programme was to develop a formulation similar to the innovator product, Suprax, from Astellas Pharma GmbH. A satisfactory account of the pharmaceutical development has been provided.
Manufacturing process
A satisfactory batch formula has been provided, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished product specification
The finished product specification is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

Container-closure system
The finished product is stored in PVC/PVdC or PVC/Aclar aluminium blister packs. Pack sizes are either 3, 5, 7, 10 or 100 tablets per pack.

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

Stability of the product
Stability studies were performed in accordance with current guidelines on the finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 24 months for this product with no special storage condition when the storage precaution ‘keep blister in the outer carton’ is applied.

Product literature
The SmPC, PIL and labels are pharmaceutically acceptable.

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

Marketing Authorisation Application (MAA) forms
The MAA forms are pharmaceutically satisfactory.

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

Quality conclusion
There are no objections to the granting of Marketing Authorisations for Cefixime 400 mg Film-coated Tablets from a quality point of view.

III. PRECLINICAL ASPECTS

Preclinical overview
The pharmacodynamic, pharmacokinetic and toxicological properties of cefixime are well known. As cefixime is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on literature review is, thus, appropriate.

The overview is written by a microbiologist and a medical doctor. The report refers to 75 publications up to year 2008. The preclinical overview on the preclinical pharmacology, pharmacokinetics and toxicology is adequate.

**Environmental risk assessment**
A suitable justification for the absence of a formal environmental risk assessment has been provided, based on the expectation that introduction of this generic product onto the market is unlikely to result in an increase in the combined sales of all cefixime containing products, which in turn is unlikely to increase exposure of the environment to cefixime.

**Product literature**
The product literature is acceptable from a preclinical point of view.

**Preclinical conclusion**
There are no objections to the approval of Cefixime 400 mg Film-coated Tablets from a preclinical point of view.

### IV. CLINICAL ASPECTS

**Pharmacokinetics**
To support the applications a randomised, open label, two treatment, two period, two sequence, single dose, crossover study of Cefixime 400 mg Film-coated Tablets from Orchid Healthcare (test product) and Cefixoral 400mg tablets from A. Menarini (reference product) was carried out.

**Method**
Twenty-six healthy adult male volunteers with age range between 18 and 55 years of age were enrolled in the study. Twenty-five subjects completed the study. Inclusion and exclusion criteria were presented and are acceptable. The study drug was administered with 240 mL of water after a supervised overnight fast of at least 10 hours.

Blood samples were withdrawn at pre-dose (0.0) and up to 24.0 hours post dose after administration of each product, with a washout period of 7 days between study drug administrations.

Two adverse events (AE) were reported from two volunteers during the entire duration of the study. One AE was mild in intensity and the other moderate in intensity. Both were followed up until resolution and resolved completely without any negative after-effects.

The concentration of cefixime was determined in plasma. The analytical, PK and statistical methods were adequate.
Results

Table 1 - Summary of pharmacokinetic data for Cefixime

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Geometric mean</th>
<th>Arithmetic Mean</th>
<th>Standard Deviation</th>
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<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (µg.h/ml)</td>
<td>54.0847</td>
<td>55.4887</td>
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<td>C&lt;sub&gt;max&lt;/sub&gt; (µg/ml)</td>
<td>5.9667</td>
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Cefixoral ® (Reference product)

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<th>Pharmacokinetic Parameter</th>
<th>Geometric mean</th>
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<td>6.0678</td>
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Table 2 - Ratio and 90% Confidence Intervals of Test versus Reference for Cefixime

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<th>Pharmacokinetic Parameter</th>
<th>Ratio</th>
<th>90% Confidence Intervals</th>
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<td>AUC&lt;sub&gt;0-t&lt;/sub&gt;</td>
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<td>0.97 to 1.10</td>
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<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt;</td>
<td>1.04</td>
<td>0.98 to 1.10</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>1.02</td>
<td>0.97 to 1.07</td>
</tr>
</tbody>
</table>

Bioequivalence conclusion

The bioequivalence study submitted by the applicant was performed according to the respective NfG and GCP requirements. The 90% CI for the ratio of AUC and C<sub>max</sub> lie within the acceptance criteria of 80-125%. Therefore, the test product, Cefixime 400 mg Film-coated Tablets, and the reference product, Cefixoral 400mg tablets, were shown to be bioequivalent under fasting conditions.

Pharmacodynamics

The pharmacodynamic characteristics of cefixime have been well-studied in the past. There would be no particular concerns for these generic medicinal products. No new data have been submitted and none are required.

Clinical efficacy and safety

No new efficacy data are presented and none is required. A comprehensive review of the published literature has been provided by the applicant, citing the well established clinical pharmacology, efficacy and safety of cefixime.

Pharmacovigilance system

The RMS considers that the pharmacovigilance system fulfils the requirements. The applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the collection and notification of any adverse reaction suspected of occurring in the Community or in a third country.

Risk management plan

No safety concerns requiring additional risk minimization activities have been identified. A detailed RMP is not considered necessary for these applications.
Expert report
A clinical overall summary, written by an appropriately qualified physician, has been provided and is a satisfactory, non-critical summary of the clinical part of the dossier.

Product literature
All product literature (SmPCs, PILs and labelling) is medically satisfactory.

Clinical conclusion
There are no objections to the approval of Cefixime 400 mg Film-coated Tablets from a clinical point of view.

V. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Cefixime 400 mg Film-coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

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

EFFICACY
The use of cefixime in the treatment of bacterial infections is well established. Bioequivalence has been demonstrated between the applicant’s Cefixime 400 mg Film-coated Tablets and its reference product. New efficacy data is, therefore, not needed.

SAFETY
No new or unexpected safety concerns arise from these applications.

The SmPCs and PILs are satisfactory and consistent with those of the reference product. Satisfactory labelling has also been submitted.

RISK-BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with cefixime is considered to have demonstrated the therapeutic value of the compound. The risk-benefit ratio is, therefore, considered to be positive. Marketing Authorisations should be granted.