Public Assessment Report

Decentralised Procedure

Cefixime 200 mg film-coated tablets
Cefixime 400 mg film-coated tablets
(cefixime)

UK/H/1659/01-02/DC
UK licence numbers: PL 32256/0015-6

Aurobindo Pharma (Malta) Limited
LAY SUMMARY

On 22nd December 2010, the MHRA granted Aurobindo Pharma (Malta) Limited Marketing Authorisations (licences) for the medicinal products Cefixime 200 mg film-coated tablets and Cefixime 400 mg film-coated tablets (PL 32256/0015-6). These are prescription-only medicines (POM).

Cefixime is one of a group of medicines called cephalosporins, which are antibiotics used for treating bacterial infections. Cefixime can be used to treat:

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

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of Cefixime 200 mg and 400 mg film-coated tablets outweigh the risks; hence Marketing Authorisations have been granted.
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</tbody>
</table>
### Module 1

**Information about Initial Procedure**

| Product Name          | Cefixime 200 mg film-coated tablets  
<table>
<thead>
<tr>
<th></th>
<th>Cefixime 400 mg film-coated tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Application</td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td>Active Substance</td>
<td>Cefixime</td>
</tr>
<tr>
<td>Form</td>
<td>Film-coated tablets</td>
</tr>
<tr>
<td>Strength</td>
<td>200 mg, 400 mg</td>
</tr>
<tr>
<td>MA Holder</td>
<td>Aurobindo Pharma (Malta) Limited</td>
</tr>
<tr>
<td></td>
<td>46/2 South Street</td>
</tr>
<tr>
<td></td>
<td>Valetta</td>
</tr>
<tr>
<td></td>
<td>MT-VT 1101</td>
</tr>
<tr>
<td></td>
<td>Malta</td>
</tr>
<tr>
<td>Reference Member State (RMS)</td>
<td>UK</td>
</tr>
<tr>
<td>Concerned Member States (CMS)</td>
<td>UK/H/1659/01/DC: Austria, Germany, Hungary</td>
</tr>
<tr>
<td></td>
<td>UK/H/1659/02/DC: Austria, Germany, Italy, Portugal</td>
</tr>
<tr>
<td>Procedure Number</td>
<td>UK/H/1659/01-02/DC</td>
</tr>
<tr>
<td>Timetable</td>
<td>End of Procedure: Day 210 – 14th November 2010</td>
</tr>
</tbody>
</table>
Module 2

Summary of Product Characteristics

The UK Summary of Product Characteristics (SmPC) for Cefixime 200 mg and 400 mg film-coated tablets (PL 32256/0015-6) is as follows. Differences between the individual SmPCs are highlighted:

1 NAME OF THE MEDICINAL PRODUCT

Cefixime 200 mg film-coated tablets
Cefixime 400 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Cefixime 200 mg / 400 mg film-coated tablets
Each film-coated tablet contains 200mg / 400mg cefixime (as cefixime trihydrate).
Each film-coated tablet contains 0.3 mg / 0.6 mg of soya-lecithin

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.

Cefixime 200 mg film-coated tablets
White to off-white, film-coated, capsule shaped, beveled edged tablets debossed with ‘E’ and scoring on edges on one side and ‘3’ and ‘8’ separated by scoring on edges on the other side.

Cefixime 400 mg film-coated tablets
White to off-white, film-coated, capsule shaped, beveled edged tablets debossed with ‘E’ and break line on one side and ‘8’ and ‘7’ separated by break line on the other side. The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cefixime is indicated for the treatment of the following infections when caused by susceptible organisms (see sections 4.4 and 5.1):

- Acute exacerbations of chronic bronchitis
- Community-acquired Pneumonia
- Lower urinary tract infections
- 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 with other commonly used antibacterial agents 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

For oral use.

Method of administration:
Absorption of cefixime is not significantly modified by the presence of food. Cefixime may be taken with water before, during or after the meal.

Dosage:

Adults and adolescents older than 12 years:
The recommended dose for adults is 400 mg daily taken as a single dose or 2 X 200 mg daily 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.

Children below 12 years (use paediatric oral suspension): The recommended dosage for children is 8 mg/kg/day administered as a single dose or in two divided doses.

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

Elderly:
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 “Dosage in renal impairment”).

Dosage in renal impairment in adult patients:
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.

4.3 Contraindications

Hypersensitivity to cefixime, soya, other cephalosporins or to any of the excipients of Cefixime.

Previous, immediate and/or severe hypersensitivity reaction to penicillin or any other 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-reaction may occur (for contra-indications 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 adult 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: the use of cefixime in these patient-groups is not recommended.

Prolonged use of cefixime may result in the overgrowth of non-susceptible organisms.
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 [see section 4.5]. This applies particularly for patients with already restricted renal function.

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 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 the appropriate treatment established. The use of preparations inhibiting the intestinal peristaltism is contra-indicated (see section 4.8 ).

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).

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

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

4.6 Pregnancy and lactation

Pregnancy:

There is not sufficient experience in the human use of cefixime. Cefixime reaches the embryo/fetus via the placenta. Animal data reveal no undesirable effects on reproduction (see section 5.3).

As a precautionary measure, cefixime should only be used during pregnancy after careful benefit/risk assessment by the physician in charge, especially during the first trimester.

Lactation:

Excretion in maternal milk has not been shown for cefixime. Nevertheless, as a precautionary measure, a decision should be made whether to discontinue breast-feeding or to abstain from cefixime therapy.

Fertility

Reproduction studies performed in mice and rats have revealed no evidence of impaired fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No effect was observed on the ability to drive and use machines.

4.8 Undesirable effects

Adverse drug reactions are listed below by system organ class and frequency. Frequencies are defined as:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000) not known (cannot be estimated from the available data)
### MedDRA System organ class

<table>
<thead>
<tr>
<th>Adverse drug reactions</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Rare</td>
</tr>
<tr>
<td>Superinfection bacterial, superinfection fungal</td>
<td>Rare</td>
</tr>
<tr>
<td>Antibiotic associated colitis (see section 4.4)</td>
<td>Very rare</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Rare</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>Rare</td>
</tr>
<tr>
<td>Leucopenia, agranulocytosis, pancytopenia, thrombocytopenia, haemolytic anaemia</td>
<td>Very rare</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Rare</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>Rare</td>
</tr>
<tr>
<td>Anaphylactic shock, serum sickness</td>
<td>Very rare</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Rare</td>
</tr>
<tr>
<td>Anorexia</td>
<td>Rare</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Headache</td>
<td>Rare</td>
</tr>
<tr>
<td>Vertigo</td>
<td>Rare</td>
</tr>
<tr>
<td>Psychomotor hyperactivity</td>
<td>Very rare</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Abdominal pain, nausea, vomit</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Flatulence</td>
<td>Rare</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Very rare</td>
</tr>
<tr>
<td>Hepatitis, cholestatic jaundice</td>
<td>Very rare</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Rash</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Angioneurotic oedema, pruritus</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Stevens-Johnson syndrome, toxic epidermal necrosis</td>
<td>Very rare</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Very rare</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>Very rare</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Rare</td>
</tr>
<tr>
<td>Mucosal inflammation, pyrexia</td>
<td>Rare</td>
</tr>
<tr>
<td>Investigations</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Hepatic enzyme increased (transaminase, alkaline phosphatase)</td>
<td>Very rare</td>
</tr>
<tr>
<td>Blood urea increased</td>
<td>Rare</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>Very rare</td>
</tr>
</tbody>
</table>

### 4.9 Overdose

There is no experience with overdoses with cefixime.

Adverse reactions seen at dose levels up to 2 g cefixime in normal subjects did not differ from the profile seen in patients treated at the recommended doses. Gastric lavage may be indicated in overdosage. No specific antidote exists. Cefixime is not removed from the circulation in significant quantities by dialysis.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Third generation cephalosporins.

ATC Code: J01DD08

**Mechanism of action**

Cefixime exerts its antibacterial activity by binding to and inhibiting the action of cell wall synthetic enzymes, penicillin binding proteins (PBP 3, 1a and 1b) which results in interruption of bacterial cell biosynthesis leading to bacterial cell lysis and 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.

**Mechanism of resistance**

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

- Hydrolysis by beta-lactamases. Cefixime 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 cefixime.
• Outer membrane impermeability, which restricts access of cefixime to penicillin binding proteins in gram-negative organisms
• Drug efflux pumps.

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

• *H. influenzae*\(^1\): sensitive ≤ 0.12 mg/L, resistant > 0.12 mg/L.
• *M. catarrhalis*\(^1\): sensitive ≤ 0.5 mg/L, resistant > 1.0 mg/L
• *Neisseria gonorrhoeae*\(^2\): sensitive ≤ 0.12 mg/L, resistant > 0.12 mg/L
• *Enterobacteriaceae*\(^3\): sensitive ≤ 1.0 mg/L, resistant > 1.0 mg/L (for uncomplicated urinary tract infections only).
• Non-species related breakpoints: insufficient data.

\(^1\)Strains with MIC values above the susceptible breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate must be sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint they should be reported resistant.

\(^2\)Neisseria gonorrhoeae without resistance mechanisms to cefixime have MICs of ≤0.06 mg/L and can be treated with current standard dosing. The implications of alternative dosing schedules and recent data relating MIC to outcome are under consideration.

\(^3\)The breakpoints for Enterobacteriaceae will detect all clinically important resistance mechanisms (including ESBL, plasmid mediated AmpC). Some strains that produce beta-lactamases are susceptible or intermediate to 3rd or 4th generation cephalosporins with these breakpoints and should be reported as found, i.e. the presence or absence of an ESBL does not in itself influence the categorization of susceptibility. In many areas, ESBL detection and characterization is recommended or mandatory for infection control purposes.

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

<table>
<thead>
<tr>
<th>Commonly susceptible species</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aerobes, Gram positive:</strong></td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
</tr>
<tr>
<td><strong>Aerobes, Gram negative:</strong></td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
</tr>
<tr>
<td><strong>Species for which acquired resistance may be a problem</strong></td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
</tr>
<tr>
<td>Citrobacter freundii $</td>
</tr>
<tr>
<td>Enterobacter cloacae $</td>
</tr>
<tr>
<td><strong>Aerobes, Gram negative:</strong></td>
</tr>
<tr>
<td>Escherichia coli % &amp;</td>
</tr>
<tr>
<td>Klebsiella oxytoca $</td>
</tr>
<tr>
<td>Klebsiella pneumoniae $</td>
</tr>
<tr>
<td>Morganella morgani $</td>
</tr>
<tr>
<td>Serratia marcescens $</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
</tr>
</tbody>
</table>
Inherently resistant species

- Chlamydia spp.
- Chlamydophila spp.
- Clostridium difficile
- Bacteroides fragilis
- Enterococi
- 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.

From in vitro studies, serum or urine concentrations of 1 mcg/mL 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 mcg/mL. Little or no accumulation of cefixime occurs following multiple dosing.

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 Cmax and AUC values were slightly greater in the elderly. Elderly patients may be given the same dose as the general population.

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.

Metabolism:
Metabolites of cefixime have not been isolated from human serum or urine.

Excretion:
Cefixime is predominantly eliminated as unchanged drug in the urine. Glomerular filtration is considered the predominant mechanism.

Transfer of 14C-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.

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 fetus 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

Core:
- Calcium Hydrogen Phosphate anhydrous
- Starch, Pregelatinised
- Hydroxy Propyl Cellulose
- Cellulose, Microcrystalline
- Magnesium stearate

Coating:
- Titanium Dioxide
- Talc
- Lecithin (Soya)
- Xanthan gum

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 25°C.

6.5 Nature and contents of container
Cefixime 200 mg & 400 mg film-coated tablets are supplied in PVC/PA/Aluminium/PVC/Aluminium blister packs containing 1, 5, 6, 7, 8, 10, 14 or 20 film-coated tablets and
White opaque round HDPE container with white opaque polypropylene closure: containing 500 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER
Aurobindo Pharma (Malta) Limited
46/2 South Street
Valetta
MT-VT 1101
Malta

8 MARKETING AUTHORISATION NUMBER(S)
PL 32256/0015
PL 32256/0016

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
22/12/2010

10 DATE OF REVISION OF THE TEXT
22/12/2010
Module 3

Patient Information Leaflet text

PACKAGE LEAFLET: INFORMATION FOR THE USER

Cefixime 200mg film-coated tablets
Cefixime 400mg film-coated tablets
Cefixime

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

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

In this leaflet:
1. What 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 is one of a group of medicines called cephalosporins, which are antibiotics used for treating bacterial infections.

Cefixime can be used to treat:

• infection of the middle ear
• sinus infection
• throat infection
• infection causing sudden worsening of long-standing bronchitis
• serious lung infections (pneumonia) acquired outside of hospital
• infections in the urinary tract

If you need any further information on your condition, please ask your doctor.

2. Before you take Cefixime

Do not take Cefixime

• if you are allergic (hypersensitive) to cefixime, to soya or any of the other ingredients of Cefixime (as listed in section 6 'Further information')
• if you have previously suffered immediate or severe allergic reactions when you are treated with penicillins or with any other beta-lactam antibiotic.

Take special care with Cefixime

Ask your doctor for advice if:

• you have ever had an allergic reaction to penicillins, or other medicines.
• you have serious kidney problems
• you suffer from severe, bloody or prolonged diarrhoea during or after taking this medicine. If this happens, you should contact your doctor as soon as possible. Do not take any medicine to stop the diarrhoea before consulting your doctor.
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 Coomb's 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 please tell your doctor if you are taking:
- anticoagulants (such as warfarin or heparins).
- oral contraceptives (the Pill), as they may be less effective at preventing pregnancy and you may need to take extra precautions.
- aminoglycoside antibiotics such as gentamicin or other antibiotics called polymyxin B, colistin or viomycin, or certain strong acting diuretics (water tablets) such as furosemide, as the doctor will want to check how your kidneys are working, especially if you already have kidney problems.
- nifedipine (a drug used to treat heart problems such as arrhythmias and high blood pressure). If nifedipine is taken along with Cefixime, then levels of Cefixime in your blood may be increased.

Taking Cefixime with food and drink
Cefixime may be taken with water before, during or after the meal.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.

If you are pregnant, think you may be pregnant or are trying to become pregnant, you should not take Cefixime unless your doctor has told you to.

If you are breast-feeding, the doctor will decide whether you need to stop taking Cefixime in order to continue breast-feeding. Alternatively your doctor may advise you to stop breast-feeding in order for you to continue taking this medicine.

Driving and using machines
Cefixime should not affect your ability to drive or operate machinery. If you are concerned or want more information you should talk to your doctor.

Important information about some of the ingredients of Cefixime
Cefixime contains soya lecithin. If you are allergic to peanut or soya, do not use this medicine.

3. How to take Cefixime
Always take use Cefixime exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

These tablets should be taken by mouth. You should try to take this medicine at about the same time(s) each day.
Adults and adolescents older than 12 years:
1 X 400mg daily as a single dose or
2 X 200mg daily at intervals of 12 hours.

Children below 12 years:
Please note that Cefixime tablets are not a suitable treatment for children. You should ask your doctor for more information.

Kidney problems:
If you have severe kidney problems or are undergoing dialysis, your doctor will reduce your dose.

Duration of treatment:
The duration of treatment will change depending on the type and severity of your infection. The usual course of treatment is 7 days. This may be continued for up to 14 days if your doctor recommends it.

If you take more Cefixime than you should
If you accidentally take too many tablets or a child swallows any tablets, contact your nearest hospital casualty department or tell your doctor immediately. Take your tablets with you even if there are no tablets left in the box so that the doctor knows exactly what you have taken.

If you forget to take Cefixime
If you miss a dose of this medicine, take it as soon as possible. Do not take a double dose to make up for a forgotten dose.

If you stop taking Cefixime
Do not stop taking your tablets without the advice of your doctor even if you feel better. It is important to complete the full course of treatment that your doctor has prescribed.

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.

Tell your doctor straight away or go to the nearest hospital casualty department if you notice any of the following serious side effects – you may need urgent medical treatment:

- you have an allergic reaction. The signs may include: redness of the skin, swallowing or breathing problems, palpitations, feeling faint, swelling of your lips, face, throat or tongue. This occurs rarely.
- severe blistering rash where layers of the skin may peel off to leave large areas of raw exposed skin over the body. Also a feeling of being generally unwell, fever, chills and aching muscles. This may be something called Lyell’s syndrome (‘toxic epidermal necrolysis’), which occurs very rarely.
- you have inflammation of the skin and soft tissues.
- you have a skin rash or skin lesions with a pink/red ring and a pale centre which may be itchy, scaly or filled with fluid. The rash may appear especially on the palms or soles of your feet. These could be signs of a serious allergy to the medicine called ‘erythema multiforme’ which occurs very rarely.
- you bruise or bleed more easily than normal or have signs of an infection such as a severe sore throat or fever. This could be because of a blood disorder. This occurs rarely.
- you have severe, bloody or prolonged diarrhoea along with feeling weak and having a fever, during or after taking this medicine. This may be a sign of an inflammation of the large intestine (pseudomembranous colitis). This occurs very rarely.
Other side effects

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

Common side effects (affecting less than 1 in 10 people):
- diarrhoea or loose stools.

Uncommon side effects (affecting less than 1 in 100 people)
- feeling sick (nausea) or being sick (vomiting)
- stomach pain, indigestion
- headaches
- skin rash
- temporary abnormalities in liver function test results

Rare side effects (affecting less than 1 in 1000 people):
- feeling dizzy or feverish
- new infections with resistant bacteria or fungi after prolonged use, such as ‘thrush’ (feeling itchy in the genital or vaginal area)
- loss of appetite, flatulence (wind)
- inflammation of the lining of the mouth and / or other internal surfaces.
- temporary increase in level of urea in your blood.

Very rare side effects (affecting less than 1 in 10,000 people):
- fall in the number of different cells in the blood (symptoms can include tiredness, new infections and easy bruising or bleeding)
- inflammation of the liver (hepatitis), yellowing of the skin and the whites of the eyes (jaundice)
- disruption in your kidney function
- feeling hyperactive.

Other antibiotics of this type (cephalosporins) can increase your risk of having a seizure. The chances of this happening while taking cefixime cannot be excluded.

Blood tests
Your doctor may ask you to have some blood tests as cefixime can rarely cause changes in the number of red or white blood cells or platelets (cells that help clotting). These changes usually go back to normal after stopping this medicine.

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

Keep out of the reach and sight of children.

Store below 25°C.

Do not use Cefixime after the expiry date which is stated on the 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 200mg or 400mg cefixime (as cefixime trihydrate).

- The other ingredients are: Calcium Hydrogen Phosphate anhydrous, Starch, Pregelatinised, Hydroxy Propyl Cellulose, Cellulose, Microcrystalline, Magnesium stearate, Titanium Dioxide, Talc, Lecithin (Soya), Xanthan gum.

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

*Cefixime 200 mg film-coated tablets*
White to off-white, film-coated, capsule shaped, beveled edged tablets debossed with ‘E’ and scoring on edges on one side and ‘3’ and ‘8’ separated by scoring on edges on the other side.

*Cefixime 400 mg film-coated tablets*
White to off-white, film-coated, capsule shaped, beveled edged tablets debossed with ‘E’ and break line on one side and ‘8’ and ‘7’ separated by break line on the other side.
The tablet can be divided into equal halves.

Cefixime 200 mg & 400 mg film-coated tablets are supplied in PVC/PE/PVDC/Aluminium blister packs containing 1, 3, 6, 7, 8, 10, 14 or 20 film-coated tablets.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**
Aurobindo Pharma (Malta) Limited,
Vault 14, Level 2,
Valetta Waterfront,
Floriana FRN 1913,
Malta.

**Manufacturer**
Pfizer Service Company BVBA,
Hoge Wei 10,
1930 Zaventem,
Belgium.

or

Pfizer PGM,
Zone industrielle,
29, route des Industries,
Pocé -Sur-Cisse 37530,
France.

This leaflet was last approved in 12 / 2010.

Ref: gxCXM 1.0 UK
Module 4

Labelling - text

PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON

1. NAME OF THE MEDICINAL PRODUCT

Cefixime 200 mg film-coated tablets
Cefixime 400 mg film-coated tablets

Cefixime

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 200 mg of cefixime (as cefixime trihydrate).
Each film-coated tablet contains 400 mg of cefixime (as cefixime trihydrate).

3. LIST OF EXCIPIENTS

Also contains soya lecithin. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

Blister pack:
1. film-coated tablets
5. film-coated tablets
6. film-coated tablets
7. film-coated tablets

8. film-coated tablets
10. film-coated tablets
14. film-coated tablets
20. film-coated tablets

Bottle pack:
500 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

POM
Use as directed by a medical doctor

8. EXPIRY DATE

EXP
9. **SPECIAL STORAGE CONDITIONS**

Store below 25°C.

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

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

Auribindo Pharma (Malta) Limited,
Vault 14, Level 2,
Valette Waterfront,
Floriana FRN 1913,
Malta.

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

200 mg - PL 32256 / 0015
400 mg - PL 32256 / 0016

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Cefixime 200 mg film-coated tablets
Cefixime 400 mg film-coated tablets
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS</th>
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<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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<td>Cefixime 200 mg film-coated tablets</td>
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<tr>
<td>Cefixime 400 mg film-coated tablets</td>
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<tr>
<td>Cefixime</td>
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<table>
<thead>
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<th>2. NAME OF THE MARKETING AUTHORISATION HOLDER</th>
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<tr>
<td>Aurobindo Pharma (Malta) Limited,</td>
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<th>3. EXPIRY DATE</th>
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<th>5. OTHER</th>
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Module 5

Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Aurobindo Pharma (Malta) Limited Marketing Authorisations for the medicinal products Cefixime 200 mg and 400 mg film-coated tablets (PL 32256/0015-6; UK/H/1659/01-02/DC) on 22nd December 2010. The products are prescription-only medicines.

These are generic applications for Cefixime 200 mg and 400 mg film-coated tablets, submitted under Article 10.1 of 2001/83 EC, as amended. The applications refer to the UK innovator products, Suprax Tablets 200mg and 400mg, originally licensed to Cynamid of Great Britain Limited (PL 00095/0212 and 0213) on 24th April 1990. These licences underwent Change of Ownership (CoA) procedures on 12th August 1998 and are currently authorised to May and Baker Limited (PL 00012/0316 and 0317). The reference, innovator products have been authorised in the UK for more than 10 years, thus the period of data exclusivity has expired.

With the UK as the Reference Member State (RMS) in these Decentralised Procedures, Aurobindo Pharma (Malta) Limited applied for Marketing Authorisations for Cefixime 200 mg film-coated tablets in Austria, Germany and Hungary, and for Cefixime 400 mg film-coated tablets in Austria, Germany, Italy and Portugal.

Cefixime 200 mg and 400 mg film-coated tablets are indicated for the treatment of the following infections when caused by susceptible organisms (as mentioned in sections 4.4 and 5.1 of the Summary of Product Characteristics):

- Acute exacerbations of chronic bronchitis
- Community-acquired pneumonia
- Lower urinary tract infections
- 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 with other commonly used antibacterial agents may carry significant risk.

Cefixime is a semi-synthetic, third generation cephalosporin antibiotic which is administered orally. It has been shown that the drug is resistant to beta lactamase enzymes and is clinically effective in treating otitis media, respiratory infections due to susceptible organisms including S. pneumoniae and S. pyogenes, H. influenzae and many Enterobacteriaceae and uncomplicated cervical/urethral gonorrhoea due to N. gonorrhoeae. Cefixime exerts its antibacterial activity by binding to and inhibiting the action of cell wall synthetic enzymes,
penicillin binding proteins (PBP 3, 1a and 1b) which results in interruption of bacterial cell biosynthesis leading to bacterial cell lysis and death.

No new non-clinical or clinical efficacy studies were conducted for these applications, which is acceptable given that the applications were for generic versions of products that have been licensed for over 10 years.

The applications are supported by two bioequivalence studies presented by the applicant; one comparing the pharmacokinetic profile of the test product, Cefixime 200 mg film-coated tablets, to that of the reference product, Oroken 200 mg tablets (sourced from France); the second comparing the pharmacokinetic profile of the test product, Cefixime 400 mg film-coated tablets, to that of the reference product, Suprax 400 mg tablets (sourced from Germany). The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The Reference Member State (RMS) has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. 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 or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) 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.

The Marketing Authorisation Holder (MAH) has provided adequate justification for not submitting a Risk Management Plan (RMP). As the applications are for generic versions of already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference products have been in use for many years and the safety profile of the active is well-established.

The Marketing Authorisation Holder has provided adequate justification for not submitting a detailed Environmental Risk Assessment (ERA). These were applications for generic products and there is no reason to conclude that marketing of these products will change the overall use pattern of the existing market. There are no environmental concerns associated with the method of manufacture or formulation of the products.
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Cefixime 200 mg film-coated tablets  
Cefixime 400 mg film-coated tablets |
<table>
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<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Cefixime</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Third generation cephalosporins (J01D D08)</td>
</tr>
</tbody>
</table>
| Pharmaceutical form and strength(s)              | Film-coated tablets  
200 mg, 400 mg                                                                         |
| Reference numbers for the Decentralised Procedure| UK/H/1659/01-02/DC                                                               |
| Reference Member State                           | United Kingdom                                                                   |
| Member States concerned                          | UK/H/1659/01/DC: AT, DE, HU  
UK/H/1659/02/DC: AT, DE, IT, PT                                                        |
| Marketing Authorisation Number(s)                | PL 32256/0015-6                                                                  |
| Name and address of the authorisation holder      | Aurobindo Pharma (Malta) Limited  
46/2 South Street  
Valetta  
MT-VT 1101  
Malta                                                                                  |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

Cefixime

Nomenclature:
INN: Cefixime
Chemical names: (6R,7R)-7\[(Z)-2-(2-aminothiazol-4-y1)-2-[\(\text{carboxymethoxy}\)imin\(\text{O}\)]acetyl]amino]-3-ethenyl-8-oxo-5-thia-2azabicyclo[4.2.0]oct-2-ene-2carboxylic acid trihydrate

Structure:

Molecular formula: C\(_{16}\)H\(_{15}\)N\(_{5}\)O\(_{7}\)S\(_{2}\)\(\cdot\)3H\(_{2}\)O
Molecular weight: 507.5 g/mol
CAS No: 79350-37-1
Physical form: White or almost white, slightly hygroscopic powder
Solubility: Slightly soluble in water, soluble in methanol, sparingly soluble in ethanol, practically insoluble in ethyl acetate

The active substance, cefixime, is the subject of a European Pharmacopeia (Ph. Eur.) monograph.

All aspects of the manufacture and control of cefixime are supported by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability (CEP). This certificate is accepted as confirmation of the suitability of cefixime for inclusion in these medicinal products.

MEDICINAL PRODUCT

Description and Composition

Cefixime 200 mg and 400 mg film-coated tablets are presented as white to off-white, film-coated, capsule-shaped, beveled edged tablets containing 200mg or 400mg of the active ingredient, cefixime. Full descriptions of the individual tablets and their markings may be found by referring to the SmPCs or patient information leaflet text. The 400mg strength tablets have a break-line on both sides and can be divided into equal halves.

Other ingredients consist of pharmaceutical excipients, namely calcium hydrogen phosphate anhydrous, pregelatinised starch, hydroxypropyl cellulose, microcrystalline cellulose and magnesium stearate making up the tablet core; and ‘Opadry AMB OY-B-28920 White’ making up the film coating. Opadry AMB OY-B-28920 White consists of titanium dioxide (E171), talc, lecithin (soya) and xantham gum. Appropriate justification for the inclusion of each excipient has been provided.
All excipients used comply with their respective European Pharmacopoeia monographs, with the exception of the film-coating, Opadry AMB OY-B-28920 White, which complies with satisfactory in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate has been confirmed as being of vegetable origin. The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed products. None of the excipients are sourced from genetically modified organisms.

There were no novel excipients used and no overages.

**Pharmaceutical development**

Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory. The objective was to develop stable, generic formulations, bioequivalent to the innovator products, Suprax Tablets 200mg and 400mg (PL 00012/0316 and 0317; May and Baker Limited).

Comparative dissolution and impurity data were provided for batches of the test and originator products. The dissolution and impurity profiles were satisfactory.

**Manufacture**

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

In-process controls are appropriate considering the nature of the products and the method of manufacture. Process validation studies were conducted and the results were satisfactory.

**Finished product specification**

The finished product specifications are provided for both release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided for both strengths of the medicinal product, and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

**Container Closure System**

The medicinal products are licensed for marketing in polyvinylchloride (PVC) / polyamide (PA) / aluminium / PVC / aluminium blister strips containing 1, 5, 6, 7, 8, 10, 14 or 20 film-coated tablets; or in round High Density Polyethylene (HDPE) containers, with white opaque polypropylene closures, containing 500 film-coated tablets. The blisters / HDPE containers are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The MAH has stated that not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Cefixime film-coated tablets are also proposed to be packed in bulk packs for repackaging into marketable packs. The bulk pack consists of a Low Density Polyethylene (LDPE) bag as
a primary packaging material followed by packing in a triple-laminated bag (i.e. secondary packing material consisting of Polyester / Aluminium foil / LDPE). The bulk pack will contain one silica gel sachet in the LDPE bag and two silica gel sachets between the LDPE bag and the triple-laminated bag.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years has been set; this is satisfactory. Storage instructions are ‘Store below 25°C’.

**Bioequivalence Study**

Two bioequivalence studies were presented by the applicant; one comparing the test product, Cefixime 200 mg film-coated tablets, to the reference product, Oroken 200 mg tablets; the second comparing the test product, Cefixime 400 mg film-coated tablets, to the reference product, Suprax 400 mg tablets.

An evaluation of the bioequivalence studies is found in the Clinical Aspects section.

**Quality Overall Summary**

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

**Product Information**

The approved Summaries of Product Characteristics (SmPCs), and Patient Information Leaflet (PIL) and labelling texts are satisfactory. The labelling text fulfils the statutory requirements for Braille.

The PIL text is in line with the SmPCs and is satisfactory. The leaflet text has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the leaflet text meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The MAH has submitted text versions of the PIL and labelling only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed.

**Conclusion**

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. There are no objections to approval of Cefixime 200 mg and 400 mg film-coated tablets from a pharmaceutical point of view.
III.2 NON-CLINICAL ASPECTS
Specific non-clinical studies have not been performed, which is acceptable considering that these are applications for generic versions of products that have been licensed for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic and toxicological properties of cefixime, a widely used and well-known active substance. The overview, dated July 2008, cites 10 references from the published literature dated up to 2008. The CV of the non-clinical expert has been supplied. For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the innovator medicinal products, Suprax Tablets 200mg and 400mg (May and Baker Limited).

There are no objections to approval of Cefixime 200 mg and 400 mg film-coated tablets from a non-clinical point of view.

III.3 CLINICAL ASPECTS
INDICATIONS
Cefixime 200 mg and 400 mg film-coated tablets are indicated for the treatment of the following infections when caused by susceptible organisms (as mentioned in sections 4.4 and 5.1 of the Summary of Product Characteristics):

- Acute exacerbations of chronic bronchitis
- Community-acquired Pneumonia
- Lower urinary tract infections
- 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 with other commonly used antibacterial agents may carry significant risk.

The indications are consistent with those for the innovator products and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION
Full details concerning the posology are provided in the SmPC. The posology is consistent with that for the innovator products and is satisfactory.

TOXICOLOGY
The toxicology of cefixime is well known. No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY
The clinical pharmacology of cefixime is well known. With the exception of the bioequivalence studies, no new pharmacodynamic or pharmacokinetic data are supplied and none are required for these applications.
Pharmacokinetics – bioequivalence studies

The applications are supported by two bioequivalence studies presented by the applicant; one comparing the pharmacokinetic profile of the test product, Cefixime 200 mg film-coated tablets, to that of the reference product, Oroken 200 mg tablets (sourced from France); the second comparing the pharmacokinetic profile of the test product, Cefixime 400 mg film-coated tablets, to that of the reference product, Suprax 400 mg tablets (sourced from Germany). The studies were of an appropriate design and were conducted to principles of Good Clinical Practice (GCP). Certificates of Analysis were provided for both the test and reference products.

Bioequivalence study A – 200mg strength

This was a standard randomised, open-label, two-treatment, two-sequence, two-period, single-dose crossover oral availability study conducted in 26 healthy adult human male subjects under fasting conditions. Following an overnight fast of at least 10 hours, a single dose of the investigational products was administered orally, with 240ml water, to each subject in each period. A satisfactory washout period of 10 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 24.0 hours after administration of test or reference product. Plasma levels of cefixime were detected by a validated HPLC-UV analytical method.

The primary pharmacokinetic parameters for this study were C\text{max}, AUC\text{0-t}, and AUC\text{0-\infty}. Bioequivalence of the test product versus the reference product was concluded if the 90% Confidence Intervals (CI) fell within the acceptance range, 0.80-1.25 (80.00%-125.00%), for ln-transformed C\text{max}, AUC\text{0-t}, and AUC\text{0-\infty}.

Results:

26 subjects were enrolled in the study; 23 of these completed the study and were included in the pharmacokinetic evaluation and statistical analysis. The discontinuation, and non-inclusion in the pharmacokinetic analysis, of 3 subjects was satisfactorily justified.

Safety - The two formulations were well tolerated; No adverse event was observed during the duration of the study.

The summary of the results of the bioequivalence study are tabulated below.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Geometric Least Squares Mean</th>
<th>90% CI (Parametric)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reference Product (X)</td>
<td>Test Product (Y)</td>
</tr>
<tr>
<td>\text{C}_{\text{max}} (ng/ml)</td>
<td>2.67</td>
<td>2.52</td>
</tr>
<tr>
<td>\text{AUC}_{0-t} (ng.h/ml)</td>
<td>22.02</td>
<td>20.38</td>
</tr>
<tr>
<td>\text{AUC}_{0-\infty} (ng.h/ml)</td>
<td>22.89</td>
<td>21.28</td>
</tr>
</tbody>
</table>

\text{C}_{\text{max}} maximum plasma concentration
\text{AUC}_{0-t} area under the plasma concentration-time curve from time zero to t hours
\text{AUC}_{0-\infty} area under the plasma concentration-time curve from time zero to infinity
Conclusion on Bioequivalence

The results of the bioequivalence study show that the 200mg strength test and reference products are bioequivalent, under fasting conditions, as the confidence intervals for $C_{\text{max}}$, $\text{AUC}_{0-t}$, and $\text{AUC}_{0-\infty}$ fall within the acceptance criteria ranges of 80.00-125.00% in line with current recommendations.

Bioequivalence study B – 400mg strength

This was a standard randomised, open-label, two-treatment, two-sequence, two-period, single-dose crossover oral availability study conducted in 24 healthy adult human male subjects under fasting conditions. Following an overnight fast of at least 10 hours, a single dose of the investigational products was administered orally, with 240ml water, to each subject in each period. A satisfactory washout period of 7 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 24.0 hours after administration of test or reference product. Plasma levels of cefixime were detected by a validated HPLC-UV analytical method.

The primary pharmacokinetic parameters for this study were $C_{\text{max}}$, $\text{AUC}_{0-t}$, and $\text{AUC}_{0-\infty}$. Bioequivalence of the test product versus the reference product was concluded if the 90% Confidence Intervals (CI) fell within the acceptance range, 0.80-1.25 (80.00%-125.00%), for ln-transformed $C_{\text{max}}$, $\text{AUC}_{0-t}$, and $\text{AUC}_{0-\infty}$.

Results:

24 subjects were enrolled in the study; all 24 completed the study and were included in the pharmacokinetic evaluation and statistical analysis.

Safety - The two formulations were well tolerated; two adverse effects were reported from two volunteers during the entire duration of the study (raised white blood cells levels and raised alkaline phosphatase (ALP) levels). These were mild and did not require concomitant medication. There were no deaths or serious or significant adverse events.

The summary of the results of the bioequivalence study are tabulated below.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Geometric Least Squares Mean</th>
<th>90% CI (Parametric)</th>
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<tbody>
<tr>
<td></td>
<td>Reference Product (X)</td>
<td>Test Product (Y)</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>4.28</td>
<td>4.32</td>
</tr>
<tr>
<td>$\text{AUC}_{0-t}$ (ng.h/ml)</td>
<td>33.64</td>
<td>33.73</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\infty}$ (ng.h/ml)</td>
<td>34.53</td>
<td>34.55</td>
</tr>
</tbody>
</table>

$C_{\text{max}}$ maximum plasma concentration
$\text{AUC}_{0-t}$ area under the plasma concentration-time curve from time zero to t hours
$\text{AUC}_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
Conclusion on Bioequivalence
The results of the bioequivalence study show that the 400mg strength test and reference products are bioequivalent, under fasting conditions, as the confidence intervals for $C_{\text{max}}$, $\text{AUC}_{0-t}$, and $\text{AUC}_{0-\infty}$ fall within the acceptance criteria ranges of 80.00-125.00% in line with current recommendations.

Clinical efficacy
No new data have been submitted and none are required. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of cefixime is well-established from its extensive use in clinical practice.

Clinical safety
No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of cefixime is well-known.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)
The approved SmPCs are consistent with those of the innovator products and are acceptable.

Patient Information Leaflet
The final PIL text is in line with the approved SmPCs and is satisfactory. The PIL user testing has been evaluated and is accepted.

Labelling
The labelling text is satisfactory.

Clinical overview
A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

CONCLUSIONS
For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the innovator medicinal products, Suprax Tablets 200mg and 400mg (May and Baker Limited).

All issues have been adequately addressed by the applicant. Sufficient clinical information has been submitted to support these applications. The risk-benefit of the products is considered favourable from a clinical perspective. The grant of Marketing Authorisations was therefore recommended on medical grounds.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Cefixime 200 mg and 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.

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

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Cefixime 200 mg and 400 mg film-coated tablets, and their respective reference products, Oroken 200 mg tablets and Suprax 400 mg tablets.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The approved SmPCs are consistent with those of the innovator products and are satisfactory.

The final PIL text is in line with the SmPCs and is satisfactory. The leaflet text has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the leaflet text meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The labelling text is satisfactory and fulfils the statutory requirements for Braille.

The MAH has submitted text versions only for the PIL and labelling, and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study and its conclusions support the claim that the applicant’s Cefixime 200 mg and 400 mg film-coated tablets are generic versions of the reference products, Suprax Tablets 200mg and 400mg (May and Baker Limited). Extensive clinical experience with cefixime is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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