Public Assessment Report

Decentralised Procedure

Cefpodoxime 40 mg/5 ml granules for oral suspension
Cefpodoxime proxetil

Procedure No: UK/H/1258/001/DC

UK Licence No: PL 20532/0143

Aurobindo Pharma Limited
LAY SUMMARY

On 20 September 2011, the MHRA granted a Marketing Authorisation to Aurobindo Pharma Limited for a medicine called Cefpodoxime 40 mg/5 ml granules for oral suspension.

This product is a prescription-only medicine (POM) used for the treatment of the following infections:

- tonsilitis
- sinusitis
- otitis media
- pneumonia

The active ingredient, cefpodoxime proxetil is an antibiotic used to kill bacteria, which cause infection in your body. It belongs to a group of antibiotics called cephalosporins.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Cefpodoxime 40 mg/5 ml granules for oral suspension outweigh the risks; hence a Marketing Authorisation was granted.
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2 Quality aspects
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Module 6 Steps taken after initial procedure
### Module 1
Information about the initial procedure

<table>
<thead>
<tr>
<th><strong>Product Names</strong></th>
<th>Cefpodoxime 40 mg/5 ml granules for oral suspension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Cefpodoxime proxetil</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Granules for oral suspension</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>40 mg/5 ml</td>
</tr>
</tbody>
</table>
| **MA Holder** | Aurobindo Pharma Limited  
Ares, Odyssey Business Park, West End Road,  
South Ruislip HA4 6QD  
United Kingdom |
| **Reference Member State (RMS)** | UK |
| **Concerned Member States (CMS)** | Austria, Germany, Spain, France and Italy |
| **Procedure Number** | UK/H/1258/001/DC |
| **Timetable** | Day 210 – 18 August 2011 |
Module 2
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Cefpodoxime 40mg/5ml granules for oral suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 5ml of suspension contains 52.18mg cefpodoxime proxetil (equivalent to 40mg cefpodoxime).

Excipients: Lactose monohydrate and sucrose.

Each 5ml volume contains 162mg lactose monohydrate and 2737.3mg sucrose.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Granules for oral suspension
Dry powder: Off-white coloured granular powder.
After reconstitution with water: Off-white coloured suspension with Banana flavour.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Cefpodoxime is indicated for the treatment of the following infections caused by cefpodoxime susceptible pathogens (see sections 4.4 and 5.1) in children up to 11 years:

Upper respiratory tract infections
- Acute bacterial sinusitis
- Tonsillitis
- Acute otitis media

Lower respiratory tract infections
- Bacterial pneumonia
In case of bacterial pneumonia cefpodoxime might not be a suitable option depending on the pathogen involved, please see section 4.4.
Consideration should be given to the official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration
Route of administration: oral.

Adults and Elderly:
Not applicable for this product

Infants (>28 days), toddlers, Children (up to 11 years):
The recommended mean dosage for children is 8mg/kg/day, administered in two divided doses at 12-hour intervals.

The dose to be taken is indicated on the measuring spoon. The graduations correspond to the child's weight in kg from 5kg (2.5ml) to 25kg (12.5ml) with intermittent graduations of 1kg (0.5ml) each. The dose to be taken is read directly from the spoon.

The following table provides dosage regimen for children as per the bodyweight graduations provided on the measuring spoon:

<table>
<thead>
<tr>
<th>Body weight in kg</th>
<th>Cefpodoxime dose in mg to be used twice daily</th>
<th>Cefpodoxime dose in ml to be used twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>20</td>
<td>2.5</td>
</tr>
<tr>
<td>10</td>
<td>40</td>
<td>5</td>
</tr>
<tr>
<td>15</td>
<td>60</td>
<td>7.5</td>
</tr>
<tr>
<td>20</td>
<td>80</td>
<td>10</td>
</tr>
<tr>
<td>25</td>
<td>100</td>
<td>12.5</td>
</tr>
</tbody>
</table>
Children who weigh at least 25kg take 12.5ml of suspension twice daily or alternatively 100mg film-coated tablet twice daily.

**Hepatic Impairment:**
The dosage does not require modification in cases of hepatic impairment.

**Renal Impairment:**
The dosage of cefpodoxime does not require modification if creatinine clearance exceeds 40ml.min\(^{-1}\).73m\(^2\).

Below this value, pharmacokinetic studies indicate an increase in plasma elimination half-life and the maximum plasma concentrations, and hence the dosage should be adjusted appropriately.

<table>
<thead>
<tr>
<th>Creatinine Clearance (ml/min)</th>
<th>Dosage Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>39 – 10</td>
<td>Single dose administered every 24 hours instead of twice a day (i.e. half of the usual dose).</td>
</tr>
<tr>
<td>&lt;10</td>
<td>Single dose administered every 48 hours (i.e. quarter of the usual dose).</td>
</tr>
<tr>
<td>Haemodialysis Patients</td>
<td>Single dose administered after each dialysis session.</td>
</tr>
</tbody>
</table>

The suspension may be taken with or without food.

**Instructions for Reconstitution**
Before preparing the suspension the silica gel desiccant contained in the stopper inside the closure must be removed and disposed off. To prepare the suspension first shake the bottle to loosen granules. Add water up to about half of the 100ml ring mark and shake vigorously. Further add water up to the 100ml ring mark of the bottle and shake vigorously to obtain an evenly dispersed suspension.

**4.3 Contraindications**
Hypersensitivity to cefpodoxime or other cephalosporines or to any of the excipients.

Previous history of immediate and/or severe hypersensitivity reactions (anaphylaxis) to penicillin or other beta-lactam antibiotic

**4.4 Special warnings and precautions for use**
Cefpodoxime is not a preferred antibiotic for the treatment of staphylococcal pneumonia and should not be used in the treatment of atypical pneumonia caused by organisms such as *Legionella*, *Mycoplasma* and *Chlamydia*. Cefpodoxime is not recommended for the treatment of pneumonia due to *S.pneumoniae* (see section 5.1).

As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported. In case of severe hypersensitivity reactions, treatment with cefpodoxime must be discontinued immediately and adequate emergency measures must be initiated.

Before beginning treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to cefpodoxime, to other cephalosporins or to any other type of beta-lactam agent (see section 4.3). Caution should be used if cefpodoxime is given to patients with a history of non-severe hypersensitivity to other beta-lactam agents.

In cases of severe renal insufficiency it may be necessary to reduce the dosage regimen dependent on the creatinine clearance (see section 4.2).

Antibacterial agent-associated colitis and pseudo-membranous colitis have been reported with nearly all anti-bacterial agents, including cefpodoxime, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of cefpodoxime (see section 4.8). Discontinuation of therapy with cefpodoxime and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Cefpodoxime should always be prescribed with caution in patients with a history of gastrointestinal disease, particularly colitis.
As with all beta-lactam antibiotics, neutropenia and more rarely agranulocytosis may develop particularly during extended treatment. For cases of treatment lasting longer than 10 days, the blood count should be monitored and treatment discontinued if neutropenia is found.

Cephalosporins may be absorbed onto the surface of red cell membranes and react with antibodies directed against the drug. This can produce a positive Coomb's test and very rarely, haemolytic anaemia. Cross-reactivity may occur with penicillin for this reaction.

Changes in renal function have been observed with cephalosporin antibiotics, particularly when given concurrently with potentially nephrotoxic drugs such as aminoglycosides and/or potential diuretics. In such cases, renal function should be monitored.

As with other antibiotics, the prolonged use of cefpodoxime may result in the overgrowth of non-susceptible organisms (candida and Clostridium difficile), which may require interruption of treatment.

**Interaction with laboratory 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.

Patients with rare hereditary problems of galactose intolerance, fructose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

**4.5 Interaction with other medicinal products and other forms of interaction**
No clinically significant drug interactions have been reported during the course of clinical studies.

Histamine H₂-antagonists and antacids reduce the bioavailability of cefpodoxime. Probencid reduces the excretion of cephalosporins. Cephalosporins potentially enhance the anticoagulant effect of coumarins and reduce the contraceptive effect of oestrogens.

**Oral anticoagulants:**
Simultaneous administration of cefpodoxime with warfarin may augment its anti-coagulant effects. There have been many reports of increases in oral anti-coagulant activity in patients receiving antibacterial agents, including cephalosporins. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the cephalosporins to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of cefpodoxime with an oral anti-coagulant agent.

Studies have shown that the bioavailability is decreased by approximately 30% when cefpodoxime is administered with drugs which neutralize gastric pH or inhibit acid secretions. Therefore such drugs as antacids of the mineral type and H₂ blockers such as ranitidine, which can cause an increase in gastric pH, should be taken 2 to 3 hours after cefpodoxime administration.

**4.6 Fertility, pregnancy and lactation**
Not applicable

**4.7 Effects on ability to drive and use machines**
Dizziness has been reported during treatment with cefpodoxime and may affect 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)

**Blood and lymphatic system disorders**
Rare: Haematological disorders such as reduction in haemoglobin, thrombocytopenia, leucopenia and eosinophilia

Very rare: Haemolytic anaemia.

Nervous system disorders
Uncommon: Headache, paraesthesia, dizziness

Ear and labyrinth disorders
Uncommon: Tinnitus

Gastrointestinal disorders
Common: Gastric pressure, nausea, vomiting, abdominal pain, flatulence, diarrhoea. Bloody diarrhoea can be seen as signs of enterocolitis. The possibility of a pseudomembranous enterocolitis should be considered if severe or persistent diarrhea occurs during or after treatment (See Section 4.4).

Metabolic and nutritional disorders
Common: Loss of appetite

Immune system disorders:
Hypersensitivity reactions of all degrees of severity have been observed (see section 4.4).

Very rare: anaphylactic reactions, bronchospasm, purpura and angioedema.

Renal and urinary disorders
Very rare: Slight increases in blood urea and creatinine

Hepatobiliary disorders
Rare: Transient moderate elevations of ASAT, ALAT and alkaline phosphatases and/or bilirubin

These laboratory abnormalities, which may also be explained by the infection, may rarely exceed twice the upper limit of the named range and elicit a pattern of liver injury, usually cholestatic and most often asymptomatic.

Very rare: liver damage

Skin and subcutaneous tissue disorders
Uncommon: hypersensitivity mucocutaneous reactions, rash, urticaria, pruritus

Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme

Infections and infestations
There can be multiplication of non-sensitive micro-organisms (see section 4.4)

General disorders and administration site conditions
Uncommon: Asthenia or malaise

4.9 Overdose
In the event of overdosage with cefpodoxime, supportive and symptomatic therapy is indicated.

In cases of overdosage, particularly in patients with renal insufficiency, encephalopathy may occur. The encephalopathy is usually reversible once cefpodoxime plasma levels have fallen.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Other beta-lactam antibacterials, 3rd generation cephalosporins.
ATC Code: J01DD13

Mode of Action:
Cefpodoxime inhibits bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death.

PK/PD relationship
For cephalosporins, the most important pharmacokinetic-pharmacodynamic index correlating with in vivo efficacy has been shown to be the percentage of the dosing interval that the unbound concentration remains above the minimum inhibitory concentration (MIC) of cefpodoxime for individual target species (i.e. %T>MIC).

Mechanism(s) of resistance:
Resistance to cephalosporins results from a variety of mechanisms:
1) alteration of the cell-wall permeability of gram-negative bacteria
2) alteration of the penicillin binding proteins (PBPs)
3) β-lactamase production
4) bacterial efflux pumps

Breakpoints:
European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints for MIC testing are presented below. EUCAST clinical MIC breakpoints for cefpodoxime (2011-01-05, v 1.3)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Susceptible (S) (mg/l)</th>
<th>Resistant (R) (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae (uncomplicated UTI only)</td>
<td>≤1</td>
<td>&gt;1</td>
</tr>
<tr>
<td>Staphylococcus spp.</td>
<td>Note¹</td>
<td>Note¹</td>
</tr>
<tr>
<td>Streptococcus groups A, B, C and G</td>
<td>Note²</td>
<td>Note²</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>≤0.25</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>≤0.25</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>≤0.25</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>IE</td>
<td>IE</td>
</tr>
<tr>
<td>Non-species related breakpoint</td>
<td>IE</td>
<td>IE</td>
</tr>
</tbody>
</table>

1 Susceptibility of staphylococci to cephalosporins is inferred from the cefoxitin susceptibility.
2 The beta-lactam susceptibility of beta-haemolytic streptococcus groups A, B, C and G is inferred from the penicillin susceptibility.
3 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.
*Insufficient evidence

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.

Antibacterial spectrum

Commonly Susceptible species

Aerobic Gram positive organisms:
Staphylococcus aureus (Methicillin-susceptible)
Streptococcus pyogenes

Aerobic Gram negative organisms:
Haemophilus influenzae
Moraxella catarrhalis
Proteus mirabilis

Species for which acquired resistance may be a problem

Aerobic Gram positive organisms
Streptococcus pneumoniae

Aerobic Gram negative organisms
Citrobacter freundii
Enterobacter cloacae
Escherichia coli
Klebsiella pneumoniae
Serratia marcescens

Inherently resistant organisms
**Cefpodoxime 40 mg/5 ml granules for oral suspension**

**Aerobic Gram positive organisms**
- Enterococcus spp.
- Staphylococcus aureus (methicillin resistant)

**Aerobic Gram negative organisms**
- Morganella morganii
- Pseudomonas aeruginosa

**Others**
- Chlamydia spp.
- Chlamydophila spp.
- Legionella pneumophila
- Mycoplasma spp.

<table>
<thead>
<tr>
<th>natural intermediate susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance rates &gt;50% in at least 1 region</td>
</tr>
<tr>
<td>ESBL producing species are always resistant</td>
</tr>
</tbody>
</table>

**5.2 Pharmacokinetic properties**

Cefpodoxime proxetil is taken up in the intestine and is hydrolysed to the active metabolite cefpodoxime. When cefpodoxime proxetil is administered orally to fasting subjects as a tablet corresponding to 100 mg of cefpodoxime, 51.5% is absorbed and absorption is increased by food intake. The volume of distribution is 32.3 L and peak levels of cefpodoxime occur 2 to 3 hrs after dosing. The maximum plasma concentration is 1.2 mg/L and 2.5 mg/L after doses of 100 mg and 200 mg respectively. Following administration of 100 mg and 200 mg twice daily over 14.5 days, the plasma pharmacokinetic parameters of cefpodoxime remain unchanged.

Serum protein binding of cefpodoxime, 40% principally to albumin. This binding is non saturable in type.

Concentrations of cefpodoxime in excess of the minimum inhibitory levels (MIC) for common pathogens can be achieved in lung parenchyma, bronchial mucosa, pleural fluid, tonsils, interstitial fluid and prostate tissue.

As the majority of cefpodoxime is eliminated in the urine, the concentration is high. (Concentrations in 0-4, 4-8, 8-12 hr fractions after a single dose exceed MIC90 of common urinary pathogens). Good diffusion of cefpodoxime is also seen into renal tissue, with concentrations above MIC90 of the common urinary pathogens, 3-12 hrs after an administration of a single 200 mg dose (1.6- 3.1μg/g). Concentrations of cefpodoxime in the medullary and cortical tissues is similar.

The main route of excretion is renal, 80% is excreted unchanged in the urine, with an elimination half-life of approx 2.4 hours.

The main route of excretion is renal, 80% is excreted unchanged in the urine, with an elimination half-life of approx 2.4 hours.

**CHILDREN**

In children, studies have shown the maximum plasma concentration occurs approximately 2-4 hours after dosing. A single 5mg/kg dose in 4-12 year olds produced a maximum concentration similar to that in adults given a 200mg dose.

In patients below 2 years receiving repeated doses of 5mg/kg 12 hourly, the average plasma concentrations, 2 hours post dose, are between 2.7mg/l (1-6 months) and 2.0mg/l (7 months-2 years). In patients between 1 month and 12 years receiving repeated doses of 5mg/kg 12 hourly, the residual plasma concentrations at steady state are between 0.2-0.3mg/l (1 month-2 years) and 0.1mg/l (2-12 years).

**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 reproductive toxicity or mutagenicity. Studies on carcinogenicity have not been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate
Maize starch
Croscarmellose sodium
Ferric oxide yellow
Hydroxypropyl cellulose
Dispersible cellulose
Silica colloidal anhydrous
Citric acid anhydrous
Sodium citrate
Sodium benzoate
Durarome flavour banana
Sucrose

6.2 Incompatibilities
Not applicable

6.3 Shelf life
Dry powder: 2 years
Reconstituted suspension: 10 days when stored in a refrigerator (2°C – 8°C).

6.4 Special precautions for storage
Bottles: Store below 25°C.
Store in the original package in order to protect from light.
For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container
HDPE container with white removable stopper containing desiccant gel closed with polypropylene child resistant closure with wad having induction-sealing liner.
Pack size of 100ml of suspension.
A measuring spoon with graduations from 5kg to 25kg is provided with the bottle for correct dosing.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Aurobindo Pharma Limited
Ares, Odyssey Business Park, West End Road
South Ruislip HA4 6QD
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 20532/0143

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/09/2011

10 DATE OF REVISION OF THE TEXT
20/09/2011
Module 3
Patient Information Leaflet

Cefpodoxime 40 mg/5 ml granules for oral suspension

UK/H/1258/001/DC

3. HOW TO TAKE CEFPODOXIME

Always take Cefpodoxime exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Instructions for Reconstitution
Before preparing the suspension the silica gel desiccant contained in the stopper inside the closure must be removed and disposed off. To prepare the suspension first shake the bottle to loosen granules. Add water up to about half of the 100 ml ring mark and shake vigorously. Further add water up to the 100 ml ring mark of the bottle and shake vigorously to obtain an evenly dispersed suspension.

The recommended dose for children (up to 11 years) is 8 mg/kg/day administered in two divided doses at 12-hour intervals.

The dose to be taken is indicated on the measuring spoon. The graduations correspond to the child's weight in kg from 5 kg to 25 kg with intermittent graduations of 1 kg each. The dose to be taken is read directly from the spoon. For example, if your child weighs 12 kg, the spoon is filled to the 12th graduation after 10 kg graduation mark.

The measuring spoon is only adequate for this oral suspension.

The following table provides dosage regimen for children as per the bodyweight graduations provided on the measuring spoon:

<table>
<thead>
<tr>
<th>Body weight in kg</th>
<th>Cefpodoxime dose in mg to be used twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>15</td>
<td>80</td>
</tr>
<tr>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>25</td>
<td>120</td>
</tr>
</tbody>
</table>

Children who weigh at least 25 kg can take 12.5 ml suspension twice daily or alternatively 100 mg film-coated tablet twice daily.

Children with kidney problems:
Depending on how serious the kidney problems are, you may need to take cefpodoxime less often, e.g. once every 48 hours or less. Your doctor will decide how much you need to take.

It is important that you take your medicine at the right times of day.

How to take:
It is important that you take your medicine at the right times of day. This medicine may be taken with or without food.

If you take more Cefpodoxime than you should
If you accidentally take too much medicine, contact your doctor or pharmacist who will recommend what action you should take.

If you forget to take Cefpodoxime
If you do forget to take a dose of your medicine at the correct time, you should take it as soon as possible. However, if it is almost time for your next dose, do not take the missed dose. Do not take a double dose to make up for a forgotten dose. Just take the next dose at the correct time.

Carry on as before.

If you stop taking Cefpodoxime
Keep taking your medicine until your doctor has told you to stop. Do not stop taking it just because you feel better. If you stop taking the medicine, your condition may return or get worse.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Cefpodoxime can cause side effects, although not everybody gets them. The side effects listed are for information only.

Conditions you need to look out for
The following serious side effects have occurred in a small number of people but exact frequency is unknown:

- Severe allergic reaction: Signs include raised and itchy rash, swelling, sometimes of the face or mouth causing difficulty in breathing.
- Skin rash, which may blister, and looks like small targets (central dark spot surrounded by a pale area, with a dark ring around the edge).
- A widespread rash with blisters and peeling skin. (These may be signs of Stevens–Johnson syndrome or toxic epidermal necrolysis.)
Cefpodoxime 40 mg/5 ml granules for oral suspension
UK/H/1258/001/DC

All of these reactions need urgent medical attention. If you think you are having any of these types of reaction, stop taking this medicine and contact your doctor or your nearest hospital accident and emergency department.

**Common side effects** (affects more than 1 person in 100 but less than 1 in 10):
- Stomach problems: Bloating, nausea, vomiting, stomach pain, flatulence (wind) and diarrhoea
- Loss of appetite
- If you have severe diarrhoea or if you see blood in your diarrhoea you should stop taking this medicine and talk to your doctor immediately.

**Uncommon side effects** (affects more than 1 person in 1,000 but less than 1 in 100):
- Hypersensitivity reactions (These are skin rashes that are less severe allergic reactions than mentioned above, lumpy rash (hives), itching)
- Headache
- Pins and needles
- Dizziness
- Ringing in the ears
- Weakness and a feeling of generally being unwell.

**Rare side effects** (affects more than 1 person in 10,000 but less than 1 in 1,000):
- Changes in blood tests that check how your liver is working
- Anaemia
- Drops in the numbers of blood cells (symptoms can include tiredness, new infections and easy bruising or bleeding)
- Increase in some types of white blood cells
- Increase in the numbers of small cells that are needed for clotting of the blood.

**Very rare side effects** (affects less than 1 person in 10,000):
- Anaphylactic reactions (e.g. bronchospasms, purpura and edema of the face and extremities)
- Worsening in the kidney function
- Liver damage
- Having a course of cefpodoxime can temporarily increase the chance that you can get infections caused by other sorts of germs. For example, thrush may occur.
- A type of anaemia that can be severe and is caused by red blood cells breaking up.

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 CEPFODOXIME

Keep out of the reach and sight of children.
Do not take Cefpodoxime after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Bottle: Store below 25°C.
Store in the original package in order to protect from light.

Reconstituted suspension: Store in a refrigerator (2°C - 8°C) for not more than 10 days.
Discard any remaining liquid after 10 days.

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 Cefpodoxime contains

The active substance is cefpodoxime.
Each 5 ml of suspension contains 52.18 mg cefpodoxime proxetil (equivalent to 40 mg cefpodoxime).

The other ingredients are lactose monohydrate, maize starch, croscarmellose sodium, ferric oxide yellow, hydroxypropyl cellulose, dispersible cellulose, silica colloidal anhydrous, citric acid anhydrous, sodium citrate, sodium benzoate, durianate flavour, banana, sucrose.

What Cefpodoxime looks like and contents of the pack

Granules for oral suspension.
Off white colored granular powder forming a off white suspension with banana flavor, on constitution with water.
Cefpodoxime 40mg/5ml granules for oral suspension is available in HDPE containers of pack size of 100ml suspension.

A measuring spoon with graduations from 5 kg to 25 kg is provided with the bottle for correct dosing.

Marketing Authorization Holder
Aurobindo Pharma Limited
Ares, Odyssey Business Park, West End Road
South Ruislip, HA4 6QD
United Kingdom

Manufacturer
APL Swift Services (Malta) Limited
HF26, Hal Far Industrial Estate, Hal Far Birzebbuga, BOQ 3000
Malta

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

<table>
<thead>
<tr>
<th>Country</th>
<th>Equivalent Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>Cefpodoxim Aurobindo 40 mg/5 ml Granulat zur Herstellung einer Suspension zum Einnehmen</td>
</tr>
<tr>
<td>France</td>
<td>Cefpodoxime Pfizer 40 mg/5 ml granulés pour suspension buvable</td>
</tr>
<tr>
<td>Germany</td>
<td>Cefpodoxim Aurobindo 40 mg/5 ml Granulat zur Herstellung einer Suspension zum Einnehmen</td>
</tr>
<tr>
<td>Italy</td>
<td>Cefpodoxima Aurobindo 40 mg/5 ml granulato per suspensione orale</td>
</tr>
<tr>
<td>Spain</td>
<td>Cefpodoxima Aurobindo 40 mg/5 ml granulados para suspension oral</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Cefpodoxime 40 mg/5 ml granules for oral suspension</td>
</tr>
</tbody>
</table>

This leaflet was last approved in 08/2011.

Advice/medical education

Antibiotics are used to cure bacterial infections. They are ineffective against viral infections. If your doctor has prescribed antibiotics, you need to take them properly for your current illness.

Despite antibiotics, some bacteria may survive or grow. This phenomenon is called resistance: some antibiotic treatments become ineffective.

Misuse of antibiotics increases resistance. You may even harm bacteria become resistant and therefore delay your cure or decrease antibiotic efficacy if you do not respect appropriate:
- dosage
- schedules
- duration of treatment.

Consequently, to preserve the efficacy of this drug:
1. Use antibiotics only when prescribed.
2. Strictly follow the prescription.
3. Do not re-use an antibiotic without medical prescription, even if you want to treat a similar illness.
4. Never give your antibiotic to another person, maybe it is not adapted to her/his illness.
5. After completion of treatment, return all unused drugs to your pharmacist's shop to ensure they will be disposed of correctly.
Each 5 ml of suspension contains 51.38 mg cefpodoxime proxetil (equivalent to 40 mg cefpodoxime).

Contains lactose and sucrose, see package leaflet for further information.

Oral use.

Read the package leaflet before use.

Shake well before use.

Keep out of the reach and sight of children.

Bottle: Store below 25°C.

Store in the original package in order to protect from light.

Reconstituted suspension: Store in a refrigerator (2°C - 8°C) for not more than 10 days.

Cefpodoxime
40 mg/5 ml
granules for oral suspension
Granules for oral solution
100 ml (after reconstitution)

Aurobindo Pharma Limited
Ares, Odyssey Business Park
West Ensl Road
South Ruislip HA4 6QD
United Kingdom

EXP:
Lot:
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Cefpodoxime 40 mg/5 ml granules for oral suspension (PL 20532/0143; UK/H/1258/001/DC) could be approved. This product is a prescription-only medicine (POM) indicated for the following infections, when caused by cefpodoxime susceptible pathogens in children up to 11 years:

- Upper respiratory tract infections
  - acute bacterial sinusitis
  - tonsillitis
  - acute otitis media.

- Lower respiratory tract infections
  - bacterial pneumonia – in case of bacterial pneumonia cefpodoxime might not be a suitable option depending on the pathogen involved.

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

This application was submitted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Austria, Germany, Spain, France and Italy as Concerned Member States (CMS). This application was submitted under Article 10.1 of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Orelox 40 mg/5 ml granules for oral suspension (Aventis Pharma Specialities, Laboratoires Aventis, France), which was first authorized on 18 February 1993.

Cefpodoxime proxetil is a broad spectrum, semi-synthetic, beta-lactam antibiotic, a third-generation oral cephalosporin. It is the prodrug of cefpodoxime. Following oral administration, cefpodoxime proxetil is taken up by the gastro-intestinal wall where it is rapidly hydrolysed to cefpodoxime, a bactericidal antibiotic, which is then absorbed systemically. The mechanism of action of cefpodoxime proxetil is based on inhibition of the bacterial cell wall. It is active against a wide range of Gram-negative and Gram-positive organisms.

No new non-clinical data have been submitted, which is acceptable given that this application was based on being for a generic medicinal product of an originator product that has been in clinical use for over 10 years.

A single-dose, bioequivalence study was submitted to support this application, comparing the test product Cefpodoxime 40 mg/5 ml granules for oral suspension (Aurobindo Pharma Limited, UK) with the reference product Orelox 40 mg/5 ml granules for oral suspension (Aventis Pharma Specialities, Laboratoires Aventis, France). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new clinical data have been submitted, which is acceptable given that this application was based on being for a generic medicinal product of an originator product that has been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product. For manufacturing sites 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.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 18 August 2011. After a subsequent national phase, a licence was granted in the UK on 20 September 2011.
II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Cefpodoxime 40 mg/5 ml granules for oral suspension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Cefpodoxime proxetil</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Beta-lactam antibacterial, a 3rd generation cephalosporin (J01DD13)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Granules for oral suspension 40 mg/5 ml</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/1258/001/DC</td>
</tr>
<tr>
<td>Reference Member State (RMS)</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Concerned Member States (CMS)</td>
<td>Austria, Germany, Spain, France and Italy</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 20532/0143</td>
</tr>
<tr>
<td>Name and address of the Authorisation Holder</td>
<td>Aurobindo Pharma Limited Ares, Odyssey Business Park, West End Road, South Ruislip HA4 6QD. United Kingdom</td>
</tr>
</tbody>
</table>
Cefpodoxime 40 mg/5 ml granules for oral suspension

UK/H/1258/001/DC

III SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS
ACTIVE SUBSTANCE

INN: Cefpodoxime proxetil
Chemical names: 5-Thia-1 -azabicyclo [4.2.0] oct-2-enecarboxylic acid, 7-[[2-amino-4-thiazolyl] (methoxyimino) acetyl] amino]-3-(methoxymethyl)-8-oxo, 1 - [(Imethylethoxy) carbonyl] oxy] ethyl ester, [6R-[6α, 7β (Z)]]

Structure:

Molecular formula: C_{21}H_{27}N_{5}O_{9}S_{2}
Molecular Mass: 557.61
Appearance: A white to light brownish white powder. Freely soluble in dehydrated alcohol, soluble in acetonitrile and in methanol, slightly soluble in ether and practically insoluble in water.

Cefpodoxime proxetil was not the subject of European Pharmacopoeia monograph at the time of assessment.

Synthesis of the active substance from the designated starting materials 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 active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

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

MEDICINAL PRODUCT
Other Ingredients
Other ingredients consist of the pharmaceutical excipients, namely lactose monohydrate, croscarmellose sodium, maize starch, ferric oxide yellow (E172), hydroxypropyl cellulose, dispersible cellulose, silica colloidal anhydrous, citric acid anhydrous, sodium citrate, sodium benzoate, Durarome flavour banana and sucrose. Appropriate justifications for the inclusion of each excipient have been provided.
With the exception of ferric oxide yellow (E172), dispersible cellulose and Durarome flavour banana all excipients comply with their respective European Pharmacopoeia monographs. Ferric oxide yellow (E172) is controlled to United States National Formulary specifications, dispersible cellulose is controlled to British Pharmacopoeia monograph and Durarome flavour banana is controlled to a suitable in-house monograph. Ferric oxide yellow (E172), is also in compliance with current European Directives concerning use of colouring agents in foodstuff. The natural flavouring substances used in the Durarome banana flavouring conform to Directive 88/388/EEC, concerning food additives and flavouring.

Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

With the exception of lactose monohydrate, none of the excipients used contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that milk is sourced from healthy animals under the same conditions as milk for human consumption.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Pharmaceutical Development**

The objective of the development programme was to produce a safe, efficacious product that could be considered a generic medicinal product of Orelox, 40 mg/5 ml, granules for oral suspension (Aventis Pharma Specialities, Laboratoires Aventis, France).

Suitable pharmaceutical development data have been provided for this application.

Comparative dissolution and impurity profiles have been provided for this product and the reference product.

**Manufacturing Process**

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. Process validation studies were conducted on two pilot-scale batches and the results were satisfactory. The validation data demonstrated consistency of the manufacturing process. A commitment has been made by the Marketing Authorisation Holder that full process validation will be conducted on the first three commercial-scale batches in accordance with the process validation protocol.

**Finished Product Specification**

The finished product specification proposed 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 packaged in a translucent high density polyethylene (HDPE) bottle fitted with removable stopper containing desiccant gel, which is closed with polypropylene child-resistant closure with wad having induction-sealing liner. A measuring spoon with graduations from 5kg to 25kg is provided with the bottle for correct dosing.

The finished product is available in pack size of 100 ml of suspension.

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 foodstuff.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for an unopened product, with the storage conditions ‘Store below 25°C. Store in the original package in order to protect from light’. For the reconstituted suspension, a shelf life of 10 days after reconstitution, when stored in a refrigerator (2°C – 8°C) has been set.

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

Summaries of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
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.

MAA Forms
The MAA form is satisfactory.

Expert Report
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of Marketing Authorisation is recommended.
III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of cefpodoxime proxetil are well-known, no new non-clinical studies are required and none have been provided.

The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product.

As this product is intended for generic substitution with a product that is already marketed, no increase in environmental burden is anticipated and no Environmental Risk Assessment is necessary. A suitable justification has been provided for non-submission of an environmental risk assessment.

There is no objection to the approval of this product from a non-clinical viewpoint.
III.3 CLINICAL ASPECTS

CLINICAL PHARMACOLOGY

Pharmacokinetics

In support of this application, the Marketing Authorisation Holder has submitted the following bioequivalence study:

A randomised, single-dose, two-period, two-treatment, two-sequence, crossover study to compare the pharmacokinetics of the test product Cefpodoxime 40 mg/5 ml granules for oral suspension versus the reference product Orelox 40 mg/5 ml granules for oral suspension (Laboratoires Aventis, France) in healthy adult male volunteers under fasted conditions.

All volunteers received a single oral dose of either the test or the reference product with 240 ml of water under fasting conditions. Blood samples were taken for the measurement of pharmacokinetic parameters pre-dose and up to 24 hours post dose. The washout period between the two treatment arms was 7 days.

The pharmacokinetic results for cefpodoxime proxetil are presented below (ln-transformed values; geometric mean, ratios and 90% confidence intervals):

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Geometric Mean</th>
<th>Ratio (T/R)</th>
<th>90% Confidence Interval</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Test</td>
<td>Reference</td>
<td>(%)</td>
</tr>
<tr>
<td>C_max (µg/ml)</td>
<td>0.97</td>
<td>1.02</td>
<td>94.85</td>
</tr>
<tr>
<td>AUC_0-t (µg/ml/hr)</td>
<td>4.54</td>
<td>4.76</td>
<td>95.28</td>
</tr>
<tr>
<td>AUC_0-inf (µg/ml/hr)</td>
<td>4.76</td>
<td>5.00</td>
<td>95.22</td>
</tr>
</tbody>
</table>

AUC_0-a area under the plasma concentration-time curve from time zero to infinity
AUC_0-t area under the plasma concentration-time curve from time zero to t hours
C_max maximum plasma concentration

The 90% confidence intervals for AUC and C_max for test versus reference product for cefpodoxime proxetil are within predefined acceptance criteria specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1). Thus, the data support the claim that the test product Cefpodoxime 40 mg/5 ml granules for oral suspension (Aurobindo Pharma Limited) is bioequivalent to the reference product Orelox 40 mg/5 ml granules for oral suspension (Laboratoires Aventis, France).

EFFICACY

The efficacy of cefpodoxime proxetil is well-known. No new efficacy data have been submitted and none are required for application of this type.

SAFETY

With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for application of this type. No new or unexpected safety issues were raised by the bioequivalence data.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels

The SmPC, PIL and labels are clinically acceptable. The SmPC is consistent with these for the originator product. The PIL is consistent with the details in the SmPC and in-line with the current guidelines. The labelling is in-line with the current guidelines.
Clinical Overview
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

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

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

Conclusion
The grant of a Marketing Authorisation is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Cefpodoxime 40 mg/5 ml granules for oral suspension 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. As the pharmacokinetics, pharmacodynamics and toxicology of cefpodoxime proxetil are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for application of this type. Bioequivalence has been demonstrated between the applicant’s Cefpodoxime 40 mg/5 ml granules for oral suspension and the reference product.

SAFETY
With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for an application of this type. No new or unexpected safety concerns arose from the bioequivalence study.

PRODUCT LITERATURE
The SmPC, PIL and labelling are acceptable. The SmPC is consistent with these for the reference product. The PIL is consistent with the details in the SmPC and in-line with the current guidelines. The labelling is in-line with the current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data provided support the claim that this product is a generic medicinal product of the reference product, Orelox 40 mg/5 ml granules for oral suspension (Laboratoires Aventis, France). Extensive clinical experience with cefpodoxime proxetil is considered to have demonstrated the therapeutic value of the product. The benefit/risk is, therefore, considered to be positive.
## Module 6

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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