Public Assessment Report

Decentralised Procedure

Cefixime 100 mg/5 ml granules for oral suspension

(cefixime)

Procedure No: UK/H/5626/001/DC

UK Licence No: PL 40168/0005

INN-FARM d.o.o.
LAY SUMMARY

Cefixime 100 mg/5 ml granules for oral suspension
(cefixime)

This is a summary of the public assessment report (PAR) for Cefixime 100 mg/5 ml granules for oral suspension (PL 40168/0005; UK/H/5626/001/DC). It explains how Cefixime 100 mg/5 ml granules for oral suspension was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

For practical information about using Cefixime 100 mg/5 ml granules for oral suspension, patients should read the package leaflet or contact their doctor or pharmacist.

What is Cefixime 100 mg/5 ml granules for oral suspension and what is it used for?
Cefixime 100 mg/5 ml granules for oral suspension is a ‘generic medicine’. This means that Cefixime 100 mg/5 ml granules for oral suspension is similar to a ‘reference medicine’ already authorised in the UK called Suprax 100 mg/5ml Powder for Paediatric Oral Suspension (Sanofi-aventis Ltd; PL 04425/0622).

Cefixime 100 mg/5 ml granules for oral suspension is used in children above 6 months, adolescents and adults 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.

How is Cefixime 100 mg/5 ml granules for oral suspension used?
Cefixime 100 mg/5 ml granules for oral suspension is taken orally. The reconstituted suspension should be administered undiluted before or during a meal.

The usual dose in:

**Adults**
400 mg once daily (= 20 ml of the reconstituted suspension) as a single dose or 2 times daily 200 mg (= 10 ml) at intervals of 12 hours.

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

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

**Children under 12 years**
Cefixime 8 mg/kg body weight/day, either as a single dose or two divided doses 12 hourly.
Renal insufficiency
Cefixime may be administered in the presence of impaired renal function. The normal dosing 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/1.73 m², it is recommended that a dose of 200 mg once daily should not be exceeded. In children under 12 years with a creatinine clearance of <20 ml/min/1.73 m², a dose of 4 mg cefixime/kg body weight should be given only once a day.

The usual course of treatment is 7 days. Treatment may be continued for up to 14 days according to the severity of the infection. For acute uncomplicated cystitis in women, the treatment period is 1-3 days.

Cefixime 100 mg/5 ml granules for oral suspension can only be obtained on prescription from a doctor.

For further information on how Cefixime 100 mg/5 ml granules for oral suspension is used, please see the Summary of Product Characteristics and package leaflet available on the MHRA website.

How does Cefixime 100 mg/5 ml granules for oral suspension work?
Cefixime 100 mg/5 ml granules for oral suspension contains an active ingredient called cefixime. This belongs to a group of antibiotics called “cephalosporins”, which is used for treating infections caused by bacteria.

How has Cefixime 100 mg/5 ml granules for oral suspension been studied?
Apart from a bioequivalence study, no additional clinical studies were needed as Cefixime 100 mg/5 ml granules for oral suspension is a generic medicine that is given orally and contains the same active substance and content as the reference medicine, Suprax Saft 100 mg/5 ml Granules for Oral suspension (Astellas Pharma GmbH).

What are the benefits and risks of Cefixime 100 mg/5 ml granules for oral suspension?
As Cefixime 100 mg/5 ml granules for oral suspension is a generic medicine and is comparable to the reference medicine, its benefits and risks are taken as being the same as those for Suprax Saft 100 mg/5 ml Granules for Oral suspension (Astellas Pharma GmbH).

Why is Cefixime 100 mg/5 ml granules for oral suspension approved?
It was concluded that, in accordance with EU requirements, Cefixime 100 mg/5 ml granules for oral suspension has been shown to have comparable quality and to be comparable to Suprax Saft 100 mg/5 ml Granules for Oral suspension. Therefore, the view was that, as for Suprax Saft 100 mg/5 ml Granules for Oral suspension, the benefit outweighs the identified risks.

What measures are being taken to ensure the safe and effective use of Cefixime 100 mg/5 ml granules for oral suspension?
A Risk Management Plan (RMP) has been developed to ensure that Cefixime 100 mg/5 ml granules for oral suspension is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Cefixime 100 mg/5 ml granules for oral suspension, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Cefixime 100 mg/5 ml granules for oral suspension
Austria, Czech Republic, Germany, Hungary, Italy, Poland, Portugal, Romania, Slovak Republic, Spain and the UK agreed to grant a Marketing Authorisation for Cefixime 100 mg/5 ml granules for oral suspension on 22th March 2015. A Marketing Authorisation was granted in the UK on 15th April 2015.

The full PAR for Cefixime 100 mg/5 ml granules for oral suspension follows this summary. For more information about treatment with Cefixime 100 mg/5 ml granules for oral suspension, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in November 2018.
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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) considered that the application for Cefixime 100 mg/5 ml granules for oral suspension (PL 40168/0005; UK/H/5626/001/DC) is approvable. This product is a Prescription Only Medicine (POM) indicated for the treatment of the following infections caused by susceptible microorganisms in children above 6 months, adolescents and adults:

- acute exacerbations of chronic bronchitis
- Community-acquired pneumonia
- Lower urinary tract infections
- Pyelonephritis.

Cefixime 100 mg/5 ml granules for oral suspension are also indicated in the treatment of:

- otitis media
- sinusitis
- pharyngitis.

The application was submitted using the Decentralised Procedure (DCP) with the UK as the RMS and Austria, Czech Republic, Germany, Hungary, Italy, Poland, Portugal, Romania, Slovak Republic and Spain as CMSs. The application was made under Article 10.1 of Directive 2001/83/EC, as amended, and cross referred to Suprax 100 mg/5 ml Powder for Paediatric Oral Suspension, which was first licensed to May & Baker Limited (PL 00012/0318) on 14th October 1998. This reference licence underwent a change of ownership procedure to the current Marketing Authorisation Holder, Aventis Pharma Limited (PL 04425/0622), on 17th July 2010.

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

One bioequivalence study was submitted to support this application comparing the test product Cefixime 100 mg/5 ml granules for oral suspension (Alkaloid AD) with the reference product Suprax Saft 100 mg/5 ml granules for oral suspension (Astellas Pharma GmbH) in 28 healthy male subjects under fasting conditions. The applicant has stated that the bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new non-clinical or clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

The 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, 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.

All involved Member States agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day 210 – 22th March 2015). After a subsequent national phase, the UK granted a Marketing Authorisation (PL 40168/0005) for this product on 15th April 2015.
II QUALITY ASPECTS

II.1 Introduction

The proposed pharmaceutical form is granules for oral suspension. Each 5 ml of reconstituted oral suspension contains 111.9 mg of cefixime trihydrate equivalent to 100 mg of cefixime (anhydrous), as active ingredient. The excipients present are sucrose, xanthan gum, sodium benzoate E 211 and flavour durarome orange (flavouring ingredients, maltodextrin, sucrose, soy-lecithin E322 and silicon dioxide E551). 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 flavour durarome orange which complies with an in-house specification.

The finished product is packaged in type III brown neutral glass bottle with an aluminium screw cap with a polyethylene sealing and the bottle is packed in a cardboard box.

Each cardboard box contains one bottle, one plastic (polypropylene) measuring cup for reconstitution only graduated to 40 ml or 66 ml, one plastic graduated oral syringe for dosing, and an instruction leaflet.

Each bottle contains 32 g granules for preparation of 60 ml oral suspension or 53 g granules for preparation of 100 ml oral suspension. The 5 ml plastic (polyethylene-polystyrene) oral syringe with scale from 0.5 ml to 5 ml is graduated on each 0.25 ml imprinted on the plunger of the syringe for measuring of the doses.

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

II.2 Drug Substance

INN: Cefixime trihydrate

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

Structure:

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   C16H15N5O7S2  3H2O
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Molecular formula: C_{16}H_{15}N_{5}O_{7}S_{2} 3H_{2}O
Molecular weight: 507.5 g/mol
Appearance: A white or almost white powder, slightly hygroscopic.
Solubility: Slightly soluble in water, soluble in methanol, sparingly soluble in anhydrous ethanol and practically insoluble in ethyl acetate.

Cefixime trihydrate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, cefixime trihydrate, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to produce safe, efficacious, granules for oral suspension containing 100 mg/5 ml cefixime that is bioequivalent to the reference product Suprax 100 mg/5 ml Powder for Paediatric Oral Suspension (Aventis Pharma Limited).
Comparative dissolution and impurity profiles have been presented for the proposed and reference products.

**Manufacture of the product**
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on commercial scale batches have been provided. The results are satisfactory.

**Finished Product Specification**
The finished product specification is satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

**Stability of the product**
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results a shelf-life of 2 years for the unreconstituted product with a storage condition ‘store below 25°C’ is set. The reconstituted suspension may be stored for 14 days at ambient conditions (below 25°C) or refrigerated conditions. These are satisfactory.

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

**II.4 Discussion on chemical, pharmaceutical and biological aspects**
There are no objections to the approval of this application, from a pharmaceutical viewpoint.

**III NON-CLINICAL ASPECTS**

**III.1 Introduction**
This generic application has been submitted in accordance with Article 10.1 of Directive 2001/83/EC, as amended.

The pharmacodynamic, pharmacokinetic and toxicological properties of cefixime trihydrate are well known. As cefixime trihydrate is a widely used, well-known active substance, no new non-clinical data have been supplied and none are required for applications of this type. The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

**III.2 Pharmacology**
No new data have been submitted and none are required for applications of this type.

**III.3 Pharmacokinetics**
No new data have been submitted and none are required for applications of this type.

**III.4 Toxicology**
No new data have been submitted and none are required for applications of this type.

**III.5 Ecotoxicity/environmental risk assessment (ERA)**
Since the proposed product is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

**III.6 Discussion on the non-clinical aspects**
There are no objections to the approval of this product, from a non-clinical point of view.
IV CLINICAL ASPECTS

IV.1 Introduction
This is a generic application submitted under the Decentralised Procedure according to Article 10.1 of Directive 2001/83/EC, as amended, for Cefixime 100 mg/5 ml granules for oral suspension.

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

With the exception of the bioavailability study, no new clinical data have been submitted and none are required for applications of this type. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
In support of this application, the Marketing Authorisation Holder has submitted results of the following bioequivalence study carried out under fasting conditions.

This was an open-label, randomised, two-way crossover, bioequivalence study comparing the pharmacokinetics of the test product Cefixime 100 mg/5 ml granules for oral suspension (Alkaid AD) with the reference product Suprax Saft 100 mg/5 ml granules for oral suspension (Astellas Pharma GmbH) in 28 healthy male subjects under fasting conditions.

The study drug was administered after an overnight fast of 10 hours with 240 ml water. Blood samples were collected at pre-dose (0.0) and at 0.250, 0.500, 0.750, 1.00, 1.25, 1.50, 2.0, 2.50, 3.00, 3.50, 4.0, 4.50, 5.0, 6.00, 7.00, 8.00, 10.0, 12.0, 14.0 and 16.0 hrs post-dose. A washout period of 7 days between drug administrations was maintained.

Bioequivalence results for ln-transformed test/reference ratios with 90% Confidence Intervals for Cefixime (N=28)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Geometric mean ratio test/reference</th>
<th>Confidence Intervals</th>
<th>CV% ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>109.15%</td>
<td>102.25% – 116.51%</td>
<td>14.40%</td>
</tr>
<tr>
<td>AUC0-t (ng/ml/h)</td>
<td>109.12%</td>
<td>102.32% – 116.38%</td>
<td>14.20%</td>
</tr>
<tr>
<td>AUC0-∞ (ng/ml/h)</td>
<td>109.66%</td>
<td>102.71% – 117.07%</td>
<td>14.42%</td>
</tr>
</tbody>
</table>

¹Calculated using least-squares means
²Estimated from the Residual Mean Squares. For replicate design studies report the within-subject CV% using only

Conclusion
The 90% confidence intervals for Cmax and AUC were within the pre-defined acceptance criteria specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**). Bioequivalence has been shown for the test formulation (Cefixime 100 mg/5 ml granules for oral suspension) and the reference formulation (Suprax Saft 100 mg/5 ml granules for oral suspension) under fasting conditions.

IV.3 Pharmacodynamics
No new data have been submitted and none are required for this type of application.
IV.4 **Clinical efficacy**
No new data on efficacy have been submitted and none are required for this type of application.

IV.5 **Clinical safety**
No new safety data were submitted and none are required.

IV.6 **Risk Management Plan (RMP)**
The Marketing Authorisation Holder (MAH) has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Cefixime 100 mg/5 ml granules for oral suspension.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

**Summary table of risk minimisation measures**

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity &amp; anaphylaxis</td>
<td>Proposed text in SmPC (Contraindications in section 4.3; Warning in section 4.4 and Undesirable effects labeled in section 4.8.)</td>
<td>N/A</td>
</tr>
<tr>
<td>Renal toxicity in concomitant administration with nephrotoxic drugs (e.g. aminoglycosides, colistin, polymyxin B &amp; high dose loop diuretics), especially in patients with existing renal impairment</td>
<td>Proposed text in SmPC (Warning in section 4.4; Interactions in section 4.5; Undesirable effects listed in 4.8)</td>
<td>N/A</td>
</tr>
<tr>
<td>Antibiotic-associated diarrhoea &amp; pseudomembranous colitis</td>
<td>Proposed text in SmPC (Warnings in section 4.4; Undesirable effects listed in 4.8)</td>
<td>N/A</td>
</tr>
<tr>
<td>Overgrowth of non-susceptible organisms with prolonged use</td>
<td>(Warnings in section 4.4; Undesirable effects listed in 4.8)</td>
<td>N/A</td>
</tr>
<tr>
<td>Increased prothrombin time in concomitant administration with anticoagulants</td>
<td>Proposed text in SmPC (Listed interaction in section 4.5)</td>
<td>N/A</td>
</tr>
<tr>
<td>Severe skin reactions: angioneurotic oedema; Stevens-Johnson syndrome, toxic epidermal necrolysis; erythema multiforme; Drug rash with eosinophilia and systemic symptoms (DRESS)</td>
<td>Proposed text in SmPC (Warning in section 4.4 and Undesirable effects labeled in section 4.8)</td>
<td>N/A</td>
</tr>
<tr>
<td>Serious haematological effects (agranulocytosis, pancytopenia, neutropenia, thrombocytopenia, haemolytic anaemia)</td>
<td>Proposed text in SmPC (Undesirable effects listed in 4.8)</td>
<td>N/A</td>
</tr>
<tr>
<td>Interference with diagnostic tests</td>
<td>Proposed text in SmPC (Listed interaction in section 4.5)</td>
<td>N/A</td>
</tr>
<tr>
<td>Interference with Coomb’s test</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
IV.7 Discussion on the clinical aspects
The grant of a marketing authorisation is recommended for this application, from a clinical viewpoint.

V USER CONSULTATION
For Cefixime 100 mg/5 ml granules for oral suspension a user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Cefixime 400 mg Tablets (UK/H/4956/01/DC). The bridging report submitted by the applicant is acceptable.

VI OVERALL CONCLUSION. BENEFIT-RISK ASSESSMENT AND RECOMMENDATION
The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. The data provided by the applicant showed that the test product is comparable to the reference product. Extensive clinical experience with cefixime trihydrate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

The currently approved labelling are listed below:
Each 5 ml of reconstituted oral suspension contains 111.9 mg of cefixime trihydrate equivalent to 100 mg of cefixime (anhydrous). Also contains sucrose and sodium benzoate (E211). See leaflet for further information.

For oral use. Read the package leaflet before use.

Before reconstitution store below 25°C.

Preparation of the suspension
Add 40 ml purified water to the bottle in two portions shaking after each addition. The reconstituted suspension may be stored for 14 days at ambient conditions (below 20°C) or refrigerated conditions.

For further instructions see package leaflet.

Shake the medicine bottle well before each use.

Use as directed by doctor.

Keep out of the sight and reach of children.

Prescription only medicine.

PL 40166/0005
Each 5 ml of reconstituted oral suspension contains 111.9 mg of cefixime (hydrate equivalent to 100 mg of cefixime (anhydrous)). Also contains sucrose and sodium benzoate (E211). See leaflet for further information.

For oral use. Read the package leaflet before use.

Before reconstitution store below 25°C.

Preparation of the suspension
Add 66 ml purified water to the bottle in two portions shaking after each addition. The reconstituted suspension may be stored for 14 days at ambient conditions (below 25°C) or refrigerated conditions.

For further instructions see package leaflet.
Shake the medicine bottle well before each use.
Use as directed by doctor.
Keep out of the sight and reach of children.

PL 40168/0005
MA Holder:
WAA (UK) Ltd.
Middletons, Styal
1088 Wythenshawe Lane
Sheffield
Annex 1 - Table of content of the PAR update for MRP and DCP

Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report

The following table lists a non-safety update to the Marketing Authorisation for Cefixime 100 mg/5 ml granules for oral suspension (PL 40168/0005; UK/H/5626/001/DC) that have been approved by the MHRA since the Decentralised Procedure (UK/H/5626/001/DC) concluded. The table includes an update that has been added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to this Marketing Authorisation.

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
<tbody>
<tr>
<td>To update section 4.1 of the SmPC and section 1 of the PIL in order to harmonize the indications with the reference product Aerocef 100 mg/5 ml - Trockensaft (MAH: Astellas Pharm Ges.m.b.H) from Austria...</td>
<td>UK/H/5626/001/II/005</td>
<td>SmPC PIL</td>
<td>06/08/2018</td>
<td>05/10/2018</td>
<td>Approval</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Annex 1.1

Our Reference: PL 40168/0005, Application 0007
Product: Cefixime 100 mg/5 ml granules for oral suspension
Marketing Authorisation Holder: INN - FARM doo
Active Ingredient(s): Cefixime trihydrate

Type of Procedure: Mutual Recognition
Submission Type: Variation
Submission Category: Type II
Submission Complexity: Standard
EU Procedure Number (if applicable): UK/H/5626/001/II/005

Reason:
To update section 4.1 of the SmPC and section 1 of the PIL in order to harmonise the indications with the reference product Aerocef 100 mg/5 ml - Trockensaft (MAH: Astellas Pharm Ges.m.b.H) from Austria.

Supporting Evidence
Revised SmPC fragment (section 4.1)
Updated PIL
Literature review

RECOMMENDATION
Based on the review of the data on quality, safety and efficacy, the RMS considers that the variation according to Article 20 of Commission Regulation (EC) No 1234/2008 for Cefixime 100 mg/5 ml granules for oral suspension (cefixime), in the treatment of bacterial infections, for the following proposed changes is approvable.

EXECUTIVE SUMMARY
Scope of the variation
The variation application is submitted in order to harmonize the indications with the reference product Aerocef 100 mg/5 ml - Trockensaft (MAH: Astellas Pharm Ges.m.b.H) from Austria.

Since the MA for the reference product with whom bioequivalence was demonstrated (Suprax Saft 100 mg/5 ml, granules for oral suspension by Astellas Pharma GmbH from DE) is no longer valid, Aerocef 100 mg/5 ml - Trockensaft from Austria is used as the appropriate Reference product for harmonisation of indications.

The reference product in RMS and other CMSs (as declared in the initial AF) has a wider scope of the indications than the current product and the applicant would like to harmonize the indications for better use of the product by patients.

The same variation for extension of indications has been recently approved for INN Farm's Cefixime 400 mg film-coated tablets, Procedure Number. UK/H/4956/001/II/011, End of Procedure 7th June 2018. The indications proposed in this variation are the same as those approved for the Cefixime 400 mg film-coated tablets.

The approach, variation type and supporting data were confirmed by RMS in a Scientific advice on 07/2014 (for the Cefixime film-coated tablets) and via email for Cefixime 100 mg/5 ml granules for oral suspension on 07/2018 (Annex 5.14 of the AF).

SCIENTIFIC DISCUSSION
Quality aspects
N/A
Non-clinical aspects
N/A

Clinical aspects
Clinical pharmacology
N/A

Clinical efficacy
N/A

Clinical safety
N/A

Product information
The applicant proposes changes to the SmPC and PIL and considers that the changes proposed are justified because the reference product in RMS and other CMSs have a wider scope of the indications than this product.

The changes proposed are as follows:

III.4.1 Summary of Product Characteristics

<table>
<thead>
<tr>
<th>Present indications in the SmPC (section 2.1)</th>
<th>Proposed indications in the SmPC (section 2.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present indications:</td>
<td>Proposed indications:</td>
</tr>
<tr>
<td>- Product name: is indicated for the treatment of the following infections caused by susceptible microorganisms in children above 6 months, adolescents and adults (see section 5.1):</td>
<td>- Product name: is indicated for the treatment of the following infections caused by susceptible microorganisms in children above 6 months, adolescents and adults (see section 4.4 and section 5.1):</td>
</tr>
<tr>
<td>- Acute exacerbations of chronic bronchitis (AECB)</td>
<td>- Acute exacerbations of chronic bronchitis</td>
</tr>
<tr>
<td>- Acute otitis media</td>
<td>- Community-acquired pneumonia</td>
</tr>
<tr>
<td>- Uncomplicated acute cystitis</td>
<td>- Lower urinary tract infections</td>
</tr>
<tr>
<td>- Uncomplicated pyelonephritis</td>
<td>- Pyelonephritis</td>
</tr>
<tr>
<td>Consideration should be given to official guidance on the appropriate use of antibacterial agents.</td>
<td>Consideration should be given to official guidance on the appropriate use of antibacterial agents.</td>
</tr>
</tbody>
</table>

III.4.2 Package leaflet and user test

<table>
<thead>
<tr>
<th>Present indications in the PIL (section 1)</th>
<th>Proposed indications in the PIL (section 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present indications:</td>
<td>Proposed indications:</td>
</tr>
<tr>
<td>- Product name: contains an active substance called cefixime. This belongs to a group of antibiotics called “cephalosporins”, which are used for treating infections caused by bacteria.</td>
<td>- Product name: contains an active substance called cefixime. This belongs to a group of antibiotics called “cephalosporins”, which are used for treating infections caused by bacteria.</td>
</tr>
<tr>
<td>- Product name: is used in children above 6 months, adolescents and adults to treat:</td>
<td>- Product name: is used in children above 6 months, adolescents and adults to treat:</td>
</tr>
<tr>
<td>- infection of the middle ear</td>
<td>- sinus infection</td>
</tr>
<tr>
<td>- infection causing sudden worsening of long-standing bronchitis</td>
<td>- throat infection</td>
</tr>
<tr>
<td>- uncomplicated acute infection of the bladder</td>
<td>- infection causing sudden worsening of long-standing bronchitis</td>
</tr>
<tr>
<td>- uncomplicated infection of the kidneys</td>
<td>- serious lung infections (pneumonia) acquired outside of hospital</td>
</tr>
</tbody>
</table>
| Labelling
N/A
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

It is agreed that the reference product has a wider range than this product. Therefore, the proposal to harmonise with a European reference product is acceptable. The changes proposed to both the SmPC and PIL are in line with the Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 rev 2) and other generic products of Cefixime in the UK.

The benefit risk of the product is considered unchanged.

In accordance with Directive 2010/84/EU, the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL is available on the MHRA website.

Decision – Approved on 05 October 2018