Public Assessment Report

Decentralised Procedure

CEFIXIME 400 MG FILM-COATED TABLETS

(Cefixime)

Procedure No: UK/H/4956/001/DC

UK Licence No: PL 40168/0002

INN-FARM d.o.o.
Cefixime 400 mg Film-coated Tablets

Lay Summary
Cefixime 400 mg film-coated tablets
(Cefixime)

This is a summary of the public assessment report (PAR) for Cefixime 400 mg film-coated tablets (PL 40168/0002; UK/H/4956/001/DC). It explains how Cefixime 400 mg film-coated tablets were assessed and their authorisation recommended as well as their conditions of use. It is not intended to provide practical advice on how to use Cefixime 400 mg film-coated tablets.

For practical information about using Cefixime 400 mg film-coated tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Cefixime 400 mg film-coated tablets and what are they used for?
Cefixime 400 mg film-coated tablets are a ‘generic medicine’. This means that Cefixime 400 mg film-coated tablets is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Suprax 400 mg film-coated tablets.

Cefixime Tablets are 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

How are Cefixime 400 mg film-coated tablets used?
Cefixime 400 mg film-coated tablets are taken by mouth.

The recommended dose in adults is 400 mg (1 tablet) daily as single oral dose or divided in two equal oral doses of 200 mg (1/2 tablet) every 12 hours. Adolescents 12 years of age and older may be given the same dose as adults. This medicine should always be taken at the same time each day.

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

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

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

The pharmaceutical form tablet is not suitable for children under 12 years of age.

Cefixime 400 mg film-coated tablets can only be obtained with a prescription.
How do Cefixime 400 mg film-coated tablets work?

Cefixime 400 mg film-coated tablets contains the active ingredient cefixime (as cefixime trihydrate). This belongs to a group of antibiotics called “cephalosporins”, which are used to treat infections caused by bacteria.

How have Cefixime 400 mg film-coated tablets been studied?

Because Cefixime 400 mg film-coated tablets is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Suprax 400 mg film-coated tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the benefits and risks of Cefixime 400 mg film-coated tablets?

Because Cefixime 400 mg film-coated tablets is a generic medicine and is bioequivalent to the reference medicine, its benefits and risks are taken as being the same as those for the reference medicine.

Why are Cefixime 400 mg film-coated tablets approved?

It was concluded that, in accordance with EU requirements, Cefixime 400 mg film-coated tablets has been shown to have comparable quality and to be bioequivalent to Suprax 400 mg film-coated tablets. Therefore, the view was that, as for Suprax 400 mg film-coated tablets, the benefit outweighs the identified risk.

What measures are being taken to ensure the safe and effective use of Cefixime 400 mg film-coated tablets?

Safety information has been included in the Summary of Product Characteristics and the package leaflet for Cefixime 400 mg film-coated tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Cefixime 400 mg film-coated tablets

Austria, Czech Republic, France, Hungary, Italy, Poland, Portugal, Romania, Slovakia, Spain, and the UK agreed to grant a Marketing Authorisation for Cefixime 400 mg film-coated tablets on 19 August 2013. A Marketing Authorisation was granted in the UK on 11 September 2013.

The full PAR for Cefixime 400 mg film-coated tablets follows this summary.

This summary was last updated in July 2018.
# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I  Introduction</td>
<td>5</td>
</tr>
<tr>
<td>II Quality aspects</td>
<td>6</td>
</tr>
<tr>
<td>III Non-clinical aspects</td>
<td>8</td>
</tr>
<tr>
<td>IV Clinical aspects</td>
<td>8</td>
</tr>
<tr>
<td>V  User consultation</td>
<td>10</td>
</tr>
<tr>
<td>VI Overall conclusion, benefit/risk assessment and recommendation</td>
<td>10</td>
</tr>
<tr>
<td>Table of content of the PAR update for MRP and DCP</td>
<td>13</td>
</tr>
<tr>
<td>Annex – 1</td>
<td>15</td>
</tr>
<tr>
<td>Annex – 2</td>
<td>16</td>
</tr>
</tbody>
</table>
I Introduction

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Cefixime 400 mg film-coated tablets (PL 40168/0002; UK/H/4956/001/DC), is approvable. The application was submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), and Austria, Czech Republic, France, Hungary, Italy, Poland, Portugal, Romania, Slovakia and Spain, as Concerned Member States (CMSs).

This product is a prescription-only medicine (legal classification POM).

This was an application made under the Decentralised Procedure (DCP), according to Article 10.1 of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Suprax 400 mg film-coated tablets (Astellas Pharma GmbH, Germany), which was initially granted a Marketing Authorisation in the EU on 30 June 1987. The UK reference product is Suprax 400 mg film-coated tablets (Cynamid of Great Britain Limited, PL 00095/0213); however, this product is no longer available in the UK as the licence has subsequently been cancelled.

Cefixime 400 mg film-coated tablets are indicated for the treatment infections caused by susceptible microorganisms:

- Acute exacerbations of chronic bronchitis
- Community-acquired Pneumonia
- Lower urinary tract infections
- Pyelonephritis

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

This product contains the active substance cefixime trihydrate, which 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.

No non-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.

With the exception of the bioequivalence study, no new 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.

A bioequivalence study was performed, which compared the pharmacokinetics of the test product Cefixime 400 mg film-coated tablets to those of the reference product Suprax 400 mg film-coated tablets (Astellas Pharma GmbH, Germany). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

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

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.

A suitable justification has been provided for not submitting a risk management plan for this product.

The RMS and CMSs considered that the application could be approved at the end of procedure on 19 August 2013. After a subsequent national phase, a licence was granted in the UK on 11 September 2013.

II  Quality aspects

II.1  Introduction

This application was submitted according to Article 10.1 of Directive 2001/83/EC, as amended. The applicant has specified Suprax 400 mg film-coated tablets (Astellas Pharma GmbH, Germany) as the EU reference medicinal product.

Cefixime 400 mg film-coated tablets are formulated as white to slightly cream, oblong, biconvex film-coated tablets with bisection line on one side of the tablet.

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

Other ingredients consist of the pharmaceutical excipients, as follows:

**Tablet core:** microcrystalline cellulose, calcium hydrogen phosphate dihydrate, pregelatinised starch and magnesium stearate.

**Film-coating:** hypromellose 5 cP (E464), macrogol 400 and titanium dioxide (E171).

All excipients used comply with their respective European Pharmacopoeia monographs.

None of the excipients are sourced from animal or human origin. The magnesium stearate is of vegetable origin. This product does not contain or consist of genetically modified organisms (GMO).

The finished product is packaged in polyvinylchloride/polyvinylidene chloride/aluminium foil blisters, containing 5 or 7 tablets per blister. Blisters are packaged in a cardboard carton in pack sizes of 5, 7 and 10 tablets.

The marketing authorisation holder has stated that not all pack sizes are intended for marketing. However, they have committed to provide the relevant licensing authority with the mock-ups for any pack size before marketing it in that country.

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

Structure:

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 and soluble in methanol

All aspects of the manufacture and control of the active substance, cefixime trihydrate, from its starting materials 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 formulate a globally acceptable, stable and bioequivalent product that could be considered a generic medicinal product of the currently licensed product, Suprax 400 mg film-coated tablets (Astellas Pharma GmbH, Germany).

A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro dissolution and impurity profiles have been provided for the proposed product and its respective reference product.

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. Suitable in-process controls are in place to ensure the quality of the finished product.

Process validation has been carried out on three commercial-scale batches of finished product. The results are satisfactory.

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

Stability of the product
Stability studies were performed, in accordance with current guidelines, on batches of finished product manufactured by the finished product manufacturer and packed in the packaging proposed for marketing. The results from these studies support a shelf-life of 2 years, with no special storage conditions.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a Marketing Authorisation is recommended.

III Non-clinical aspects
III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of cefixime trihydrate are well-known, no further non-clinical studies are required and none have been provided.

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

III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since this product is intended for substitution of an originator product, 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 viewpoint.

IV Clinical aspects
IV.1 Introduction
The clinical pharmacology of cefixime trihydrate is well-known. With the exception of data from the bioequivalence studies detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for this application.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of cefixime trihydrate.

Based on the data provided, Cefixime 400 mg Film-coated Tablets can be considered bioequivalent to Suprax 400 mg film-coated tablets (Astellas Pharma GmbH, Germany).
IV.2 Pharmacokinetics
In support of this application, the Marketing Authorisation Holder has submitted the following bioequivalence study:

A randomised, open-label, two-way crossover, bioequivalence study comparing the pharmacokinetics of the test product Cefixime 400 mg film-coated tablets to those of the reference product Suprax 400 mg film-coated tablets (Astellas Pharma GmbH, Germany) in healthy adult male subjects under fasting conditions.

Volunteers were given each treatment after an overnight fast of 10 hours. Blood samples were collected for the measurement of pharmacokinetic parameters pre-dose and up to 24 hours post dose. Each regimen was separated by a 7-day washout period.

A summary of the main pharmacokinetic results is presented in the tables below:

**Table 1. Summary of pharmacokinetic parameters for cefixime for each treatment**

<table>
<thead>
<tr>
<th>(Mean ± SD (CV%))</th>
<th>Cefixime</th>
<th>Suprax</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;0-24&lt;/sub&gt;</td>
<td>34690.24 ± 9764.42 (28.15)</td>
<td>36880.86 ± 10853.12 (29.43)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt;</td>
<td>35300.37 ± 10129.35 (28.65)</td>
<td>37532.05 ± 11272.47 (30.03)</td>
</tr>
<tr>
<td>Residual Area (%)</td>
<td>1.79 ± 1.17 (65.30)</td>
<td>1.62 ± 0.86 (53.07)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (pg/mL)</td>
<td>4310.02 ± 1104.27 (25.02)</td>
<td>4561.15 ± 1143.48 (25.07)</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (hr)</td>
<td>4.00 (2.50 - 7.00)</td>
<td>4.00 (2.50 - 5.50)</td>
</tr>
<tr>
<td>K&lt;sub&gt;el&lt;/sub&gt; (1/hr)</td>
<td>0.1858 ± 0.0232 (12.46)</td>
<td>0.1892 ± 0.0226 (11.92)</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; (hr)</td>
<td>3.79 ± 0.47 (12.34)</td>
<td>3.71 ± 0.43 (11.67)</td>
</tr>
</tbody>
</table>

*Median (Min - Max)*

**Table 2. Ratios, 90% geometric confidence intervals for AUC and C<sub>max</sub> for cefixime**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment Comparisons</th>
<th>Ratio&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Lower</th>
<th>Upper</th>
<th>IntrSuCV</th>
<th>InterSuCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;0-24&lt;/sub&gt;</td>
<td>Test (A) - Reference (B)</td>
<td>94.12%</td>
<td>87.90%</td>
<td>100.77%</td>
<td>15.07%</td>
<td>24.88%</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt;</td>
<td>Test (A) - Reference (B)</td>
<td>94.28%</td>
<td>88.12%</td>
<td>100.86%</td>
<td>14.89%</td>
<td>25.39%</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Test (A) - Reference (B)</td>
<td>94.44%</td>
<td>87.57%</td>
<td>101.38%</td>
<td>15.67%</td>
<td>21.83%</td>
</tr>
</tbody>
</table>

<sup>1</sup> Calculated using least-squares means according to the formula: $e^{\bar{X} \pm S}$ X 100.

<sup>2</sup> 90% Geometric Confidence Interval using ln-transformed data.
Compared with the reference product, the 90% confidence intervals for the test product are within 80.00-125.00% for C_{max} and AUC. Cefixime 400 mg film-coated tablets are, therefore, considered bioequivalent with Suprax 400 mg film-coated tablets.

IV.3 Pharmacodynamics
No new pharmacodynamics data are required for this application and none have been submitted.

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

IV.6 Risk Management Plan (RMP)
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.

A suitable justification has been provided for not submitting a risk management plan for this product.

IV.7 Discussion on the clinical aspects
The grant of a Marketing Authorisation is recommended for this application.

V User consultation
The results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC (as amended) for the package leaflet for Cefixime 400 mg film-coated tablets was provided. 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.

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

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type.
CLINICAL
Bioequivalence has been demonstrated between the applicant’s product and the reference product.

No new or unexpected safety concerns arose from this application.

The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. Bioequivalence has been demonstrated between the applicant’s product and 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.
The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product. In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website. The approved labelling is presented in annex 2.
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
(Type II variations, PSURs, commitments)

The following table lists a non-safety update to the Marketing Authorisation for this product that has been approved by the MHRA since the product was first licensed. The table includes updates that are detailed in the 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 numbers</th>
<th>Product information affected</th>
<th>Date of start of procedure</th>
<th>Date of end of procedure</th>
<th>Approval / non approval</th>
<th>Assessment report attached Y/N (version)</th>
</tr>
</thead>
<tbody>
<tr>
<td>To update section 4.2 of the SmPC in line with the posology of the EU reference product and to update the SmPC in line with the Quality Review Documents (QRD) template. Consequently, the patient information leaflet (PIL) has been updated.</td>
<td>UK/H/4956/001/IB/004</td>
<td>SmPC and PIL</td>
<td>25/09/2015</td>
<td>21/12/2015</td>
<td>Approved</td>
<td>Yes</td>
</tr>
<tr>
<td>To update section 4.1 of the SmPC to harmonize the indications with the reference product Suprax 400 mg film-coated tablets, by Astellas Pharma SpA from Italy. Consequently, impacting the PIL. Additionally, the Safety features have been</td>
<td>UK/H/4956/001/II/011</td>
<td>SmPC, PIL and Label</td>
<td>01/12/2017</td>
<td>07/06/2018</td>
<td>Approved</td>
<td>Yes</td>
</tr>
</tbody>
</table>
implemented (QRD version 4, 02/2016) in the Labelling.
Annex 1

Reference: PL 40168/0002-0006

Product: Cefixime 400 mg film-coated tablets

Marketing Authorisation Holder: INN-FARM d.o.o

Active Ingredient: Cefixime

Reason:
To update section 4.2 of the SmPC in line with the posology of the EU reference product and to update the SmPC in line with the QRD template. Consequently, the patient information leaflet (PIL) has been updated.

Supporting evidence
The applicant has submitted an updated section 4.2 of the SmPC and an updated PIL.

Evaluation
The amended section of the SmPC and PIL are satisfactory.

Conclusion
The proposed changes are acceptable. The updated SmPC and PIL have been submitted and are acceptable.

In accordance with Directive 2010/84/EU, the current granted UK SmPC and PIL are available on the MHRA website.

Decision
Grant

Date: 21 December 2015
Annex 2

Reference: PL 40168/0002-0018

Product: Cefixime 400 mg film-coated tablets

Marketing Authorisation Holder: INN-FARM d.o.o

Active Ingredient: Cefixime

Reason:
To update section 4.1 of the SmPC to harmonize the indications with the reference product Suprax 400 mg film-coated tablets, by Astellas Pharma SpA from Italy. Consequently, impacting the PIL. Additionally, the Safety features have been implemented (QRD version 4, 02/2016) in the Labelling.

Supporting evidence
The applicant has submitted an updated section 4.1 of the SmPC, PIL and label.

Evaluation
The amended section of the SmPC, PIL and labelling are satisfactory.

Conclusion
The proposed changes are acceptable. The updated SmPC, PIL and labelling have been submitted and are acceptable.

In accordance with Directive 2010/84/EU, the current granted UK SmPC and PIL are available on the MHRA website.

Decision
Grant

Date: 07 June 2018
Labelling

Cefixime 400 mg Film-coated Tablets

MA Holder: INN - FARM d.o.o.
Makalaka ulica 14, 1000 Ljubljana
Slovenia
PL 40/16/002

5 film-coated tablets
CeFIXime 400 mg
film-coated tablets
cef ixime

POM

CeFIXime 400 mg film-coated tablets
Each film-coated tablet contains 400 mg cefixime as cefixime trihydrate. See leaflet for further information.
For oral use. Read the package leaflet before use.
Keep out of the sight and reach of children.

Please affix dispensary label here
CeFIXime 400 mg film-coated tablets

Each film-coated tablet contains 400 mg cefixime as cefixime trihydrate. See leaflet for further information.
For oral use. Read the package leaflet before use.
Keep out of the sight and reach of children.

please affix dispensary label here