Public Assessment Report

Scientific discussion

Deferasirox Pharmascience 125 mg, 250 mg, and 500 mg, dispersible tablets

(deferasirox)

NL/H/4066/001-003/DC

Date: 6 November 2018

This module reflects the scientific discussion for the approval of Deferasirox Pharmascience 125 mg, 250 mg, and 500 mg, dispersible tablets. The procedure was finalised at 26 June 2018. For information on changes after this date please refer to the ‘steps taken after finalisation’ at the end of this PAR.
List of abbreviations

ASMF  Active Substance Master File
CEP   Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP  Committee for Medicinal Products for Human Use
CMD(h) Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS   Concerned Member State
EDMF  European Drug Master File
EDQM  European Directorate for the Quality of Medicines
EEA   European Economic Area
ERA   Environmental Risk Assessment
ICH   International Conference of Harmonisation
MAH   Marketing Authorisation Holder
Ph.Eur. European Pharmacopoeia
PL    Package Leaflet
RH    Relative Humidity
RMP   Risk Management Plan
SmPC  Summary of Product Characteristics
TSE   Transmissible Spongiform Encephalopathy
I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Deferasirox Pharmascience 125 mg, 250 mg, and 500 mg, dispersible tablets from Pharmascience International Limited.

The product is indicated for the treatment of chronic iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged six years and older.

Deferasirox Pharmascience is also indicated for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the following patient groups:

- in paediatric patients with beta thalassaemia major with iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) aged two to five years,
- in adult and paediatric patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells) aged two years and older,
- in adult and paediatric patients with other anaemias aged two years and older.

Deferasirox Pharmascience is also indicated for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged ten years and older.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Exjade 125 mg, 250 mg, and 500 mg, dispersible tablets for oral suspension (EU/1/06/356) which has been centrally registered in the EEA by Novartis Europharm Limited since 28 August 2006 (original product).

The concerned member states (CMS) involved in this procedure were Bulgaria, Cyprus and Malta.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Deferasirox Pharmascience is a dispersible tablet.
• The 125 mg strength is an off-white, round, bevel-edged flat tablet, debossed with “D” on top and “125” below on one side and plain on the other side.
• The 250 mg strength is an off-white, round, bevel-edged flat tablet, debossed with “D” on top and “250” below on one side and plain on the other side.
• The 500 mg strength is an off-white, round, bevel-edged flat tablet, debossed with “D” on top and “500” below on one side and plain on the other side.

Each tablet contains as active substance 125 mg, 250 mg, or 500 mg of deferasirox.

The dispersible tablets are packed in PVC/PCTFE/Aluminium blisters.

The excipients are crospovidone (type A) (E1202), microcrystalline cellulose PH102 (E460), povidone K30 (E1201), sodium laurilsulfate (E487), colloidal anhydrous silica (E551), lactose monohydrate, and magnesium stearate (E572).

The three tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is deferasirox, an established active substance that is not described in the European Pharmacopoeia (Ph. Eur.). Deferasirox is a white to slightly yellow colour powder. It is freely soluble in dimethyl formamide; sparingly soluble in dimethylsulfoxide and practically insoluble in water deferasirox exhibits polymorphism. The polymorph produced is prior art form A.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The drug substance is manufactured at one site. The synthesis consists of two steps. A sufficiently detailed description of the manufacturing process and process controls has been provided. The proposed starting materials are considered acceptable. The drug substance has been sufficiently characterised.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three batches.
Stability of drug substance
Stability data is provided of four lower sized batches stored at 25°C/60% RH for up to 60 months. In addition 24 months long term data of three higher sized batches are provided as well as nine months data from a reprocessed batch. All batches were stored at 40°C/75% RH for up to six months. No trends in any of the parameters were observed. Based on the data submitted, a retest period could be granted of five years when stored well closed, light resistant containers and at controlled room temperature i.e. between 20°C and 25°C (excursions are allowed between 15°C and 30°C)

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients has been justified and their functions have been explained. The product is intended to be used in the paediatric population above two years of age. The suitability of the formulation for use in children has been sufficiently addressed in the dossier including all aspects applicable for the product for registration in line with the Guideline on pharmaceutical development of medicines for paediatric use.

A bioequivalence study has been preformed in which Deferasirox Pharmascience 500 mg was compared with Exjade 500 mg. Satisfactory results of in vitro dissolution tests in three different buffers (pH 1.2, 4.5 and 6.8) and the media intended for drug product release (QC media) have been reported. Dissolution profiles of the biobatches are comparable.

The MAH performed dissolution studies to support a biowaiver for the additional tablet strengths: Deferasirox Pharmascience 250 mg and Deferasirox Pharmascience 125 mg.

Pharmaceutical development has been adequately performed.

Manufacturing process
The tablets are manufactured using wet granulation. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches per strength in accordance with the relevant European guidelines.

Control of excipients
All excipients are of the Ph.Eur. quality. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for tests for description, identification, assay, uniformity of dosage units, dissolution, degradation products, disintegration, fineness of
dispersion, water and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three batches per strength stored at long term (25°C/60% RH) and accelerated (40°C/75% RH) conditions in accordance with applicable European guidelines. On basis of the data submitted, a shelf life was granted of 30 months.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Deferasirox Pharmascience has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Deferasirox Pharmascience 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.2 Discussion on the non-clinical aspects

This product is a generic formulation of Exjade which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.
IV. CLINICAL ASPECTS

IV.1 Introduction

Deferasirox is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Deferasirox Pharmascience 500 mg, dispersible tablets (Pharmascience International Limited, Cyprus) is compared with the pharmacokinetic profile of the reference product Exjade 500 mg dispersible tablets (Novartis Europharm Limited, United Kingdom).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

A biowaiver is granted for Deferasirox Pharmascience 125 mg and 250 mg dispersible tablets:

- The 500 mg strength of deferasirox is used in the bioequivalence study. The same excipients are used for all strengths with a proportional amount. Dissolution tests at pH 1.2, 4.5 and 6.8 have been provided for all three strengths of Deferasirox Pharmascience.
- Similarity in the dissolution profile between the 500 mg biobatch and the 250 mg has been demonstrated as f2 factor was above 50. Similarity in the dissolution testing has been shown between the 500 mg biobatch and 125 mg strength at the same dose (500 mg vs 4x 125 mg) since f2 factor was between 50 and 100.

Bioequivalence studies

Design

A monocentric, open label, randomised, two-treatment, two-sequence, single dose, crossover bioequivalence study was carried out under fasted conditions in 40 healthy male subjects (32 ± 6 years). Each subject received a single dose (500 mg) of one of the two deferasirox formulations. The tablets were prepared as a suspension in 100 ml water, any residue remaining in the glass was resuspended in the remaining 50 ml water and subjects
were asked to swallow this volume. All subjects fasted overnight for at least ten hours before and four hours after dosing. There were two dosing periods, separated by a washout period of ten days.

Blood samples were collected pre-dose and at 0.5, 1.0, 1.5, 2, 2.33, 2.67, 3.0, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 7, 8, 12, 24, 36, 48 and 60 hours after administration of the products.

The design of the study is acceptable.

**Analytical/statistical methods**

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

**Results**

One subject withdrew on own accord in period II, and one subject was withdrawn due to abnormal total bilirubin level and serum iron level at check-in of period II. Neither of them received the administration of deferasirox in period II. Therefore, 38 subjects were eligible for pharmacokinetic analysis.

**Table 1.** Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, \( t_{\text{max}} \) (median, range)) of deferasirox under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( N=38 )</th>
<th>AUC(_{0-t} ) (ng.h/ml)</th>
<th>AUC(_{0-\infty} ) (ng.h/ml)</th>
<th>( C_{\text{max}} ) (ng/ml)</th>
<th>( t_{\text{max}} ) (h)</th>
</tr>
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<tr>
<td>Test</td>
<td>137.5 ± 46.8</td>
<td>133.1 ± 48.3</td>
<td>11.8 ± 3.2</td>
<td>4.33</td>
<td>4.33 (1.5 - 5.5)</td>
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<tr>
<td>Reference</td>
<td>142.5 ± 37.8</td>
<td>146.0 ± 38.4</td>
<td>13.5 ± 4.1</td>
<td>3.84</td>
<td>3.84 (1.5 - 5)</td>
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<tr>
<td>*Ratio (90% CI)</td>
<td>0.91 (0.85 - 0.99)</td>
<td>0.92 (0.85 - 1.0)</td>
<td>0.88 (0.81 - 0.95)</td>
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*In-transformed values

**Conclusion on bioequivalence study**

The 90% confidence intervals calculated for AUC\(_{0-t}\), AUC\(_{0-\infty}\) and \( C_{\text{max}} \) are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Deferasirox Pharmascience is considered bioequivalent with Exjade.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).
IV.3 Risk Management Plan

The MAH has submitted a risk management plan, 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 Deferasirox Pharmascience.

Table 2. Summary table of safety concerns as approved in RMP

| Important identified risks                                      | • Renal disorders (increased serum creatinine, acute renal failure, renal tubular disorders (acquired Fanconi’s syndrome)) |
|                                                                 | • Increased liver transaminases                                      |
|                                                                 | • Gastrointestinal haemorrhage and ulcers; esophagitis               |
|                                                                 | • Hearing loss                                                       |
|                                                                 | • Lens opacities, retinal changes and optic neuritis                 |
|                                                                 | • Stevens-Johnson syndrome and severe cutaneous adverse reactions (TEN and DRESS) |
|                                                                 | • Interaction with food                                               |
|                                                                 | • Interaction with aluminium-containing antacids                     |
|                                                                 | • Induction of CYP3A4                                                |
|                                                                 | • Inhibition of CYP1A2                                               |
|                                                                 | • UDP-glucuronosyltransferase (UGT) inducers                         |
|                                                                 | • Inhibition of CYP2C8                                               |
|                                                                 | • Interaction with cholestyramine                                    |
|                                                                 | • Hepatic failure                                                   |
| Important potential risks                                       | • Peripheral blood cytopenias                                       |
|                                                                 | • Compliance with posology and biological monitoring                |
|                                                                 | • Medication errors                                                 |
| Missing information                                              | • Long term safety in paediatric NTDT patients aged 10 to 17 years |
|                                                                 | • Safety in pregnant women                                          |

Additional risk minimisation measures in the form of educational materials for physicians and patients are deemed necessary for the safety concern ‘compliance with posology and biological monitoring’.

Healthcare professionals and patients who are expected to prescribe, dispense and use Deferasirox Pharmascience are provided with the following educational package:
• Physician educational materials containing the SmPC and guide for health care professionals
• Patient information pack containing the patient information leaflet and patient guide
In each Member State, the MAH shall agree the content, format and distribution of the educational material with the national competent authority. In line with the reference product the risk minimisation materials should be part of the conditions to the marketing authorisation.

Routine risk minimisation activities for all other safety concerns are considered sufficient for this product.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Exjade. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of: a pilot test, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Deferasirox Pharmascience 125 mg, 250 mg, and 500 mg, dispersible tablets has a proven chemical-pharmaceutical quality and is a generic form of Exjade 125 mg, 250 mg and 500 mg dispersible tablets. Exjade is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Deferasirox Pharmascience
with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 June 2018.
## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Procedure number*</th>
<th>Scope</th>
<th>Product Information affected</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Summary/ Justification for refuse</th>
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