COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Deferasirox Synthon 90 mg, 180 mg, 360 mg, film-coated tablets

(deferasirox)

NL/H/4517/001-003/DC

Date: 14 November 2019

This module reflects the scientific discussion for the approval of Deferasirox Synthon 90 mg, 180 mg, 360 mg, film-coated tablets. The procedure was finalised at 15 October 2019. 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
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
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 Synthon 90 mg, 180 mg, 360 mg, film-coated tablets from Synthon B.V.

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 6 years and older.

Deferasirox Synthon 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 2 to 5 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 2 years and older,
- in adult and paediatric patients with other anaemias aged 2 years and older.

Deferasirox Synthon 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 10 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 90 mg, 180 mg, 360 mg film-coated tablets (EU/1/06/356) which has been centrally registered in the EEA by Novartis Europharm limited since 28 August 2006.

The concerned member states (CMS) involved in this procedure werr Bulgaria, Czech Republic, Germany, Spain, and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Deferasirox Synthon is an oval, biconvex, film-coated tablet debossed with 'D7FX' on one side:

- 90 mg film-coated tablets are light blue, oval coloured and debossed with '90' on the other side.
- 180 mg film-coated tablets are medium blue coloured and debossed with '180' on another side.
- 360 mg film-coated tablets are blue coloured debossed with '360' on another side.

And contains as active substance 90 mg, 180 mg, or 360 mg of deferasirox.

The film-coated tablets are packed in PVC/PVDC/Aluminium blisters and Al/Al blisters.

The excipients are:
Tablet core

- Cellulose, microcrystalline (types 101 and 102)
- Povidone K-30
- Crospovidone (Types A and B)
- Poloxamer 188
- Silica, colloidal anhydrous
- Magnesium stearate

Tablet coating

- Hypromellose (E464)
- Lactose monohydrate
- Titanium dioxide (E171)
- Triacetin
- Indigo carmine aluminium lake (E132)

The three tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is deferasirox, an established active substance for which no monograph is available yet. The active substance is a crystalline white powder, is soluble in DMSO and DMF and not soluble in water. Deferasirox has no chiral centres and is not optically active. Deferasirox has two polymorphic forms; the substance used in drug product at issue is pure form A.

The Active Substance Master File (ASMF) procedure is used by both manufacturers 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

Manufacturer I

The synthesis of deferasirox is a four-step synthesis starting from three starting materials. Two intermediates are identified. No class 1 solvents are used in the final steps. The proposed starting materials are acceptable in view of the synthesis outline and properties of the materials.

Manufacturer II

The synthesis of deferasirox is a three-step synthesis starting from three starting materials. One intermediate is identified. No class 1 solvents are used in the final steps. The manufacturing process, control of intermediates and critical steps are described in sufficient detail. The proposed starting materials are acceptable in view of the synthesis outline and properties of the materials.

For both manufacturing processes an exhaustive characterisation has been performed. Potential impurities are addressed, including residual solvents and elemental impurities, in line with the European guidelines. The possibility of carry-over of solvents and impurities from the synthesis of the starting materials is adequately investigated.

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 per manufacturer.

Stability of drug substance

Manufacturer I

Stability data on the active substance have been provided for three commercial scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). No significant changes have been observed at both storage conditions. The drug substance was shown to be photostable. Based on the provided stability data, a retest period is granted of 48 months with storage conditions 'Store in an air tight container at a temperature up to 25°C'.

Manufacturer II

Stability data on the active substance have been provided for six full scale batches stored at 25°C/60% RH (up to 72 months for the first three batches and 36 months for the other three) and 40°C/75% RH (up to 6 months). One micronized and one reprocessed batch is

included in the stability studies as well. Based on the results included in the ASMF, a retest period is granted of 60 months. No special storage conditions are necessary.

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 characteristics of drug substance and excipients which are important for the performance and manufacturability of drug product are adequately discussed, as the compatibility with the excipients. The process and formulation development studies are presented in detail, including the evaluation of critical quality attributes of drug product and drug substance, and the composition and results of all test batches produced. Critical quality attributes (CQAs) were identified as appearance, solid state form (polymorph), identity, assay, uniformity of dosage units (UDU), impurities, disintegration, dissolution, hardness, water content and microbial limits. The pharmaceutical development of the product has been adequately performed.

In vitro dissolution tests complementary to bioequivalence studies have been performed in accordance with the *Guideline on the Investigation of Bioequivalence*. The obtained dissolution data for the batches of test and reference products that were used in the bioequivalence study have been reported. Dissolution profiles at pH 1.2, pH 4.5 and pH 6.8 are considered similar. For the dissolution profiles obtained with the QC method, the f2 values cannot be determined and the visual similarity between the dissolution profile of the reference and test product cannot be confirmed, therefore the assessment of bioequivalence is only based on *in vivo* results. The MAH has sufficiently addressed the reason of this discrepancy *in vitro*.

The MAH claims a biowaiver of bioequivalence studies for the 90 mg and 180 mg strengths. The MAH conducted dissolution studies as recommended by the *Guideline on the Investigation of Bioequivalence*. Dissolution studies were conducted at the same strength, four tablets of 90 mg and two tablets of 180 mg strengths were compared with one tablet of the 360 mg strength, because sink conditions were not reached. At pH 1.2 and 4.5, the amount of dissolved deferasirox is negligible. At pH 6.8, similarity of *in vitro* dissolution between additional strengths and the 360 mg strength has been demonstrated (f2 >50). As no clear differences between formulations can be observed at different pH values, a biowaiver can be granted for the 90 mg and 180 mg strengths from a chemical pharmaceutical point of view.

Manufacturing process

The manufacturing process consists of the steps granulation, sizing, blending, compression and film-coating. The provided flow-chart contains a sufficiently detailed description of the process and applied in process controls. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
All the excipients, with the exception of the colourant, can refer to a Ph.Eur. monograph and are well known excipients broadly used in similar pharmaceutical forms. Sufficient information has been provided on testing methods and specifications for the non compendial coating mixture. 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 appearance, identity, assay, related substances, dissolution, uniformity of dosage units, and microbiological contamination. 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 of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product stored in the PVC/PVDC-Al blister has been provided on nine batches (three per strength) full scale batches (with the exception of one batch of 180 mg and one of 360 mg tablets) stored at 25°C/60% RH (up to 18 months), 30°C/75% RH (up to 12 months) and 40°C/75% RH (up to 6 months).
Stability data on the product stored in the Al/Al blister has been provided on eight batches (three per strength, except for 90 mg strength where two batches were tested). The batches were stored at 30°C/75% RH (up to 12 months) and at 40°C/75% RH (up to 6 months).

Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 24 months with no special storage conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Deferasirox Synthon 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 Synthon 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 two bioequivalence studies, which are discussed below. The SmPC of Exjade states that for patients unable to swallow whole tablets, the film-coated tablets may be crushed. According to the EMA clinical pharmacology and pharmacokinetics: Q&A document, bioequivalence must also be demonstrated for this additional method of administration. The MAH has therefore also submitted a bioequivalence study with crushed tablets.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Deferasirox Synthon 360 mg film-coated tablets (Synthon B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Exjade 360 mg film-coated tablets (Germany).

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

Biowaiver

A biowaiver was granted for the lower strengths. The biowaiver is based on the following conditions:

- The qualitative and quantitative composition of the different strengths is dose proportional and only differs in their film-coating.
- The strengths of Deferasirox Synthon are manufactured by the same process.
- Deferasirox has linear pharmacokinetics over the therapeutic dose range after a single dose administration.
- Initially the provided dissolution studies were not in line with the *Guideline on the investigation of Bioequivalence*. Due to poor solubility of deferasirox, the MAH conducted dissolution studies using surfactant and a higher rpm for pH 6.8. This was not accepted. In response, the MAH provided the results of conducted dissolution studies without surfactant and with a rotation speed of 50 rpm, as requested and recommended by the *Guideline on Bioequivalence*. Dissolution studies were conducted at the same strength: four tablets of 90 mg and two tablets of 180 mg were compared with one tablet of 360 mg, because sink conditions were not reached. No clear differences between formulations were observed.

Bioequivalence study

Single dose fasting study with intact tablet (0224-17)

Design

A single-dose, randomized, open label, laboratory blinded, two treatment, two period, two sequence, cross-over bioequivalence study was carried out under fasted conditions in 36 healthy subjects. Each subject received a single dose (360 mg) of one of the two deferasirox formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 10.0, 12.0, 13.0, 16.0, 24.0, 48.0 and 72.0 hours after administration of the products.

The design of the bioequivalence study is acceptable. The washout period is sufficient, and the sampling scheme seems to be sufficient to estimate pharmacokinetic parameters of interest. The bioequivalence study is conducted under fasting conditions as recommended by the *Guideline on the investigation of Bioequivalence*, as the SmPC recommends to take deferasirox under fasting conditions.

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 dropped out for medical reasons (fever) in the second period. Two subjects were withdrawn for personal reasons. Therefore 33 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=33	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	162.0 ± 47.2	166.7 ± 46.3	16.3 ± 4.1	3.5 (0.5 - 5.0)
Reference	165.1 ± 46.0	172.4 ± 45.2	17.9 ± 4.9	3.5 (1.0 - 6.0)
***Ratio (90% CI)**	0.98 (0.93 – 1.03)	--	0.92 (0.85 – 0.99)	--

$AUC_{0-\infty}$ 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
t_{max} time for maximum concentration

**ln-transformed values*

Single dose fasting study with crushed tablet (0540-17)
Design
A single-dose, randomized, open label, laboratory blinded, two treatment, two period, two sequence, cross-over bioequivalence study was carried out under fasted conditions in 36 healthy subjects. Each subject received a single dose (360 mg) of one of the two deferasirox formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. The tablet was crushed and sprinkled onto 15 ± 0.5 g applesauce on a tablespoon, before administration in each period. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 10.0, 12.0, 13.0, 16.0, 24.0, 48.0 and 72.0 hours after administration of the products.

The design of the bioequivalence study is acceptable. The washout period is sufficient, and the sampling scheme seems to be sufficient to estimate pharmacokinetic parameters of interest. The bioequivalence study is conducted under fasting conditions as recommended by the *Guideline on the investigation of Bioequivalence*, as the SmPC recommends to take deferasirox under fasting conditions. The SmPC indicates that deferasirox tablets can be

crushed before administration. It is therefore adequate to conduct a bioequivalence study evaluating bioequivalence between the two crushed formulations (test vs reference).

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
A total of four subjects dropped out. Two subjects discontinued the study on their own accord. Two subjects were withdrawn due to medical grounds. Therefore 32 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of deferasirox under fasted conditions.

Treatment N=33	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	132.7 ± 55.2	137.8 ± 56.0	15.2 ± 4.7	4.0 (2.0 – 4.5)
Reference	139.2 ± 64.3	144.9 ± 68.9	165.5 ± 5.1	3.75 (2.0 - 6.0)
***Ratio (90% CI)**	0.96 (0.89 – 1.04)	--	0.93 (0.85 – 1.01)	--

$AUC_{0-\infty}$ 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
t_{max} time for maximum concentration

**ln-transformed values*

Conclusion on bioequivalence studies
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Deferasirox Synthon is considered bioequivalent with Exjade.

The MEB has been assured that the bioequivalence studies have 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 Synthon.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	• Gastrointestinal haemorrhage and ulcers; Oesophagitis • Hearing loss • Increased liver transaminases/hepatic failure • Lens opacities, retinal changes and optic neuritis • Renal disorders (increased serum creatinine, acute renal failure (ARF), renal tubular disorders (acquired Fanconi's syndrome) • Severe cutaneous adverse reactions (including Stevens-Johnson syndrome. Toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms (DRESS)
Important potential risks	• Compliance with posology and biological monitoring • Medication errors
Missing information	• Long term safety in paediatric patients with non-transfusion-dependant thalassaemia syndromes aged 10 to 17 years • Safety of new formulation (film-coated tablets/granules)

Prior to launch of Deferasirox Synthon in each Member State the MAH must agree about the content and format of an educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority. The educational programme is aimed to inform healthcare professionals (HCPs) and patients to minimise the risks of non-compliance of the posology and biological monitoring

The MAH shall ensure that, at launch, in each Member State where Deferasirox Synthon is marketed, all HCPs and patients who are expected to prescribe, dispense and use Deferasirox Synthon are provided with the following educational package for both formulations and on all indications:

- Physician educational materials containing the SmPC and guide for HCPs
- Patient information pack containing the patient information leaflet and patient guide

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the other risks and areas of missing information.

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 bioequivalence studies 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Exjade. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

In addition, the MAH has submitted a previously performed successful user test of a Clozapine 12.5 mg orodispersible tablets PL. This user test is used to support the changes made to the proposed PL compared to the parent PL (e.g. house style).

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Deferasirox Synthon 90 mg, 180 mg, 360 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Exjade 90 mg, 180 mg, 360 mg, film-coated 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 Synthon with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 15 October 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/Justification for refuse