COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Deferasirox SUN 90 mg, 180 mg and 360 mg, film-coated tablets (deferasirox)

NL/H/5582/001-003/DC

Date: 27 August 2024

This module reflects the scientific discussion for the approval of Deferasirox SUN 90 mg, 180 mg and 360 mg, film-coated tablets. The procedure was finalised on 20 September 2023. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
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 SUN 90 mg, 180 mg and 360 mg, film-coated tablets, from Sun Pharmaceutical Industries Europe 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.

The product 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.

The product 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 up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator products Exjade 90 mg, 180 mg and 360 mg, film-coated tablets (NL RVG 117181 - 117183) which have been registered in the European Economic Area by Novartis Europharm Limited since 22 March 2016 via a centralised procedure (EMEA/H/C/000670).

The concerned member states (CMS) involved in this procedure were France, Germany, Italy and Spain.

II. QUALITY ASPECTS

II.1 Introduction

Deferasirox SUN 90 mg, 180 mg and 360 mg are film-coated tablets containing either 90 mg, 180 mg or 360 mg deferasirox as active substance. The tablets are presented in three strengths which can be distinguished by their color, debossing and size.

- 90 mg: light blue, biconvex oval, film-coated tablet with bevelled edges and debossed

with “90” on one side and plain on the other side, 10.80 mm x 4.30 mm
- 180 mg: medium blue, biconvex oval, film-coated tablet with bevelled edges and debossed with “180” on one side and plain on the other side, 14.10 mm x 5.60 mm
- 360 mg: dark blue, biconvex oval, film-coated tablet with bevelled edges and debossed with “360” on one side and plain on the other side, 16.60 mm x 6.60 mm

The excipients are:
Tablet core - cellulose microcrystalline; crospovidone; povidone; poloxamer; colloidal silicon dioxide; and magnesium stearate.
Tablet coating - hypromellose; titanium dioxide (E171); macrogol; talc; and indigo carmine lake (E132).

The three tablet strengths are dose proportional.

The film-coated tablets are packed in Polyvinyl chloride/polyvinylidene dichloride/Aluminium (PVC/PVDC/Aluminium) blisters.

II.2 Drug Substance

The active substance is deferasirox, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a crystalline powder which shows polymorphism, and is practically insoluble in water. The active substance is not chiral.

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 manufacturing process is covered by the ASMF and consists of three synthetic steps and one purification step. There are two isolated intermediates. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional requirements for polymorphic form, residual solvents, benzene content, clarity, colour index, and iron.
All in-house methods have been sufficiently validated. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided for six full-scale batches in accordance with applicable European guidelines demonstrating the stability of the active substance for five years. Based on the data submitted, a retest period could be granted of four years when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. Formulation and process development was carried out through a Quality by Design approach. The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

Manufacturing process

The medicinal product is manufactured by wet granulation through the following steps: dry mixing, granulation, drying sifting, blending, lubrication, compression, film-coating, visual inspection, and packaging. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three batches of each strength in accordance with the relevant European guidelines.

Control of excipient

The excipients comply with Ph.Eur and in-house requirements, as well as relevant EC Regulations. 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 description, identification of the active by high-performance liquid chromatography (HPLC) and chemical test, identification of the colorant by color test, assay, dissolution, uniformity of dosage units by mass variation, uniformity of dosage units by content uniformity, water content, related substances, and microbial enumeration. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from seven batches from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three batches of each strength stored at 25°C/60% RH (24 months for the 360 mg product, 18 months for the 90 mg and 180 mg products), 30°C/65% RH (12 months, only for the 90 mg and 180 mg products) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines

demonstrating the stability of the product for 18 months. Photostability study in accordance with ICH Q1B shows that the drug product is stable when exposed to light. On basis of the data submitted, a shelf life for the 360 mg product was granted of 18 months. The labelled storage conditions are “store below 25°C”. On basis of the data submitted, a shelf life for the 90 mg and 180 mg products was granted of 12 months.

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 SUN 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 SUN is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was 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 was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 member states agreed that no further clinical studies are required, besides the two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted one bioequivalence study under fasted conditions and one bioequivalence under fed conditions in which the pharmacokinetic profile of the test product Deferasirox SUN 360 mg, film-coated tablets (Sun Pharmaceutical Industries Europe B.V., the Netherlands) was compared with the pharmacokinetic profile of the reference product Exjade 360 mg, film-coated tablets (Novartis Europharm Limited, Ireland).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

The following general requirements must be met where a waiver for additional strength is claimed, according to the EMA Bioequivalence guideline:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

All requirements are met.

The dissolution was investigated according to the EMA Bioequivalence guideline. The calculated f_2 similarity factor values were within criteria (>50%). An f_2 value between 50 and 100% suggests that the two dissolution profiles are similar. A biowaiver for the additional 90 and 180 mg strengths is acceptable as dissolution similarity at all required pH has been demonstrated.

Bioequivalence studies, fasted conditions

Design

An open label, balanced, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 42 healthy male subjects, aged 19-43 years. 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 10 hours. There were two dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 36, 48 and 72 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
All 42 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of deferasirox, 360 mg under fasted conditions.

Treatment N=42	**AUC_{0-t}** (ng.h/mL)	**$AUC_{0-\infty}$** (ng.h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)
Test	178 ± 54	-	19.2 ± 4.7	3.33 (1.00 – 4.40)
Reference	180 ± 53	-	19.9 ± 4.3	2.67 (1.00 – 4.67)
***Ratio (90% CI)**	0.99 (0.95 – 1.03)	-	0.96 (0.90 – 1.03)	-

$AUC_{0-\infty}$	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 the last measurable plasma concentration / to t = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Bioequivalence studies, fed conditions
Design
An open label, balanced, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 42 healthy male subjects, aged 20-43 years. After an overnight fast of at least 10 hours, subjects were served standard breakfast (low fat, light meal; approximately 250 to 300 kcal, meal fat content <10% of calories) starting 30 minutes prior to drug administration. Each subject received a single dose (360 mg) of one of the two deferasirox formulations. The tablet was orally administered with 240 mL water. There were two dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, 24, 36, 48 and 72 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 from the study due to personal reasons. 41 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of deferasirox, 360 mg under fed conditions.

Treatment N=41	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	188 ± 46	-	22.8 ± 3.4	4.00 (2.00 – 4.67)
Reference	181 ± 45	-	22.9 ± 4.3	4.33 (2.33 – 4.67)
***Ratio (90% CI)**	1.04 (0.97 – 1.04)	-	1.00 (1.01 – 1.07)	-

$AUC_{0-\infty}$	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 the last measurable plasma concentration / to t = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**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 SUN 360 mg is considered bioequivalent with Exjade 360 mg.

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 SUN.

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

Important identified risks	• Renal disorders (increased serum creatinine, acute renal failure (ARF), renal tubular disorders (acquired Fanconi's syndrome) • Increased liver transaminases / Hepatic failure • Gastrointestinal hemorrhage and ulcers; esophagitis • Hearing loss • Lens opacities, retinal changes and optic neuritis • Severe cutaneous adverse reactions (SCARs) (including Stevens-Johnson syndrome [SJS], Toxic epidermal necrolysis [TEN] 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 NTDT patients aged 10 – 17 years • Safety of new formulation film-coated tablets

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the 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 two 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

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 language used for the purpose of user testing the PL was English.
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 90 mg, 180 mg and 360 mg, film-coated tablets, EMEA/H/C/000670 for content and to Morphine 1 mg/ml solution for infusion in pre-filled syringe, DE/H6814/001-002/DC for design and layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Deferasirox SUN 90 mg, 180 mg and 360 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Exjade 90 mg, 180 mg and 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 SUN with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 September 2023.

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
NL/H/5582/003 /IB/001	Type IB: B.II.f.1.b.1: Extension of the shelf life of the finished product. (Shelf-life for the 360 mg product is increased to 24 months when stored below 25°C) -As packaged for sale (supported by real time data)	Yes	22 March 2024	Approved	N.A.
NL/H/5582/003 /IA/002	Type IA(IN): B.II.e.z: addition of or change to a calendar package for a pack size already registered in the dossier	Yes	1 August 2024	Approved	N.A.
NL/H/5582/001 -3/IA/003	Type IA: A.7: Deletion of manufacturing sites for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)	No	1 August 2024	Approved	N.A.