LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Deferasirox STADA
(deferasirox)

SE/H/2905/001-003

This module reflects the scientific discussion for the approval of Deferasirox STADA. The Public Assessment Report was written in 2020 by the previous RMS NL after initial procedure NL/H/4448/001-003 and is attached at the end of this document. RMS transfer from NL to SE was completed 18 February 2026. For information on changes after this date please refer to the module 'Steps taken after the finalisation of the initial procedure - summary'.

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STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

CBG MEB

COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

(deferasirox)

NL/H/4448/001-003/DC

Date: 7 August 2020

This module reflects the scientific discussion for the approval of Deferasirox CF 90 mg, 180 mg, 360 mg, film-coated tablets. The procedure was finalised at 23 December 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 CF 90 mg, 180 mg, 360 mg, film-coated tablets from Centrafarm 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 CF 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 CF 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 were Austria, Germany, Denmark, Finland, France, Italy, Malta, Romania, Sweden, 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 CF is an ovaloid biconvex film-coated tablet, with bevelled edges and plain on one side, that is available in three strengths:

- 90 mg film-coated tablets are light blue, and embossed with '90' on the other side.
- 180 mg film-coated tablets are medium blue, and embossed with '180' on the other side.
- 360 mg film-coated tablets are dark blue, and embossed with '360' on the other side.

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

The film-coated tablets are packed in aluminium-PVC/PE/PVDC blisters. The blister foil consists of the PVC/PE/PVDC base film sealed against an aluminium lidding foil.

The excipients are:
Tablet core

- Crospovidone (E1202)
- Povidone (E1201)
- Cellulose, microcrystalline (E460)
- Magnesium stearate (E470b)
- Poloxamer
- Silica, colloidal anhydrous (E551)

Coating material

- Hypromellose (E464)
- Titanium dioxide (E171)
- Macrogol (E1521)
- Talc (E553b)
- 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. Deferasirox is a crystalline white to light yellow powder, is soluble in DMSO and DMF and not soluble in water. It has no chiral centres and is not optically active. Deferasirox has two polymorphic forms, the substance used is pure 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 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 active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

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 on the active substance have been provided for three full scale batches stored at 25°C/60% RH (up to 36 months) and 40°C/75% RH (up to 6 months). The batches were stored in the proposed final packaging. Based on the data submitted, a retest period could be granted of 48 months when stored 'in an air tight container at a temperature up to 25°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 same pharmaceutical form, strengths and excipients as for the reference product have been chosen. The process and formulation development studies are presented, including the evaluation of critical quality attributes (CQA) of drug product and drug substance, and the composition and results of all trial batches produced. CQA were identified as appearance, size, identity, assay, content uniformity, degradation products, disintegration and dissolution and microbial limits. The optimization of quantitative composition is described, considering the impact of increasing or decreasing the most critical excipients. The pharmaceutical development of the product has been adequately performed.

The dissolution profile of the 360 mg strength has been compared with that of the reference product and found to be similar in line with the relevant guidelines. The MAH claims a biowaiver for the strengths 90 mg and 180 mg. The dissolution profiles of one batch of 90 mg tablets and one of 180 mg tablets have been compared to that of the 360 mg strength biobatch. For batch comparison the f2 calculation has been performed, and in the cases with too high RSD the bootstrap analysis is used. Based on the information provided and on the requirements in the Guideline on investigation of Bioequivalence, from a pharmaceutical point of view the biowaiver of strength is acceptable.

Manufacturing process

The product is manufactured using conventional manufacturing techniques. The manufacturing process consists of granulation, sizing, blending, compression and film-coating.

The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product has been presented for two full scale batches.

Control of excipients
All the excipients can refer to a Ph.Eur. monograph with the exception of the ready-to-use coating materials which comply with in-house requirements. 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, dimensions, related substances, dissolution, uniformity of dosage units, uniformity of mass, water content, microbial 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 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 have been provided on nine (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 24 months) and 40°C/75% RH (up to 6 months). The conditions and planned time points used in the stability studies are according to the stability guideline. The batches were stored in the proposed packaging. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. The available results show no trends or significant change in results, at all tested conditions. On basis of the data submitted, a shelf life was granted of 36 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 CF 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 CF 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 three bioequivalence studies with the highest strength of the reference product (360 mg):

- *17-VIN-0833* - whole tablets under fasted conditions
- *18-VIN-0140* - crushed tablets under fasted conditions
- *Bioequivalence study 2360* - whole tablets under fed conditions

For the two lower strengths a biowaiver is requested.

IV.2 Pharmacokinetics

The MAH conducted the bioequivalence studies in which the pharmacokinetic profile of the test product Deferasirox CF (Pharos Pharmaceutical Oriented Services Ltd, Greece) is compared with the pharmacokinetic profile of the reference product Exjade (Novartis Europharm Ltd, United Kingdom).

Reference product
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.

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.

Biowaiver

The MAH has performed bioequivalence studies with the 360 mg strength and applied for a biowaiver for 90 mg and 180 mg tablets, as all three tablets have the same qualitative composition, are dose-proportional to each other and show similar dissolution profiles at pH pf 1.2, 4.5 and 6.8. For all the four tested media the f2 calculation has been performed, in the cases with too high RSD using the bootstrap analysis. All the f2 values are within acceptable limits (50-100). A biowaiver was granted for both strengths.

Bioequivalence studies

17-VIN-0833

Design

An open label, balanced, randomized, two-treatment, two-sequence, two-period, single-dose, crossover bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 20-44 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 at least ten hours. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected at 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 8.00, 10.00, 12.00, 24.00, 36.00, 48.00 and 72.00 hours after administration of the products.

The design of the study is acceptable.

Results

Two subjects were withdrawn from the study. Therefore, 26 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=26	AUC_{0-t} (µg.h/ml)	C_{max} (µg/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	184.772	17.582		
Reference	189.040	18.191		
*Ratio (90% CI)	0.98 (0.92 – 1.04)	0.97 (0.89 – 1.04)	--	--
CV (%)	12.69	16.27	--	--

$AUC_{0-\infty}$	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
$t_{1/2}$	half-life
CV	coefficient of variation

**In-transformed values*

18-VIN-0140

Design

An open label, balanced, randomized, two-treatment, two-sequence, two-period, single-dose, crossover bioequivalence study was carried out under fasted conditions in 32 healthy male subjects, aged 22-44 years. Each subject received a single dose (360 mg) of one of the two deferasirox formulations. The subjects fasted overnight for at least 10 hours before the scheduled time of dosing. One tablet was crushed in mortar and the fine powder of the crushed tablet was sprinkled on approximately 10 g of apple sauce immediately prior to administration. The apple sauce drug mixture was administered orally at the scheduled dosing time in sitting posture. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected at 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 8.00, 10.00, 12.00, 24.00, 36.00, 48.00 and 72.00 hours after administration of the products.

The design of the study is acceptable.

Results

Five subjects were withdrawn from the study. Therefore, 25 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=25	AUC_{0-t} (µg.h/ml)	C_{max} (µg/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	169.469	15.921		
Reference	166.469	16.523		
*Ratio (90% CI)	1.02 (0.97 – 1.06)	0.96 (0.91 – 1.02)	--	--
CV (%)	9.41	11.69	--	--

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
$t_{1/2}$	half-life
CV	coefficient of variation

**In-transformed values*

Bioequivalence study 2360
Design
A single-dose, randomized, crossover, two-treatment, two-sequence, two-period, open-label bioequivalence study was carried out under fed conditions in 30 healthy male subjects, aged 22-44 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 at least ten hours and after completely consuming a light meal. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected at 0.5, 1, 1.5, 2, 2.5, 3.0, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 18, 24, 36, 48, 60 and 72 hours after administration of the products.

The design of the study is acceptable.

Results
Two subjects were withdrawn from the study. Therefore, 28 subjects were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of deferasirox under fasted conditions.

Treatment N=28	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
*Ratio (90% CI)	1.02 (0.99 – 1.06)	1.01 (0.97 – 1.05)	1.03 (0.98 – 1.07)	--	--
CV (%)	7.56	8.47	9.68	--	--

$AUC_{0-\infty}$ 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
$t_{1/2}$ half-life
CV coefficient of variation

**In-transformed values*

Conclusion on bioequivalence studies
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Deferasirox CF 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 CF.

Table 4. 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/Hepatic failure • Gastrointestinal haemorrhage and ulcers; esophagitis • Hearing loss • Lens opacities, retinal changes and optic neuritis • Severe cutaneous reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis, Stevens-Johnson syndrome and toxic epidermal necrolysis
Important potential risks	• Compliance with posology and biological monitoring • Medication errors
Missing information	• Long term safety in paediatric NTDT patients aged 10 to 17 years • Safety of the film-coated tablets

The MAH will provide, in each Member State where Deferasirox CF is marketed, all healthcare professionals and patients who are expected to prescribe, dispense and use Deferasirox CF with the following educational package for all available formulations (e.g. dispersible tablets, film-coated tablets and granules) for all indications:

- Physician educational material
- Patient information pack

The educational program is aimed to inform healthcare professionals and patients to minimise the risks of:

- Non-compliance of the posology and biological monitoring
- Medication errors due to switching between formulations (dispersible tablets and film-coated tablets/granules).

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 for the key safety messages/content to Exjade dispersible tablets (EMEA/H/C/000670) and for the design/lay-out to Tenofovir disoproxil film-coated tablets (NL/H/3437/001/DC). 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 CF 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 CF with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 23 December 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
NL/H/4448/001-003/IB/001	To add the manufacturing site as an alternative site for the production of the bulk tablets.	--	15 April 2020	Approved	--