COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Deferasirox Teva 90 mg, 180 mg and 360 mg, film-coated tablets

(deferasirox)

NL/H/4793/001-003/DC

Date: 27 September 2021

This module reflects the scientific discussion for the approval of Deferasirox Teva. The procedure was finalised on 28 July 2020. 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 Teva 90 mg, 180 mg and 360 mg, film-coated tablets from Teva 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 Teva 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 Teva 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 (EMEA/H/C/000670), registered by Novartis Europharm Limited. Initially, dispersible tablets were registered for the reference product, 28 August 2006. The film-coated tablets were approved in March 2016 with a line extension (EMEA/H/C/000670/X/0043).

The concerned member states (CMS) involved in this procedure were Germany and Spain (only the 90 mg and 360 mg strengths).

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

II. QUALITY ASPECTS

II.1 Introduction

Deferasirox Teva 90 mg is a light blue, ovaloid, biconvex, film-coated tablet with bevelled edges, debossed with '90' on one side and plain on the other side.
Deferasirox Teva 180 mg is a medium blue, ovaloid, biconvex, film-coated tablet with bevelled edges, debossed with '180' on one side and plain on the other side.
Deferasirox Teva 360 mg is a dark blue, ovaloid, biconvex, film-coated tablet with bevelled edges, debossed with '360' on one side and plain on the other side.

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

The excipients are:
Tablet core - crospovidone (E1202), povidone (E1201), microcrystalline cellulose (E460), magnesium stearate (E470b), poloxamer, colloidal anhydrous silica (E551)
Coating - hypromellose (E464), titanium dioxide (E171), macrogol (E1521), talc (E553b), indigo carmine aluminium lake (E132)

The tablet cores 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 to light yellow powder, is soluble in dimethyl sulfoxide and dimethylformamide and not soluble in water. Deferasirox has no chiral centres and is not optically active. Deferasirox has two polymorphic forms, the substance used in finished product 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.

<u>Manufacturing process</u>
The synthesis of deferasirox is a four-steps 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. Moreover, 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 has been established in-house by the MAH. The MAH applies the same specification as the ASMF holder, with additional acceptance criteria for particle size distribution and microbial quality.

The analytical methods and their validation have been adequately described. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches.

Stability of drug substance

The stability study protocol is in line with the prescriptions in the EMA Guideline on Stability testing of existing active substances. 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). A retest date of 48 months in the proposed packaging and storage conditions 'Store in an air tight container at a temperature up to 25°C' have been granted.

II.3 Medicinal Product

Pharmaceutical development

The same pharmaceutical form, strengths and excipients as for the reference product have been chosen. The characteristics of drug substance 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, including the evaluation of critical quality attributes of drug product and drug substance, and the composition and results of all trial batches produced.

The optimization of quantitative composition has been described. The pharmaceutical development of the product has been adequately performed.

The development of the QC method for dissolution is discussed and is in line with the relevant guideline. The dissolution profile of the biobatch has been compared with that of the reference product and found to be satisfactory similar. The MAH claims a biowaiver of bioequivalence studies for the strengths 90 mg and 180 mg. 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 can be considered acceptable.

Manufacturing process

The manufacturing process consists 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. The product is manufactured using conventional manufacturing techniques.

Control of excipients
For all excipients a Ph. Eur. monograph is available, 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 product specification includes tests for appearance, identity, assay, dimensions, related substances, dissolution, uniformity of dosage units, uniformity of mass, water content, microbial quality. The specification at release and shelf-life are adequate and in line with Guideline ICH Q6A. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three batches of each strength, demonstrating compliance with the release specification. For the higher strengths one of the batches is under the minimal commercial size, which is acceptable at moment of application.

Stability of drug product
Stability data on the product has been provided on up to nine (three per strength) full-scale batches 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 commercial 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.
Based on the stability data provided, a shelf life of 36 months without any special storage conditions has been granted.

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 Teva 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 Teva 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, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted three bioequivalence study in which the pharmacokinetic profile of the test product Deferasirox Teva 360 mg (Teva B.V., the Netherlands is compared with the pharmacokinetic profile of the reference product Exjade 360 mg film-coated tablets (Novartis Europharm Limited, Ireland):

- a pivotal single dose bioequivalence study under fasting conditions with 360 mg tablet
- a pivotal single dose bioequivalence study under fasting conditions with 360 mg crushed tablet
- a pivotal single dose bioequivalence study under fed conditions with 360 mg tablet

The choice of the reference product in the bioequivalence study is justified, as the reference product has been authorised through a centralised procedure.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

The submitted studies with the highest strength are appropriate to support the application. Fasting conditions are acceptable and the most sensitive to distinguish differences between the formulations as the reference product should be taken either under fasting conditions or with a light meal. In addition, the SmPC of the reference product allows for the possibility to administer the tablet crushed and dispersed in food. The bioavailability of an active substance may be altered if products are crushed to assist swallowing and also if a crushed tablet is mixed with food. This change in bioavailability may be formulation/product-specific as well as drug-dependent. Therefore, the study with a crushed tablet is considered necessary and thus agreed.

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

Biowaiver
The MAH has performed bioequivalence studies with the highest 360 mg strength and requested a biowaiver for 90 and 180 mg tablets. All three tablet strengths have the same qualitative composition, are dose-proportional and show similar dissolution profiles at pH 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 relative standard deviation. All the f2 values are within acceptable limits (50-100). Th biowaiver has been granted.

Bioequivalence studies

- **Bioequivalence study I - single dose bioequivalence study under fasting conditions**

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, 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 2 deferasirox formulations. The tablet was orally administered with 240 ml water after an overnight fast of 10 hours. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and 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. The sampling time period until 72 hours post-dose is sufficient to provide a reliable estimate of the extent of exposure for an immediate-release product as the absorption phase is covered.

Results
One subject was found positive in drug of abuse test on the day of Period 2 admission. Another subject was withdrawn from the study due to AE after dosing of period 2. A total of 26 subjects completed the study as per the protocol and 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)	$AUC_{0-\infty}$ (µg.h/ml)	C_{max} (µg/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	195.406 ± 61.7220	199.761 ± 62.8510	18.151 ± 4.3580	3.00 (1.50-4.50)	11.732 ± 3.2475
Reference	201.456 ± 66.3432	205.774 ± 67.2684	18.891± 4.7012	3.00 (1.50-4.50)	11.136 ± 2.0439
***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

**ln-transformed values*

- **Bioequivalence study II - Single dose bioequivalence study under fasting conditions, crushed tablet**

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 30+2 healthy male subjects, aged 22-44 years. Each subject received a single dose (360 mg) of one of the 2 deferasirox formulations after an overnight fast of 10 hours. The 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. There were 2 dosing periods, separated by a washout period of at least 7 days.

Blood samples were collected pre-dose and 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. The sampling time period until 72 hours post-dose is sufficient to provide a reliable estimate of the extent of exposure for an immediate-release product as the absorption phase is covered.

Results

A total of 30 were enrolled in the study. Two subjects withdrew consent before dosing of period 1, hence withdrawn from the study and replaced by two other subjects. Five subjects were withdrawn from the study:

- Three subjects experienced adverse events after dosing in period 1
- One subject did not report to the clinical facility during period 2 admission
- One subject experienced an adverse event after dosing in period 2, hence withdrawn from the study.

A total of 25 subjects completed the study as per the protocol and 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)**	**$AUC_{0-\infty}$ (µg.h/ml)**	**C_{max} (µg/ml)**	**t_{max} (h)**	**$t_{1/2}$ (h)**
Test	176.168 ± 51.4886	180.071 ± 51.1876	16.542 ± 4.5965	3.50 (1.52-4.50)	10.968 ± 2.3367
Reference	174.841 ± 49.0323	178.331 ± 49.0271	17.332 ± 4.4746	3.50 (1.50-4.50)	10.894 ± 2.5786
***Ratio (90% CI)**	1.02 (0.97-1.06)	--	0.96 (0.91-1.02)	--	--
CV (%)	9.41	--	11.69	--	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

- **Bioequivalence study III - Single dose bioequivalence study under fed conditions**

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 28 healthy male subjects, aged 19-53 years. Each subject received a single dose (360 mg) of one of the 2 deferasirox formulations, after at least a 10-hour fast and after completely consuming a light meal, with 240 mL of water. There were 2 dosing periods, separated by a washout period of at least 7 days.

Blood samples were collected pre-dose and 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. The sampling time period until 72 hours post-dose is sufficient to provide a reliable estimate of the extent of exposure for an immediate-release product as the absorption phase is covered.

Results
Thirty subjects were planned to be dosed. Twenty-eight subjects were dosed in Period 1 and in Period 2 and completed the study as per the protocol and were eligible for pharmacokinetic analysis.

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

Treatment N=25	**AUC_{0-t}** (µg.h/ml)	**$AUC_{0-\infty}$** (µg.h/ml)	**C_{max}** (µg/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	124731.85 ± 34471.61	127779.98 ± 35055.18	14858.64 ± 3477.11	3.50 (2.00-5.00)	--
Reference	121856.99 ± 34480.38	127901.13 ± 34592.89	14440.34 ± 3386.33	3.50 (1.50-6.00)	--
***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

**ln-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 Teva 360 mg is considered bioequivalent with Exjade 360 mg film-coated tablets, under fasted and fed conditions, and when administered as a crushed tablet dispersed in food.

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 Teva.

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; oesophagitis • 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 non-transfusion-dependent thalassaemia (NTDT) patients aged 10 to 17 years • Safety of the new formulation

Pharmacovigilance Plan

The MAH will conduct routine pharmacovigilance for Deferasirox Teva. Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are proposed, i.e. specific adverse event targeted follow-up checklists for the following risks:

- Acute renal failure
- Serum creatinine increase
- Increased liver transaminases and hepatic failure
- gastrointestinal haemorrhage, ulcer and 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])

Risk minimisation measures

The MAH provided an adequate overview of the routine risk minimisation measures implemented for each safety concern.

Additional risk minimisation measures are proposed for the following safety concerns:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Compliance with posology and biological monitoring	Routine risk minimisation measures: *SmPC sections 4.2 and 4.4.* – Prescription only medicine. Additional risk minimisation measures: *Educational materials for physicians and patients regardless of indication.*	Routine pharmacovigilance.
Medication errors	Routine risk minimisation measures: *SmPC sections 4.2.* – Prescription only medicine. Additional risk minimisation measures: *Educational materials for physicians and patients regardless of indication.*	Routine pharmacovigilance.

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

Prior to launch of Deferasirox Teva in each Member State the MAH must agree about the content and format of the 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 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).

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

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 with 2 participants, followed by two rounds with 10 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 package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Deferasirox Teva 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 Teva with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 28 July 2020.

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