COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Deferasirox Teva 900 mg, film-coated tablets (deferasirox)

NL/H/5120/001/DC

Date: 6 June 2022

This module reflects the scientific discussion for the approval of Deferasirox Teva 900 mg, film-coated tablets. The procedure was finalised on 10 November 2021. 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 900 mg, film-coated tablets, from Teva B.V.

The products are 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 hybrid application claiming essential similarity with 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 Bulgaria, Germany and France.

The marketing authorisation has been granted pursuant to Article 10(3), a hybrid application, since this product strength differs from the reference product strengths.

Rationale for development of the new dose of 900 mg

Since the maximum daily dose of Deferasirox, as per the SmPC of the innovator, is 28 mg/kg/day for treatment of chronic transfusional iron overload and 14 mg/kg/day for treatment of non-transfusion-dependent thalassaemia syndromes, the MAH decided to develop a tablet of 900 mg in order to cover the needs of administration of the maximum dose with use of two or one single tablets, respectively, instead of a combination of multiple tablets

of the lower strengths available by the innovator and as such reduce the pill burden and increase compliance for the patients.

Assessment of orphan similarity
The MAH listed all products designated as orphan medicinal products for an indication relating to the indication proposed in the application, and provided a similarity report, indicating that Deferasirox Teva is not similar to the products for which an orphan designation has been granted.

II. QUALITY ASPECTS

II.1 Introduction

Deferasirox Teva 900 mg film-coated tablets are white to off-white, ovaloid, biconvex, film-coated tablets with beveled edges, with a break line on one side and plain on the other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

The film-coated tablets contain as active substance 900 mg of deferasirox.

The film-coated tablets are packed in aluminium-PVC/PE/PVDC blisters or in aluminium-PVC/PE/PVDC perforated unit-dose blisters.

The excipients are:
Tablet core - crospovidone (type A) (E1202), povidone K30 (E1201), microcrystalline cellulose (type 101) (E460), microcrystalline cellulose (type 102) (E460), magnesium stearate (E470b), poloxamer 188 and colloidal anhydrous silica (E551).

Film-coating - hypromellose 2910 (3mPa·s) (E464), titanium dioxide (E171), macrogol 4000 (E1521) and talc (E553b).

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 white to light yellow powder, is soluble in dimethyl sulfoxide (DMSO) and dimethyl fumarate (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 the drug products at issue 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 manufacturing process consists of a four-steps synthesis starting from adequate starting materials. The starting materials are acceptable in view of the synthesis outline and properties of the materials. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

The active substance specification has been established in-house by the MAH. The drug product manufacturer applies the same specification as the ASMF holder, with additional acceptance criteria for particle size distribution (PSD), polymorphism, and microbial quality.
The analytical methods and their validation are adequately described in the ASMF. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full scale batches.

Stability of drug substance

Stability data on the active substance have been provided for six full scale batches stored at 25°C/60% RH (up to 48 months) and 40°C/75% RH (up to six months). The batches were stored in double LDPE bags in HDPE drums, which is the 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. The stability study protocol is in line with the prescriptions in the EMA Guideline on Stability testing of existing active substances.

II.3 Medicinal Products

Pharmaceutical development

The products are established pharmaceutical forms and their development is adequately described in accordance with the relevant European guidelines. The chosen packaging is considered standard for the proposed dosage form, sufficient information about the used material is included in the dossier. The same pharmaceutical form and excipients as for the reference products have been chosen, except for one colourant, which is used in the reference products but not in the test products. The characteristics of drug substance which are important for the performance and manufacturability of drug product, and the compatibility with the excipients are discussed. As dissolution of the active substance in the gastro-intestinal tract is particle size dependent, particle size distribution is considered a critical quality attribute of the drug product.

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 optimisation of quantitative composition is described, considering the impact of increasing or decreasing the most critical excipients.

Adequate *in vitro* dissolution tests at three pHs complementary to bioequivalence studies were performed. The bioequivalence studies will be discussed in section IV on Clinical aspects.

Manufacturing process

The manufacturing process of Deferasirox film-coated tablets includes dispensing, granulation, blending, compression, film coating and packaging. The products are manufactured using conventional manufacturing techniques. Suitable results of process validation have been provided. Process validation data on the products have been presented for two batches of each strength, in accordance with the relevant European guidelines.

Control of excipients

All the excipients, comply with the Ph. Eur., except for the Opadry film coating agent. Suitable in-house specifications are applied for Opadry. Functionality related characteristics have been discussed. The specifications are acceptable.

Quality control of drug products

The finished products specifications are adequate to control the relevant parameters for the dosage form. The specifications 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 and in line with Guideline ICH Q6A. The method for related substances and assay is proven to be stability indicating, by means of forced degradation studies. The MAH has provided a risk evaluation concerning the presence of nitrosamine impurities, from which it was concluded that routine testing of nitrosamine impurities was not considered necessary.

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 products

Stability studies were carried out under ICH conditions using three commercial scale batches, covering 24 months long term and six months accelerated storage conditions. 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. No specific storage conditions need to be included in the SmPC or on the label.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the products 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 products.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Deferasirox Teva is intended for hybrid 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

Deferasirox Teva is a hybrid formulation of Exjade which is available on the European market. Reference is made to the preclinical data obtained with the innovator products. 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 application the MAH has submitted two bioequivalence studies with Deferasirox Teva which are discussed below.

IV.2 Pharmacokinetics

The MAH has performed two bioequivalence studies Deferasirox Teva. The bioequivalence studies will be discussed in IV.2.1.

IV.2.1 Bioequivalence studies

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Deferasirox Teva 900 mg, film-coated tablets (Teva Ltd., Greece) is compared with the pharmacokinetic profile of the reference product Exjade 5 x 180 mg film-coated tablets (Novartis Europharm Ltd., Germany).

The choice of the reference products in the two bioequivalence studies has been justified by comparison of dissolution results and compositions of the test and reference products. The formula and preparation of the bioequivalence batches are identical to the formulas proposed for marketing.

The analytical methods in all bioequivalence studies have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in the studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

The MEB has been assured that the four 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).

Studies with Deferasirox Teva

The MAH submitted two bioequivalence studies with Deferasirox Teva under fasting conditions and under fed conditions (light meal), which will be discussed below.

As it is known from the innovator product that different tablet formulations may have a different absorption under fed conditions, and that the tablet may be administered either with or without food, submission of an additional fed study was agreed. In the fed study a light meal was administered, which is acceptable as under these conditions the highest impact was observed on bioavailability for the innovator formulation. These conditions are also in line with the draft product specific guidance for deferasirox.

Furthermore, the SmPC indicates that the tablets should be swallowed whole with some water. For patients who are unable to swallow whole tablets, the tablets may be crushed and administered by sprinkling the full dose onto soft food, e.g. yogurt or apple sauce. In certain cases with critical excipients crushing may affect bioavailability and could lead to a difference in bioavailability between the innovator and the generic formulation. However, considering the comparability in excipients between the innovator and test formulation, this is not expected, therefore, a waiver for additional studies to support crushing is acceptable.

- *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 78 healthy male subjects, aged 19-41 years. Each subject received a single dose (900 mg (test) or 5 x 180 mg (reference)) of one of the two deferasirox formulations. The tablets were orally administered in solid form

with 240 ml water after an overnight fasting period. There were two dosing periods, separated by a washout period of 11 days. Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products. The design of the study is acceptable.

Results
Four subjects were withdrawn from the study due to adverse events (three subjects) and due to not reporting to the study facility (one subject). 74 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of deferasirox (900 mg dose) under fasted conditions.

Treatment N=74	**AUC_{0-t}** (µg.h/ml)	**$AUC_{0-\infty}$** (µg.h/ml)	**C_{max}** (µg/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	564 ± 230	597 ± 240	37 ± 10	4.0 (1.0 – 6.0)	13 ± 4
Reference	568 ± 223	602 ± 237	37 ± 9	3.67 (1.0 – 8.0)	13 ± 4
***Ratio (90% CI)**	0.99 (0.95 – 1.04)	-	0.98 (0.95 – 1.02)	-	-
CV (%)	15.9	-	11.7	-	-

$AUC_{0-\infty}$ 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 intra-subject coefficient of variation

**ln-transformed values*

- *Study under fed conditions*

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 78 healthy male subjects, aged 19-41 years. Each subject received a single dose (900 mg tablet (test) or 5 x 180 mg tablet (reference)) of one of the two deferasirox formulations after an overnight fasting period, and 30 minutes after the start of a light meal. The tablets were orally administered in solid form with 240 ml water. There were two dosing periods, separated by a washout period of 16 days. Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products. The design of the study is acceptable.

Results
One subject withdrew from the study due to personal reasons. 77 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of deferasirox (900 mg dose) under fed conditions.

Treatment N=77	AUC_{0-t} (µg.h/ml)	$AUC_{0-\infty}$ (µg.h/ml)	C_{max} (µg/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	567 ± 180	598 ± 186	47 ± 11	4.0 (2.5 - 6.0)	12 ± 4
Reference	602 ± 193	638 ± 204	48 ± 10	4.5 (2.5 - 6.0)	13 ± 4
***Ratio (90% CI)**	0.94 (0.90 – 0.98)	-	0.96 (0.93 – 1.00)	-	-
CV (%)	15.7	-	12.1	-	-

$AUC_{0-\infty}$ 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 intra-subject coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence studies with Deferasirox Teva
In both the study under fasting and fed conditions, 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 Teva is considered bioequivalent with 5 tablets of the 180 mg strength of Exjade.

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 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 haemorrhage and ulcers; esophagitis • Hearing loss • Lens opacities, retinal changes and optic neuritis
Important potential risks	• Compliance with posology and biological monitoring • Medication errors
Missing information	• Long term safety in paediatric non-transfusion-dependent thalassemia patients aged 10 to 17 years • Safety of new formulation

Next to routine pharmacovigilance activities and routine risk minimisation measures, it has been agreed that additional risk minimisation measures will be taken. The MAH shall ensure that in each Member State where the products are marketed, all healthcare professionals and patients/carers who are expected to prescribe or use deferasirox have access to the following educational package to be disseminated through professional bodies:

- Physician educational material (which also includes a prescriber checklist)
- Patient information pack

The objectives and goals of the educational materials are to provide further detailed information to prescribers of deferasirox and their patients to minimise the potential safety risk of compliance with posology and biological monitoring and medication errors due to switching between formulations, and to ensure more effective dissemination of the information of the key safety elements. Furthermore, the educational material aims to provide a prescribing decision tool for physicians to support calculation of appropriate posology and tracking of biological monitoring, through the provision of a prescriber checklist.

One of the important key elements in the educational package is:

- Advice for Deferasirox 900 mg film-coated tablets that the tablet must not be split to achieve a lower dose. The tablet might be split to facilitate swallowing only, but both fragments must be taken. The score line is only to facilitate breaking and does not divide the tablet into equal doses. In transfusional iron overload, this 900 mg strength is not suitable for patients with a body weight below 32 kg. In non-transfusion-dependent thalassaemia syndromes, this 900 mg strength is not suitable for patients with a body weight below 64 kg.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator products Exjade. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of Deferasirox Teva is similar to the pharmacokinetic profiles of the 5 x 180 mg reference product. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference products.

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 dispersible tablets 120, 250 and 500 mg (EU/1/06/356). 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 Teva 900 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic and hybrid forms of Exjade 90 mg, 180 mg and 360 mg, film-coated tablets. Exjade are well-known medicinal products with established favourable efficacy and safety profiles. Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

A CMDh referral was requested for Deferasirox Teva, as the objecting CMS considered that the indication should be restricted as the corresponding posology for the proposed indication in paediatric patients aged 2-5 years could not be reached with the proposed 900 mg tablet, and minimum body weight limits should be added, corresponding to the recommended maximum daily dose for the indications concerned, to reduce the risk of medication errors. All CMS agreed to a new proposal by the MAH to retain the originator's indications unchanged in section 4.1, but to include information in section 4.2 of the SmPC and section 1 of the package leaflet that the 900 mg product is unsuitable for patients below a certain weight. The educational material has been updated accordingly.

Overall, the benefit/risk balance is considered positive and the member states have granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 10 November 2021.

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