COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

(deferasirox)

NL/H/4316/001-003/DC

Date: 23 Augustus 2019

This module reflects the scientific discussion for the approval of Deferasirox Vivanta 90 mg, 180 mg, 360 mg film-coated tablets. The procedure was finalised at 20 June 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
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 Vivanta 90 mg, 180 mg, 360 mg film-coated tablets from Vivanta Generics s.r.o.

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 Vivanta 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 Vivanta 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 Germany, Spain and Italy.

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

II. QUALITY ASPECTS

II.1 Introduction

Deferasirox Vivanta is a yellow coloured, oval, biconvex, film-coated tablet with bevelled edges debossed with 'D' on one side:

- 90 mg film-coated tablets are debossed with '90' on the other side.
- 180 mg film-coated tablets are debossed with '180' on another side.
- 360 mg film-coated tablets are debossed with '360' on another side.

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

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

The excipients are:
Tablet core

- Microcrystalline cellulose (E460)
- Croscarmellose sodium
- Low-substituted hydroxypropyl cellulose (E463)
- Poloxamer 188
- Povidone K30
- Lactose monohydrate
- Colloidal anhydrous silica (E551)
- Sodium stearyl fumarate
- Hydrogenated castor oil

Tablet coating

- Opadry yellow 03H520019:
    - HPMC 2910/Hypromellose (E464)
    - Titanium dioxide (E171)
    - Propylene glycol (E1520)
    - Talc (E553b)
    - Iron oxide yellow (E172)

The three tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is deferasirox, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). Deferasirox is a white to slightly yellow colour powder. It is freely soluble in dimethyl formamide, sparingly soluble in dimethyl sulfoxide and practically insoluble in water. The manufacturing process results in polymorphic form A. Deferasirox does not contain a stereochemic centre.

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

A schematic and descriptive overview of the two-step synthesis is provided. The level of details is sufficient. The statements regarding reprocessing, reworking and recovery of solvents/reagents are also acceptable.

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 four batches.

Stability of drug substance

No trends are observed in the results of a six months stability study at accelerated conditions (40°C/75% RH) nor at 60 months long term conditions (25°C/60% RH). Slight fluctuations in water content are observed but these remain well within the specification. Based on the data submitted, a retest period could be granted of 60 months. No special storage conditions are necessary.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The critical aspects of this formulation are poor flow due to the micronized particle size of the active ingredient (leading to the formation of agglomerates and adherence to equipment) and poor solubility of the active ingredient in water. The product is intended to be used in the paediatric population above 2 years of age. This is sufficiently justified. The final formula is based on the formulation development trials, the manufacturing process development studies and the successful pilot bio-equivalence study.

A bioequivalence study was conducted with the 360 mg strength test product against the reference product. For the other strengths comparative dissolution studies have been performed in support of a biowaiver of strengths. The criteria to apply for biowaiver are met and the *in vitro* dissolution data justify omission of bioequivalence studies.

Manufacturing process

The manufacturing process has been described in sufficient detail. The process product includes sifting, dry mixing, preparation of binder solution, wet granulation, drying, milling and sifting of dried granules, prelubrication and lubrication, compression, coating and packaging. The proposed in-process controls are considered to be suitable for the control of the manufacturing process taking into consideration the content of deferasirox in the drug product and the straightforward nature of the manufacturing process.

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches per strength in accordance with the relevant European guidelines.

Control of excipients

All excipients used are tested according to the Ph.Eur., with the exception of the coating solution which has an in-house specification. 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 specification, identification of colouring agents, average mass, water determination, dissolution, assay, related substances and microbial enumeration. 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 sufficient batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Three production scale batches have been stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). Batches have also been stored at 30°C/65% RH; these samples will be tested, if significant changes occur at the accelerated condition. The testing carried out on tablets showed that the packaging is sufficiently protective of the drug product given that very little degradation was observed. There are no trends observed in the quality parameters tested during long-term and accelerated stability studies.

On basis of the data submitted, a shelf life was granted of 24 months. No special storage conditions are required.

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

Lactose monohydrate which is obtained from milk collected for human consumption. So a theoretical risk of transmitting TSE can be excluded. There are no other 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 Vivanta 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 Vivanta 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 one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Deferasirox Vivanta 360 mg (Vivanta Generics s.r.o., Czech Republic) is compared

with the pharmacokinetic profile of the reference product Exjade 360 mg (Novartis Europharm Limited, United Kingdom).

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

Biowaiver

A biowaiver is requested for the additional 90 mg and 180 mg strengths. The MAH has provided comparative dissolution profiles between deferasirox 360 mg, 180 mg and 90 mg film-coated tablets using paddle apparatus with 50 rpm in pH 1.2 (0.1N HCl), pH 4.5 acetate buffer and pH 6.8 phosphate buffer without surfactant. Similarity has been shown between the 360 mg tablet and 180 mg tablet at all three pH levels and between the 360 mg and the 90 mg tablet at pH 6.8 and 4.5. At pH 1.2, due to solubility limitations there is a difference in dissolution and therefore comparability at the same dose, i.e. 360 mg vs 4x 90 mg tablet is considered appropriate. Similarity at pH 1.2 has also been shown.
All conditions for biowaiver of strengths have been fulfilled and a biowaiver for 90 mg and 180 mg tablets is granted.

Bioequivalence study

Design

An open-label, balanced, two-treatment, randomized, two-treatment, two-period, two-sequence, single-oral dose, two-way crossover bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 24-44 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 eight days.

Blood samples were collected at 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 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

Two subjects were withdrawn/discontinued in period 1, one was due to medical grounds and the other withdrew on his own accord. Therefore, 34 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=34	**AUC_{0-t} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	172.62 ± 47	19.56 ± 4	2.67 (1.33– 4.50)
Reference	167.30 ± 51	18.51 ± 4	2.83 (1.67– 7.02)
***Ratio (90% CI)**	1.05 (0.99 – 1.10)	1.07 (0.99 – 1.14)	--
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity **AUC_{0-t}** area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration			

**ln-transformed values*

Conclusion on bioequivalence study

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 study Deferasirox Vivanta 360 mg film-coated tablets is considered bioequivalent with Exjade 360 mg film-coated tablets.

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 Vivanta.

Table 2. 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 • Gastrointestinal haemorrhage and ulcers; esophagitis

	• Hearing loss • Lens opacities, retinal changes and optic neuritis • Stevens-Johnson syndrome and toxic epidermal necrolysis • Hepatic failure • Interaction with food • Interaction with aluminium-containing antacids • Induction of CYP3A4 • Inhibition of CYP1A2 • Uridine Diphosphate Glycosyltransferase (UGT) inducers • Inhibition of CYP2C8 • Interaction with cholestyramine
Important potential risks	• Peripheral blood cytopenias • Compliance with posology and biological monitoring • Medication errors • Severe cutaneous adverse reactions (Drug reaction with eosinophilia and systemic symptoms - DRESS)
Missing information	• Long term safety in paediatric non transfusion dependent thalassaemia (NTDT) patients aged 10 to 17 years • Safety in pregnant women • Safety of new formulation (film-coated tablets - FCT/granules)

Additional risk minimisation measures in the form of educational materials for physicians and patients are deemed necessary for the safety concern 'compliance with posology and biological monitoring'.

Healthcare professionals and patients who are expected to prescribe, dispense and use Deferasirox Vivanta are provided with the following educational package:

- Physician educational materials containing the SmPC and guide for health care professionals
- Patient information pack containing the package leaflet (PL) and patient guide

In each Member State, the MAH shall agree the content, format and distribution of the educational material with the national competent authority. In line with the reference product the risk minimisation materials should be part of the conditions to the marketing authorisation.

Routine risk minimisation activities for all other safety concerns are considered sufficient for this product.

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 a bioequivalence study 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 design and lay-out of the PL have 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 results showed no issues. Readability testing of the contents of the PL is not necessary, as the contents of the PL are identical to the PL of Exjade, which contents have been user tested.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Deferasirox Vivant 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 Vivanta with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 June 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