14 November 2019
EMA/659255/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Deferasirox Accord

International non-proprietary name: deferasirox

Procedure No. EMEA/H/C/005156/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	adverse event
ANOVA	analysis of variance
AUC	the area under the plasma concentration
AUC0-t	the area under the plasma concentration - time curve from time 0 to t hours
AUC0-∞	the area under the plasma concentration - time curve from time 0 to infinity
AUC_%Extrap_obs	residual area in percentage
BE	bioequivalence
BMI	body mass index
CHMP	the Committee for Medicinal Products for Human Use
CI	confidence interval
Cmax	maximum plasma concentration
CV%	the coefficient of variation
ECG	electrocardiogram
EC	European Committee
ERA	environmental risk assessment
GCP	good clinical practice
GLP	good laboratory practice
GMP	good manufacturing practice
HCl	hydrochloric acid
LPI	labile plasma iron
LC/MS/MS	liquid chromatography coupled with tandem mass spectrometry
LoOI	list of outstanding issues
MO	major objection
NTDT	non-transfusion-dependent thalassaemia
OTC	over the counter
PK	pharmacokinetic
PL	package leaflet
QC	quality control
Rpm	rotation per minute
RSD	relative standard deviation
SD	standard deviation
SmPC	summary of product characteristics
Tmax	time of the maximum measured plasma concentration
t1/2	the elimination or terminal half-life
TF	transferrin
λ z	first order rate constant associated with the terminal portion of the curve

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 3 November 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Deferasirox Accord, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 September 2018.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Deferasirox Accord 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 Accord 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 Accord 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.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Exjade instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 6/8/10 years in the EEA:

- Product name, strength, pharmaceutical form: Exjade; 90 mg, 180 mg, 360 mg; film-coated tablets
- Marketing authorisation holder: Novartis Europharm Limited, Vista Building Elm Park, Merrion Road, Dublin 4, Ireland
- Date of authorisation: 28-08-2006
- Marketing authorisation granted by:

- Union
- Marketing authorisation numbers:

90 mg: EU/1/06/356/011-013

180 mg: EU/1/06/356/014-016

360 mg: EU/1/06/356/017-019

Medicinal product authorised in the Union /Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Exjade; 90 mg, 180 mg, 360 mg; film-coated tablets
- Marketing authorisation holder: Novartis Europharm Limited, Vista Building Elm Park, Merrion Road, Dublin 4, Ireland
- Date of authorisation: 28-08-2006
- Marketing authorisation granted by:
- Union
- Marketing authorisation numbers:

90 mg: EU/1/06/356/011-013

180 mg: EU/1/06/356/014-016

360 mg: EU/1/06/356/017-019

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Exjade, 360 mg, film-coated tablet
- Marketing authorisation holder: Novartis Europharm Limited, Vista Building Elm Park, Merrion Road, Dublin 4, Ireland
- Date of authorisation: 28-08-2006
- Marketing authorisation granted by:
- Union
- Marketing authorisation numbers: EU/1/06/356/017-019
- Bioavailability study number: 0382-17

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The applicant did not seek Scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Milena Stain Co-Rapporteur: N/A

The application was received by the EMA on	3 November 2018
The procedure started on	29 November 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	18 February 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	04 March 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	28 March 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 July 2019
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	29 August 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	09 September 2019
The CHMP agreed on a list of outstanding issues > to be sent to the applicant on	19 September 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	14 October 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	30 October 2019
The outstanding issues were addressed by the applicant during an oral	N/A

explanation before the CHMP during the meeting on	
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Deferasirox Accord on	14 November 2019
The CHMP adopted a report on similarity of Deferasirox Accord with Revlimid and Zynteglo on (see Appendix 1)	14 November 2019

2. Scientific discussion

2.1. Introduction

This centralised application for marketing authorisation concerns a generic application according to article 10(1) of Directive 2001/83/EC for Deferasirox Accord 90 mg, 180 mg and 360 mg film-coated tablets. The originator product is Exjade 90 mg, 180 mg and 360 mg film-coated tablets (MAA No: EU/1/06/356/011-019, Novartis Europharm Limited) for which marketing authorisation was granted in the European Union on 28 August 2006 on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

To support the application, the applicant submitted one BE study No. 0382-17 of Deferasirox 360 mg film-coated tablets with Exjade 360 mg film-coated tablets. A biowaiver is requested for additional lower strengths (90 mg and 180 mg) based on claims that pharmacokinetics is linear over dose range, used manufacturing process is the same, the same qualitative composition of different strengths, quantitatively proportional composition of the strengths, and appropriateness of submitted in vitro dissolution data.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 90 mg, 180 mg or 360 mg of deferasirox as active substance.

Other ingredients of the tablet core are: cellulose, microcrystalline; croscarmellose sodium, low-substituted hydroxypropyl cellulose, povidone (K30), poloxamer 188, lactose monohydrate, silica colloidal anhydrous, sodium stearyl fumarate, hydrogenated castor oil. Other ingredients in the film coating are: hypromellose (E464), propylene glycol (E1520), talc (E553b), iron oxide yellow (E172) and titanium dioxide (E171).

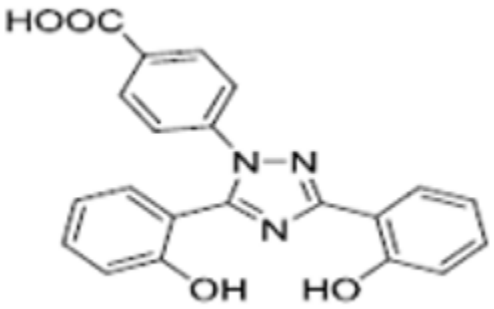
The finished product is available in PVC/PE/PVdC-Aluminium blisters as described in section 6.5 of the SmPC.

2.2.2. Active substance

General Information

The chemical name of deferasirox is 4-[3,5-Bis(2-hydroxyphenyl)-1H-1,2,4-triazol-1-yl]benzoic acid corresponding to the molecular formula $C_{21}H_{15}N_3O_4$. It has a relative molecular mass of 373.36 g/mol and the following structure:

Figure 1: active substance structure



The chemical structure of deferasirox was elucidated by a combination of various analytical and spectral techniques likewise CHN analysis, DSC analysis, Ultraviolet, Infra-Red, 1H NMR, 13C NMR, and Mass spectroscopy analysis studies.

Deferasirox appears as a white to slightly yellow coloured non hygroscopic crystalline powder.

Deferasirox has very poor solubility in the majority of solvents.

Deferasirox' structure does not contain chiral or asymmetric carbon atoms. It exists in various polymorphic forms. The polymorph produced is prior art form-A. This has been confirmed by the powder XRD analytical technique. The data provided confirms that the manufacturing process of Deferasirox Accord consistently produces prior art form-A.

Manufacture, process controls and characterisation

For deferasirox an Active Substance Master File (ASMF) has been provided by the active substance manufacturer.

The manufacturing site, including the micronization process, is listed as the manufacturer of the final active substance deferasirox. The analytical laboratory is placed at the same address as the manufacturing site.

The manufacturing process and the chemical reaction, a two-step synthesis, has been sufficiently described. The synthesis of deferasirox active substance involves two stages.

Reprocessing has been adequately described. The flow chart and a narrative description of the manufacturing process have also been provided. The critical steps have been defined and appropriate in-process controls have been established. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory. The starting materials are well

described, and sufficient data has been provided. The specifications for the reagents and solvents used in the process are considered suitable.

The characterisation of the active substance and its impurities have been confirmed by aid of various analytical and spectral techniques including UV, IR, ^{I}H NMR and ^{13}C NMR. Sufficient data has been presented. The methods used for elucidation of structure are adequate. All residual solvents have been sufficiently discussed (including absence of benzene) and specified.

Specification, analytical procedures, reference standards, batch analysis, and container closure

The specifications include tests and limits for appearance, solubility (Ph. Eur.) identity (IR, HPLC), assay (HPLC), related substances (HPLC), residual solvents (GC) and identification of polymorph (PXRD).

The specification for deferasirox has been established in line with ICH Q3A, Q3C, Q6A and the requirements of the general monograph Ph. Eur. 2034.

All relevant parameters have been included in the specification with acceptable limits (description, solubility, identification, water content, residue on ignition, related substances, residual solvents and polymorphism). The active substance is for use in an oral film-coated tablet. It has been sufficiently justified that microbiological quality testing is not necessary. All tests and limits are appropriate to guarantee a sufficient quality of the active ingredient.

According to SmPC the maximum daily dose (MDD) for deferasirox is up to 2.8 grams which corresponds to the following levels for reporting (RT): 0.03%, identification (IT) and qualification (QT): 0.05%. No impurity above the qualification threshold according to ICH Q3A has been observed. The limit for "highest individual unspecified impurity" is in-line with the identification limit. The limits are in line with the batch data and the stability results. Impurities have been evaluated and found to be acceptable from the point of view of safety.

The overall control of related substances and potential impurities (including genotoxic impurities) is considered acceptable. Although the process contains no added elements, class 1 and class 2A elements have been tested (in line with the requirements of oral dosage forms according to ICH Q3D) and the level in three batches was less than 30% of the PDE for each element. Therefore, it is acceptable that no element is specified in the final API. A satisfactory elemental impurities risk assessment was conducted following the principles outlined in ICH Q3D.

Analytical procedures and reference standards

Several methods are adopted from official compendia (Ph. Eur.). For the assay an isocratic HPLC is used, with UV detection. For the related substances a gradient HPLC is used, with UV detection. For the residual solvents three different HS-GCs (equipped with FID) are used. Polymorphic identification is done by PXRD. In general, validation is done in accordance to ICH Q2. All methods have been suitably described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines.

Reference standards (primary and working standard of API) and impurity standards have been well described.

Batch analysis

Three batches from the proposed manufacturing site have been analysed according to the specification. Moreover, one micronized batch and one reprocessed batch have been analysed. All results are well within

the specification. The results comply with the proposed specification and indicate that a consistent quality of the active substance can be obtained based on the proposed manufacturing process.

Container closure

Specifications and test procedures of the packaging materials, including IR spectra of the primary bag have been provided. Compliance of the primary packaging material with Ph. Eur. Monograph 3.1.3 and food grade has been stated. The information presented on the packaging materials is sufficient and adequate.

Stability

Stability data from several batches, commercial scale batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market for up to 60 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* description, identification, impurities, assay. The analytical methods used were the same as for release and were stability indicating.

Stability studies have been conducted in accordance with the ICH guidelines. All results comply with the requirements. Long-term and accelerated stability study data indicate that all physical and chemical parameters were well within limits during different storage conditions without showing any sign of degradation. The active substance is photostable.

Based on the stability data presented and given that all tested parameters were within the specifications, the proposed re-test period can be accepted.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical Development

The finished product (Deferasirox Accord 90 mg, 180 mg and 360 mg film-coated tablets) is developed as yellow coloured, film coated oval, biconvex tablets with bevelled edges debossed with 'D' on one side and '90', '180' or '360' on the other side, corresponding to 90 mg, 180 mg or 360 mg deferasirox per tablet.

The description and composition of the finished product have been satisfactorily described. The qualitative and quantitative composition of the excipients is different to the reference product. Nevertheless, dissolution and impurity levels are similar to the reference product.

The different strengths come from the same blend, are dose-proportional and can be differentiated based upon their mass and their markings.

Excipients are of Ph. Eur. quality and/or conform to the relevant guidance. The excipients have been sufficiently described, relevant functionality-related characteristics (FRC-s) are specified.

Pharmaceutical development

Formulation development was based on the reference product (Exjade) and the available literature. Due to the poor flowability of the micronized drug a wet granulation process was established. Key physico chemical properties of the active substance (such as polymorphism and solubility) and compatibility to excipients have been sufficiently discussed.

The description of the manufacturing process development is sufficiently detailed. The choice of process variables has been adequately justified.

The effect of the manufacturing process steps on the polymorphic stability of the active substance has been adequately investigated.

A method for dissolution was established taking low solubility of Deferasirox (BCS class II) into consideration. The method has the discriminatory power to detect changes in the formulation.

A batch of the highest tablet strength 360 mg of Deferasirox Accord was used for the bioequivalence study. The dissolution characteristics, assay and impurity profile of the biobatch was shown to be comparable to Exjade 360 mg film coated tablet.

Comparative dissolution profiles data show, pH dependent dissolution and similar dissolution profiles of the test and reference products. Data on dissolution profiles show good dissolution and similar dissolution profiles across lower strengths.

Crushing and administration by sprinkling the product onto soft food (as suggested in the SmPC), has been sufficiently discussed and tests on parameters, which might have an influence on crushing (e.g. hardness) suggest that there is no influence on crushing. Physical stability and compatibility data provided on mixtures of Deferasirox Accord and soft food/ vehicles i.e. apple sauce and yogurt has been sufficiently demonstrated.

No overages were added during development as well as manufacturing of batches.

Container closure system

The container closure system (PVC/PE/PVDC-Aluminium Blister Pack) has been sufficiently described and is in conformance to Commission Regulation (EU) No. 10/2011 (including amendments).

The choice of the primary packaging is adequate for this kind of product. The information provided on primary packaging (PVC/PE/PVdC – Alu Blister Pack), microbiological control and compatibility are sufficient.

Manufacture of the product and process controls

The manufacturing process of the finished product can be considered as a standard process. The manufacturing process of deferasirox film-coated tablets comprises: sifting, dry mixing, preparation of binder solution, wet granulation, drying, milling and sifting of dried granules, pre-lubrication & lubrication, compression, coating and packaging as outlined in Figure 2. A detailed flow chart and a narrative description of the process have been provided.

The critical steps of the manufacturing process are drying, lubrication, compression, coating and packing steps. In-process control (IPCs) of critical steps and acceptance criteria are described in sufficient detail. Limits are in line with the ranges proposed in pharmaceutical development. The proposed holding times were

validated in a hold time study. The containers used for storage of the bulk product have been sufficiently described.

Data on common blend has been presented, showing that after division of blend assay and blend uniformity results are within specifications, and a high yield in granulation stage was obtained. For process validation, data on three commercial batches have been presented, showing that a reproducible process was established, leading to a product that meets all limits as set in the specifications and a high yield.

Product specification, analytical procedures, batch analysis

The specification covers most of the relevant parameters for this kind of dosage form as described in the relevant guidance and includes appropriate tests for appearance (visual), identification (UV absorption and retention time), identification of colouring reagents, average mass (gravimetry), uniformity of dosage units (Ph. Eur. 2.9.40), water content (KF, Ph. Eur. 2.5.12), dissolution (HPLC), assay (HPLC), related substances (HPLC) and microbial quality (Ph. Eur. 2.6.12 and 2.6.13).

Identification (UV), identification of colorants, uniformity of dosage units are performed only at release.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The information on the control of elemental impurities is satisfactory.

Analytical procedures

The methods proposed are adequate to control the finished product on a routine basis, i.e. for batch release. The analytical methods have been sufficiently described, suitably validated and the relevant analytical method validation protocols and reports have been provided. Satisfactory information regarding the reference standards has been presented. Detectability of impurities is shown by related substance HPLC and the method is validated for these impurities. Stress studies show that the method for is stability indicating.

Batch analysis

Certificates of Analysis (CoAs) of several batches per strength have been presented. The presented data are in line with the specifications, confirming the quality, consistency and uniformity of the product, and indicate that the process is under control. Impurities/degradation products have been evaluated and found to be acceptable from the point of view of safety.

Stability of the product

Stability data from several commercial scale batches of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of finished product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing. Batches of proposed commercial batch size have been used for the study in the commercial container closure system.

An acceptable matrixing approach has been applied for stability analysis. At all relevant time-points the highest and lowest strength only are tested. The specification is based on the release-specification, using the same validated methods as for release.

All tested parameters were within specification limits (at accelerated and long-term conditions). No obvious trends could be identified. Photostability was performed, showing that the product is not sensitive to light.

Therefore, based on the stability data the claimed shelf-life of 24 months, without storage conditions is acceptable.

A post-approval stability protocol and stability commitment has been provided by the applicant.

Adventitious agents

TSE/BSE certificates for the active pharmaceutical ingredient and excipients are enclosed in the dossier. No materials of animal origin/human origin are used except for lactose monohydrate. It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Sufficiently detailed data and documents have been provided indicating that the product can be reproducibly manufactured and is adequately controlled. The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. In conclusion, the quality part of the dossier is sufficiently detailed and acceptable.

2.3. Non-clinical aspects

2.3.1. Introduction

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. The non-clinical

aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

No Environmental Risk Assessment was originally submitted. This was justified by the Applicant as the introduction of Deferasirox Accord manufactured by drug substance manufacturer is considered unlikely to result in any significant increase in the combined sales volumes for all deferasirox containing products and the exposure of the environment to the active substance. Thus, the ERA was expected to be similar and not increased.

To support the claim that there is no increase in the consumption, the applicant submitted the consumption data of the reference medicinal product that showed decrease in the consumption (see below). However, no data on generic medicinal products were submitted.

Table 2 - consumption data of Exjade in mg

	Q2 2016	Q2 2017	Q2 2018	Q1 2019
FCT [mg]	--	472,874,220	2,690,538,840	3,987,079,030
SLB [mg]	4,288,508,750	3,762,822,250	1,112,888,250	304,477,250
Total [mg]	4,288,508,750	4,254,630,310	3,950,349,570	3,987,029,030

The applicant also submitted experimentally-determined logkow: log Kow = log P = 3.52 (PubChem, 2019).

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was justified by the Applicant as the introduction of Deferasirox Accord manufactured by drug substance manufacturer is considered unlikely to result in any significant increase in the combined sales volumes for all deferasirox containing products and the exposure of the environment to the active substance. Thus, the ERA was expected to be similar.

2.3.3. Discussion on non-clinical aspects

The non-clinical sections of the SmPC are acceptable. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology seems adequate.

2.3.4. Conclusion on the non-clinical aspects

The non-clinical sections of the SmPC are acceptable. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology seems adequate.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for containing deferasirox. To support the marketing authorisation application the applicant conducted one bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study for the assessment.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

A biowaiver is requested for the additional 90 mg and 180 mg strengths of Deferasirox Accord based on the conditions mentioned in the Guideline on the Investigation of Bioequivalence. All the conditions were met.

The Applicant submitted a comparison of dissolution profiles of Deferasirox 360 mg vs. Deferasirox 180 mg and Deferasirox 90 mg in three different pHs without surfactant.

Comparative dissolution testing of the three strengths of the test product was done using 75 rpm paddle apparatus in a volume of 900 ml in the following buffers: 0.1N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer. Since deferasirox is a BCS class II compound that easily penetrates the relevant physiological barriers, and possesses poor solubility in the aqueous body fluids, the applicant investigated the dissolution also in presence of surfactant.

- Comparing 360 mg strength of Deferasirox with 180 mg strength of Deferasirox, dissolution profiles were comparable in pH 4.5 and pH 6.8. The dissolution profiles were not comparable in 0.1 N HCl, therefore, applicant provided comparison of dissolution profiles of 1 tablet of Deferasirox 360 mg vs. 2 tablets of Deferasirox 180 mg in 0.1 N HCl with the presence of surfactant. Under these conditions, dissolution profiles were comparable.

- Comparing 360 mg strength of Deferasirox with 90 mg strength of Deferasirox, dissolution profiles were comparable in pH 6.8. The dissolution profiles were not comparable in 0.1 N HCl and pH 4.5, therefore, applicant provided comparison of dissolution profiles of 1 tablet of Deferasirox 360 mg vs. 4 tablets of Deferasirox 90 mg in 0.1 N HCl and in pH 4.5 with the presence of surfactant. Under these conditions, dissolution profiles were comparable.

Due to limited sink conditions, the Applicant provided also comparisons of dissolution profiles of Deferasirox 180 mg vs. Exjade 180 mg and Deferasirox 90 mg vs. Exjade 90 mg in three different pHs without surfactant. In this case, dissolution profiles were comparable.

As per the current BE guideline, where sink conditions may not be achievable for all strengths in vitro dissolution may differ between different strengths. However, the comparison with the respective strength of the reference medicinal product should then confirm that this finding is drug substance rather than formulation related. In addition, the applicant could show similar profiles at the same dose (e.g. as a possibility two tablets of 180 mg versus one tablet of 360 mg AND four tablets of 90 mg versus one tablet of 360 mg could be compared). The applicant provided comparative dissolution profiles with the respective strengths of the reference medicinal product. The dissolution profiles at the same dose were provided by the applicant as well.

The applicant used bootstrapping method to calculate f2 factor with the following justification: as f2 statistics cannot be applied due to incomplete drug release from both the formulations, bootstrapping technique was applied to show the similarity. However, incomplete drug release is not an obstacle in assessing similarity with the f2 calculations. Therefore, where RSDs were within the limits, f2 statistics should be used instead of

bootstrapping method. As this was the case for both dissolution tests at pH 6.8, the applicant was asked to calculate f2 factor with f2 statistics here.

Secondly, in the submitted dissolution profiles, not all prerequisites for calculating the similarity factor as stated in the BE guideline have been met. Several RSDs were not within the limits to enable the calculation of f2 factor. As per the current guideline, when the $f2$ statistic is not suitable, similarity may be compared using alternative methods (e.g. bootstrapping). Therefore, the applicant used bootstrapping method for calculation of f2 factors where RSDs were not within the limits and calculated 90% confidence intervals of f2 factors by DDsolver using 5000 bootstraps. The applicant also calculated f2 factor with f2 statistics where use of bootstrapping was not appropriate. All of the calculated f2 factors were above 50. The dissolution profiles are therefore considered similar and the biowaiver for lower strengths is supported.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study.

Table 1. Tabular overview of clinical studies

Study Identifier	Location of Study Report	Objective(s) of the study	Study Design and Type of control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects
Not Applicable					
Project No. 0382-17	Clinical Study Report & PK Report and Adverse Event Listing, Individual Subject Listings and CRFs 5.3.1.2 Bio-Analytical Report & Method validation Report 5.3.1.4 Literature References 5.4	**Efficacy:** To characterize the pharmacokinetic profile of the sponsor's test product in comparison to the reference product in healthy, adult, human subjects under fasting conditions and to assess the bioequivalence. **Safety:** To monitor the adverse events and to ensure the safety of the subjects.	**Study Design:** An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, two-way crossover, bioequivalence study in healthy, adult, human subjects under fasting conditions. **Type of Control:** No control groups	**Test Product-T** Deferasirox tablets 360 mg **Dosage Regimen:** 360 mg **Route of administration:** Oral **Reference Product-R** EXJADE® (Deferasirox) film coated tablets 360 mg **Dosage Regimen:** 360 mg **Route of administration:** Oral	Planned-36 Checked in-37 Dosed-36 Completed-34 Analysed-36 (in which, 02 withdrawn subjects were also analysed as per protocol requirement) Discontinued/ Withdrawn-02

2.4.2. Pharmacokinetics

Study No. 0382-17: An open label, balanced, randomised, two-treatment, two-period, two-sequence, single oral dose, two way crossover, bioequivalence study of Deferasirox tablets 360 mg of drug substance manufacturer with Exjade (deferasirox) film coated tablets 360 mg of Novartis Europharm Limited, United Kingdom in healthy adult, human subjects under fasting conditions.

Methods

Clinical, bioanalytical study site, as well as PK and statistical analysis was done at the Lambda Therapeutic Research Ltd. The study code was 0382-17. The Conscience-Independent Ethics Committee, Ahmedabad, India approved study protocol.

A statement about conduction of the study in line with GCP is provided.

Study design

Study is designed as comparative, randomized, balanced, two-treatment, two-period, two-sequence, two-way crossover open label bioequivalence study on healthy volunteers with a single dose administration under fasting conditions. In each study period, subjects received a single oral dose of 360 mg of a deferasirox tablet (test) or a reference with 240 ml of water after an overnight fast (10 hrs). Wash-out period was 8 days. Blood samples were collected at pre-dose (0.0) and at 0.50, 1.00, 1.333, 1.667, 2.000, 2.333, 2.667, 3.000, 3.333, 3.667, 4.000, 4.500, 5.000, 5.500, 6.000, 7.000, 8.000, 10.000, 12.000, 16.000, 24.000, 36.000, 48.000 and 72.000 hours post-dose. Deferasirox in human plasma was analysed by LC/MS/MS.

Test and reference products

Deferasirox Accord 360mg manufactured by Accord Healthcare S.L.U. has been compared to Exjade 360mg manufactured by Novartis.

Population(s) studied

The screening procedures to determine subjects' eligibility for participation in the study were to be performed within 28 days prior to the first dosing; they included medical- and drug history, demographic data including name, sex, age, weight (kg), height (cm), BMI, race, alcohol and tobacco consumption, complete physical examination and vital signs measurements, respiratory rate, blood pressure, pulse and body temperature, electrocardiogram 12 lead, haematology, biochemistry, serology and urinalysis. 37 subjects were checked-in. Enrolled subjects were free to withdraw at any time during the course of the study.

The inclusion criteria were: Healthy male and female subjects, aged 18-45 years; BMI within 18.5-30 kg/m2 (both inclusive); non-smoker, not pregnant, not having any significant diseases or clinically significant abnormal findings during screening, medical history, clinical examination, laboratory evaluations, 12-lead ECG and chest X-ray (postero-anterior view) recordings; having clinically acceptable laboratory value for liver function test and renal function test; no known allergy to the investigated product; able to understand and comply with the study procedures and having given their written informed consent were checked in for the study.

The exclusion criteria complementing the inclusion criteria above were: Use of any prescribed medication during last four weeks (28 days) or OTC (over the counter) product during last two weeks (14 days) preceding the first dosing; recent history of harmful use of alcohol (less than 2 years) or consumption of alcohol or alcoholic products within 48 hours prior to receiving study medicine in Period-I; difficulty in swallowing solid dosage forms; an unusual diet, for whatever reason (e.g. low-sodium), for four weeks prior to receiving the study medicine in Period-I; consumption of grapefruit or grapefruit products within 72 hours prior to dosing in Period-I; nursing mothers (females); use of any recreational drugs or history of drug addiction or testing positive in pre-study drug scans; a history of difficulty in donating blood, donation of blood (1 unit or 350 mL) or receipt of an investigational medicinal product or participation in a drug research study within a period of 90 days prior to the first dose of study medication.

All the subjects were instructed to abstain from any xanthine containing food or beverages (like tea, coffee, chocolates or cola drinks or any other), tobacco, tobacco containing products (like Gutkha, Pan / Pan Masala) for 24 hours prior to IMP administration in each period and throughout their stay in the clinical facility.

A total of 36 Asian subjects were dosed and 34 completed the study. Data from these 34 subjects were used for pharmacokinetic and statistical analysis. Case report forms have been submitted.

Analytical methods

Bioanalytical report concerning LC/MS/MS method for the determination of deferasirox in human plasma (K2EDTA) was submitted. Analytical part of the study was conducted. Analysis was performed by Pravin Patel, M.Sc. Method used was validated, validation report (MV(I)-263-17) is included. GLP statement is enclosed.

During the bioequivalence study, blood samples were collected into tubes containing K2EDTA as an anticoagulant and kept in ice cold water, then centrifuged at 3,000 rcf for 5 minutes. After centrifugation, the resulting plasma was transferred directly into two pre-labelled polypropylene tubes. These samples were stored at -65+/-10°C. The longest period of sample storage was 29 days, what is covered by the long-term stability data in biological matrix for 250 days.

Total number of collected samples was 1,719. The total number of analysed analytical runs is 23 including one analytical run due to re-injection and two incurred samples batches. Total number of re-assayed samples was 33 due to the following reasons: significant variability of the internal standard response, concentration above the highest standard and poor chromatography as per SOP No. LTR.BA-03-03.

Internal standard was deferasirox-D4, certificate of analysis is submitted. A set of 8 non-zero standards with calibration range (0.102 µg/mL to 25.045 µg/mL) and quality controls (0.104 µg/mL, 0.301 µg/mL, 2.279 µg/mL, 9.909 µg/mL 19.899 µg/mL and 74.819 µg/mL) were prepared and stored at a nominal temperature of -65+/-10°C.

The quality control sample data for deferasirox were assessed with between-run precision of 1.6 - 3.2% CV and accuracy of 93.8 – 104.4%.

A total number of 140 incurred samples were re-analysed, corresponding to 8% of 1,719 study samples and 88.6% of them met the acceptance criteria specified in the Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009).

Pharmacokinetic variables

The pharmacokinetic calculations were performed with Phoenix® WinNonlin® Version 6.4 (Certara L.P.). Following pharmacokinetic parameters were calculated for deferasirox using standard non-compartmental methods:

Primary:

C_{max}: maximum measured plasma concentration over the time span specified

AUC_{0-t}: the area under the plasma concentration versus time curve, from time (0) to the last measurable concentration (t), as calculated by the linear trapezoidal method.

Secondary:

$AUC_{0-\infty}$: the area under the plasma concentration versus time curve from time (0) to infinity.

T_{max}: time of the maximum measured plasma concentration.

$t_{1/2}$: the elimination or terminal half-life.

λ z: first order rate constant associated with the terminal (loglinear) portion of the curve.

AUC_%Extrap_obs: residual area in percentage.

Statistical methods

Statistical analysis was performed using PROC GLM of SAS® Version 9.3 (SAS Institute Inc., USA).

The statistical evaluation of bioequivalence included following: analysis of variance (ANOVA) in all derived pharmacokinetic parameters, calculation of formulations ratios (point estimates) and parametric 90% confidence interval for ln-transformed AUC_{0-t} and C_{max} parameters.

ANOVA: 5 % significance level for logarithmically transformed (with the 90% confidence intervals) and untransformed data of C_{max} and AUC_{0-t}. The influence of sequence, subject (sequence), formulation and period effect was tested.

Descriptive statistics: all pharmacokinetic parameters: arithmetic mean, SD, CV%, median, min and max.

90% Confidence intervals: logarithmically transformed Test/Reference ratios had to be within 80.00-125.00% for C_{max} and AUC_{0-t}.

Handling of missing values is described in the comment to the population. No specific method for handling of outliers was reported.

Results

Table 5 The mean pharmacokinetic parameters of deferasirox after treatment with test product and reference product

Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T	Reference Product-R
T_{max} (h)[#]	2.667 (1.333 - 4.500)	2.834 (1.667 - 7.017)
C_{max} (µg/mL)	19.556 ± 4.1757	18.508 ± 4.2196
AUC_{0-t} (µg.h/mL)	172.615 ± 47.8134	167.297 ± 50.8708
$AUC_{0-\infty}$ (µg.h/mL)	176.161 ± 49.3554	170.898 ± 51.9419
λ_z (1/h)	0.070 ± 0.0178	0.064 ± 0.0174
$t_{½}$ (h)	10.612 ± 2.7841	11.739 ± 3.2807
AUC_%Extrap_obs (%)	1.947 ± 0.8842	2.123 ± 1.0707

[#]T_{max} is represented in median (min-max) value.

Table 6 90% confidence interval for ln-transformed AUC_{0-t} and C_{max} parameters

Parameters	Geometric Least Squares Means			90%Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%			
lnC_{max}	19.176	18.005	106.5	99.26 - 114.27	17.2	100.0
$lnAUC_{0-t}$	166.527	159.389	104.5	98.90 - 110.37	13.4	100.0
$lnAUC_{0-\infty}$	169.851	162.882	104.3	98.78 - 110.08	13.2	100.0

Figure 1 Mean deferasirox plasma concentrations after single dose administration of one tablet of test product and one tablet of reference product to healthy subjects under fasting conditions

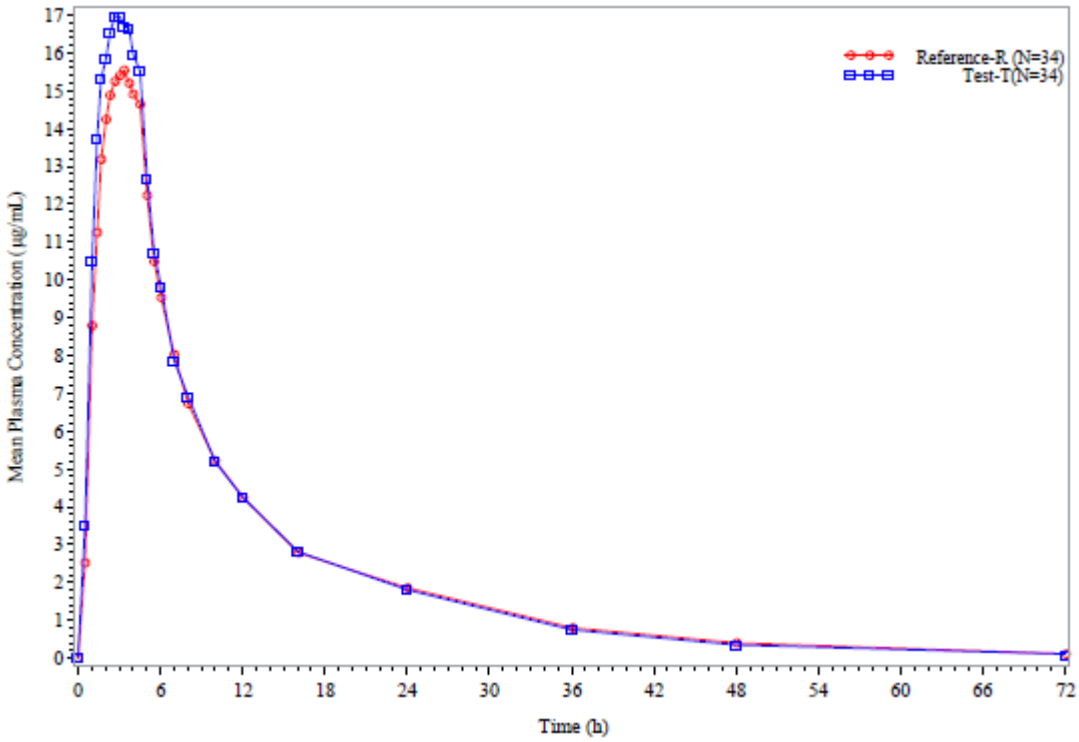


Table 7 P-values obtained from deferasirox ANOVA results after single dose administration of test and reference product

ANOVA p-values for Deferasirox

Parameters	ANOVA (p-value)			
	Formulation	Sequence	Period	Subject (Sequence)
lnC_{max}	0.1395	0.0290	0.1038	0.0022
$lnAUC_{0-t}$	0.1855	0.3682	0.0292	<0.0001
$lnAUC_{0-\infty}$	0.1996	0.3027	0.0307	<0.0001

Note: Significant value if p-value < 0.05.

There were no pre-dose concentrations of deferasirox in the period II. C_{max} was not observed in any case at the first time point after dosing. Extrapolated AUC less than 20% does not apply as AUC was followed until 72 hrs time point.

Safety data

Three (03) adverse events (AEs) were reported by two (02) subjects during the conduct of the study. Two (02) AEs were reported in the Period-I in the subject No. 1027 (diarrhoea and abdominal pain, both resolved) and one (01) AE was reported during the post-study safety assessment in the subject No. 1028 (eosinophilia, the outcome unknown). All the AEs were reported in the subjects after administration of Reference Product-R. All the AEs were mild in nature.

Subject No. 1027 was followed up until resolution of his AEs and subject No. 1028 did not report for his AE follow-up and hence he was considered as lost to follow-up.

The causality assessment was judged as possibly related for all the AEs.

There were no deaths or serious AEs during the conduct of the study.

However, out of the total reported three (03) AEs, two (02) AEs in the subject No. 1027 were significant. The subject was withdrawn from the study on medical grounds. He was treated appropriately and followed up until resolution of his AEs. The causality assessment was judged as possibly related for both the AEs.

Other individual laboratory measurements (biochemistry, haematology, immunology and urine analysis) were, in some cases, outside their reference intervals but not to an extent to be considered clinically significant by the study physician.

Pharmacokinetic Conclusions

Based on the presented bioequivalence study Deferasirox Accord is considered bioequivalent with Exjade.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

In this generic application, essential similarity is claimed to the reference medicinal product Exjade. To support this application, the applicant submitted the review of non-clinical and clinical data as well as a bioequivalence study (study 0382-17).

Deferasirox Accord 360 mg film-coated tablets were compared with Exjade 360 mg film-coated tablets (Novartis Europharm Ltd. (IE) in a bioequivalence study in healthy adult volunteers under fasting conditions. The study design is deemed appropriate regarding the number of randomized subjects, wash-out period, sampling periods and test- and reference products.

The SmPC of the originator (Exjade 360 mg film coated tablets) allows to crush tablets and to administer them dispersed in a light meal in case patients are unable to swallow the whole. In line with the revised PKWP position, it is highly unlikely that the change in bioavailability will be different between test and reference, once bioequivalence has been shown between test and reference with the intact or non-dispersed tablet. Consequently, if the SmPC of the reference product allows for the possibility to administer the tablet crushed/disintegrated (and dispersed in food), bioequivalence does not need to be demonstrated with this additional mode of administration. Thus, based on the results of the presented bioequivalence study, Deferasirox Accord 360 mg film-coated tablets can be considered bioequivalent with Exjade 360 mg film-coated tablets.

A biowaiver was requested for the additional 90 mg and 180 mg strengths of Deferasirox Accord, based on the conditions mentioned in the Bioequivalence guideline. As all the conditions were met, the results of study No. 0382-17 with the 360 mg tablets can be extrapolated to the strengths of 90 mg and 180 mg.

2.4.6. Conclusions on clinical aspects

To support this generic application, the Applicant submitted one bioequivalence study. The results of this study support the claim of essential similarity of Deferasirox Accord 360 mg film-coated tablets to the reference medicinal product Exjade 360 mg tablets.

The biowaiver requested for the additional 90 mg and 180 mg strengths of Deferasirox Accord is acceptable and thus, the results of study No. 0382-17 for the 360 mg tablets can be extrapolated to the other strengths, 90 mg and 180 mg.

2.5. Risk management plan

Safety concerns

Summary of safety concerns	
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 • Severe cutaneous adverse reactions (SCARs) (including Stevens-Johnson syndrome [SJS], Toxic epidermal necrolysis [TEN] and Drug reaction with eosinophilia and systemic symptoms [DRESS])
Important potential risks	• Compliance with posology and biological monitoring • Medication errors
Missing information	• Long term safety in paediatric NTDT patients aged 10 to 17 years

Pharmacovigilance plan

No additional pharmacovigilance activities.

Risk minimisation measures

Safety concern	Risk minimisation measures
Important identified risks	
Renal disorders (increased serum creatinine, acute renal failure (ARF), renal tubular disorders [acquired Fanconi's syndrome])	Routine risk minimization measures : Sections 4.2, 4.3, 4.4, 4.8, 5.2 and 5.3 of Deferasirox SmPC and corresponding section of PL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: None
Increased liver transaminases / Hepatic failure	Routine risk minimisation measures: Sections 4.2, 4.4 and 4.8 of Deferasirox SmPC and corresponding section of PL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: None
Gastrointestinal hemorrhage and ulcers; esophagitis	Routine risk minimisation measures: Sections 4.4, 4.5 and 4.8 of Deferasirox SmPC and corresponding section of PL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: None
Hearing loss	Routine risk minimisation measures: Sections 4.4 and 4.8 of Deferasirox SmPC and corresponding section of PL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: None
Lens opacities, retinal changes and optic neuritis	Routine risk minimisation measures: Sections 4.4, 4.8 and 5.3 of Deferasirox SmPC and corresponding section of PL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: None
Severe cutaneous adverse reactions (SCARs) (including SJS, TEN and DRESS)	Routine risk minimisation measures: Sections 4.4 and 4.8 of Deferasirox SmPC have information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures:

Safety concern	Risk minimisation measures
	None
Important Potential Risks	
Compliance with posology and biological monitoring	Routine risk minimisation measures: Sections 4.2 and 4.4 of Deferasirox SmPC and corresponding section of PL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: Educational materials for physicians and patients
Medication errors	Routine risk minimisation measures: Section 4.2 of Deferasirox SmPC and corresponding section of PL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: Educational materials for physicians and patients
Missing information	
Long term safety in pediatric NTDT patients aged 10 to 17 years	Routine risk minimisation measures: Sections 4.2 and 4.4 of Deferasirox SmPC have information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable. However, the applicant should submit a variation with one month of marketing authorisation, aligning the specific adverse reaction follow-up checklists with those described in the RMP of the originator and replacing "PIL" by "PL".

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet 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.

3. Benefit-risk balance

This application concerns a generic version of deferasirox tablets. The reference product Exjade 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.

Exjade 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.

Exjade 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.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with a comparative, randomized, balanced, two-treatment, two-period, two-sequence, two-way crossover open label bioequivalence study on healthy volunteers with a single dose administration under fasting conditions. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied and adequately presented.

The test formulation of Deferasirox Accord met the protocol-defined criteria for bioequivalence when compared with the Exjade. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Deferasirox Accord is favourable in the following indication:

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 Accord 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 Accord 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,

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

The MAH must inform the European Medicines Agency and the CHMP of the results of the surveillance programme in each Member State.

As well as the requirements in the legislation, the following serious ADRs should be forwarded on an expedited basis to the appropriate competent authority as well as summarised in the periodic safety update reports:

- Increase in hepatic enzymes >10x ULN
- Serious rise in creatinine
- Results of renal biopsies, if available
- Cataracts
- Hearing loss
- Gallstones

Prior to launch of Deferasirox Accord in each Member State the Marketing Authorisation Holder (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 available on the market by different MAHs (dispersible tablets and film-coated tablets/granules)]

The MAH shall ensure that, at launch, in each Member State where Deferasirox Accord is marketed, all healthcare professionals and patients who are expected to prescribe, dispense and use Deferasirox Accord are provided 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

Additional periodic distributions after launch should be performed, notably after substantial safety modifications of the product information justifying educational material updates.

The physician educational material should contain:

- The Summary of Product Characteristics
- Guide for healthcare professionals

The Guide for healthcare professionals shall contain the following key elements:

- Description of available deferasirox formulations on the market (e.g. dispersible tablets, film-coated tablets and granules)
    - Different posology regimen
    - Different conditions of administration
    - Dose conversion table when switching from one formulation to another
- The recommended doses and the rules for starting treatment
- The need to monitor serum ferritin monthly
- That deferasirox causes rises in serum creatinine in some patients
    - The need to monitor serum creatinine
        - On two occasions prior to initiation of treatment
        - Every week during the first month of initiation of treatment or after therapy modification
        - Monthly thereafter
    - The need to reduce by 10 mg/kg the dose if serum creatinine rises:
        - Adults: >33% above baseline and creatinine clearance <LLN (90 ml/min)
        - Paediatrics: either >ULN or creatinine clearance falls to <LLN at two consecutive visits.
    - The need to interrupt treatment after a dose reduction if serum creatinine rises:
        - Adults and Paediatrics: remain >33% above baseline or creatinine clearance
        - <LLN (90 ml/min)
    - The need to consider renal biopsy:
        - When serum creatinine is elevated and if another abnormality has been detected (e.g. proteinuria, signs of Fanconi syndrome).

- The importance of measuring creatinine clearance
- Brief overview of methods of measuring creatinine clearance
- That rises in serum transaminases may occur in patients treated with Deferasirox Accord
    - The need for liver function tests prior to prescription, then at monthly intervals or more often if clinically indicated
    - Not to prescribe to patients with pre-existing severe hepatic disease
    - The need to interrupt treatment if persistent and progressive increase in liver enzyme were noted.
- The need for annual auditory and ophthalmic testing

- The need for a guidance table highlighting pre-treatment measurements of serum creatinine, creatinine clearance, proteinuria, hepatic enzymes, ferritin, such as:

Before initiating treatment	
Serum creatinine at Day – X	Value 1
Serum creatinine at Day – Y	Value 2

  X and Y are the days (to be determined) when pre-treatment measurements should be performed.

- A warning on the risk of overchelation and on the necessity of close monitoring of serum ferritin levels and renal and hepatic function.
- The rules for treatment dose adjustments and interruption when target serum ferritin +/− liver iron concentration are reached.
- Recommendations for treatment of non-transfusion-dependent thalassaemia (NTDT) syndromes:
  - Information that only one course of treatment is proposed for NTDT patients
  - A warning on the necessity of closer monitoring of liver iron concentration and serum ferritin in the paediatric population
  - A warning on the currently unknown safety consequences of long-term treatment in the paediatric population

The patient information pack should contain:

- Patient information leaflet
- Patient guide

Patient guide should contain the following key elements:

- Information on the need for regular monitoring, and when it should be carried out, of serum creatinine, creatinine clearance, proteinuria, hepatic enzymes, ferritin
- Information that renal biopsy may be considered if significant renal abnormalities occur
- Availability of several oral formulations (e.g. dispersible tablets, film-coated tablets and granules) and the main differences associated with these formulations (i.e., different posology regimen, different conditions of administration notably with food)

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.