25 July 2019
EMA/CHMP/509090/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Deferasirox Mylan

International non-proprietary name: deferasirox

Procedure No. EMEA/H/C/005014/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

%	Percentage
µg/L	Microgram per liter
µg/ml	Microgram per millilitre
µmol/l	Micromole per litre
5-HT1	5-hydroxy tryptamine receptor 1
5-HT2	5-hydroxy tryptamine receptor 2
5-HT3	5-hydroxy tryptamine receptor 3
AA	Aplastic anaemia
ADR	Adverse drug reactions
AE	Adverse events
Al	Aluminium
ALP	Alkaline phosphate
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the concentration versus time curve
AUC	Plasma concentration-time curve
AUC_{0-inf}	Plasma concentration-time curve extrapolated to infinity
AUC_{0-t},	Plasma concentration-time curve to the last measured concentration
BCRP	Breast Cancer Resistance Protein
BE	Bioequivalence
BLOQ	Below limit of quantification
BUN	Blood urea nitrogen
BW	Body weight
Cd	Cadmium
CI	Confidence Intervals
CL	Plasma clearance
Cmax	Maximum Plasma Concentration
C_{max}	Peak plasma concentration
CNS	Central nervous system
CoA	Certificate of Analysis
Cr	Chromium
CRF	Case Report Form
CV	Coefficient of Variation
CYP	Cytochrome
CYP1A1	Cytochrome P450 family 1, member A1
CYP1A2	Cytochrome P450 family 1, member A2
CYP2C8	Cytochrome P450 2C8
CYP2D6	Cytochrome P450 family 2, member D6

CYP3A4	Cytochrome P450 3A4
CYP450	Cytochrome P450
DFX	Deferasirox
ECG	Electrocardiogram
EDTA	Ethylene diamine tetra-acetic acid
EUSPC	European Summary of Product Characteristics
FC	Food consumption
FCT	Film-Coated Tablets
Fe^{3+}	Iron
GABA-A	Gama amino butyric acid receptor A
GABA-B	Gama amino butyric acid receptor B
GCP	Good clinical practice
GI	Gastrointestinal
GLP	Good laboratory practice
h	Hour
Hb	Haemoglobin
Hct	Haematocrit
HD	High dose
HDPE	High Density Polyethylene
hERG	Human ether-a-go-go-related gene
Hg	Mercury
HPLC	High Performance Liquid Chromatography
HPMC	Hydroxyl propyl methylcellulose
HS	Head Space
IC_{50}	Median inhibitory concentration
ICH I	nternational Council for Harmonization
IEC	Institutional ethical committee
IgG	Immunoglobin G
IPC	In Process Control
IR	Infrared
IgM	Immunoglobin M
K_{el}	Elimination Rate Constant
KG	Kilogram
K_i	Inhibitory constant
K_m	Michaelis constant
LD	Low dose
LD_{50}	Median lethal dose
LDPE	Low Density Polyethylene
LIC	Liver iron concentration
LLC-PK1	Pig kidney epithelial cells
LLOQ	Lower limit of quantification

LOD	(1) Loss on Drying (2) Limit of Detection
LPI	Labile plasma iron
M1	5-hydroxy deferasirox presumably by CYP1A
M3	Acyl glucuronide
M4	5'-hydroxy deferasirox, by CYP2D6
M6	2-O-glucuronide
MAA	Marketing Authorisation Application
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MD	Middle dose
MDR	Multidrug-resistance transporter
MDS	Myelodysplastic syndrome
mg	Milligram
Mg	Milligram
mg/kg	Milligram per kilogram
mg/kg/day	Milligram per kilogram per day
MLD	Minimum lethal dose
mM	Millimolar
MNLD	Maximum non-lethal dose
MRHD	Maximum recommended human dose
MRP2	Multidrug resistance-associated protein 2
MTD	Maximum tolerated dose
MXR	Multixenobiotic resistance transporter
NDA	New drug application
ng/mL	Nanograms per milliliter
NMDA	N-methyl-D-aspartate receptor
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
NSAIDs	Non-steroidal Anti-inflammatory Drugs
NTDT	Non-transfusion-dependent thalassemia
NTDT	Non-transfusion-dependent thalassemias
PK	Pharmacokinetics
pK_a	Acid dissociation constant
PM	Product monograph
QC	Quality control
R2 MRI	Relaxation rates magnetic resonance imaging
RBC	Red blood cell
RLD	Reference list drug
SAS	Statistical Analysis Software
SBOA	Summary Basis of Approval
SD	Standard Deviation

SOP	Standard Operating Procedure
T/R	Test/reference ratio
$t_{½}$	The Elimination Half-Life
T1/2	Half life
TF	Transferrin
TG	Triglyceride
TI	Thallium
Tmax	Time to peak plasma concentration
TMAX	Plasma Concentration Reaches a Peak
T_{max}	Time of The Maximum Measured Plasma Concentration
UGT	Uridine diphosphate Glucuronosyl Transferase
UGT	UDP glucuronosyltransferase
UGT1A1	UDP glucuronosyltransferase family 1 member A1
UGT1A3	UDP glucuronosyltransferase family 1 member A3
ULOQ	Upper limit of quantification
Vss	Steady-state volume of distribution
WBC	White blood cell
XR(P)D	X-RAY (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mylan S.A.S submitted on 29 June 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Deferasirox Mylan, 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 22 March 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 has been granted in the Union on 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 Mylan 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 Mylan 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 Mylan 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.

The chosen reference product is:

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

- Product name, strength, pharmaceutical form: Exjade, 90 mg, 180 mg and 360 mg film-coated tablets
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: 28-08-2006
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/06/356/011-019

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 and 360 mg film-coated tablets
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: 28-08-2006
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/06/356/011-019

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 tablets
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: 28-08-2006
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/06/356/017-019
- Bioavailability study number(s): C17305

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 submitted a critical report addressing the possible similarity with authorised orphan medicinal products. The Assessment Report on similarity is annexed.

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: Agnes Gyurasics

The application was received by the EMA on	29 June 2018
The procedure started on	19 July 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	8 October 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	23 October 2018
The CHMP agreed on the consolidated List of Questions to be sent to the	15 November 2018

applicant during the meeting on	
The applicant submitted the responses to the CHMP consolidated List of Questions on	29 March 2019
The Rapporteur circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	13 May 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 May 2019
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	29 May 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 June 2019
The Rapporteur circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	16 July 2019
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 Mylan on	25 July 2019
The CHMP adopted a report on similarity of Deferasirox Mylan with Revlimid and Zynteglo	25 July 2019

2. Scientific discussion

2.1. Introduction

Transfusion and iron chelation therapy can be a lifelong requirement for many patients with transfusion-dependent anemias. Compliance with iron chelation therapy can influence the frequency and severity of iron overload-related complications, with demonstrated improvement in organ dysfunction and survival in patients compliant with iron chelation therapy (Taher AT et al., 2017). Iron homeostasis is a complex system that balances both the absorption of intestinal iron and release of stored iron, with the body's iron requirements. There are several molecules, such as hepcidin, ferritin, and ferroportin that provide tight regulation of this process, and contribute to iron homeostasis. Under normal circumstances, almost all absorbed iron is rapidly bound to transferrin (TF), an abundant, high-affinity iron-binding protein. Iron occupies approximately 30% of TF iron-binding sites. In heavily transfused patients, non-TF bound iron begins to accumulate. Labile plasma iron (LPI), a directly chelatable form of non-TF bound iron, is readily taken up by cells, leading to expansion of the cellular iron pool and generation of reactive oxygen species, resulting in cellular dysfunction and death. (Chalmers AW et al., 2016). The aim of treatment is to remove excess iron storage from the body. Deferasirox is an orally active iron chelator belonging to a new class of tridentate iron chelators, the N-substituted bis-hydroxyphenyl-triazoles. Deferasirox is claimed to mobilize tissue iron and promote its excretion, primarily in the faeces.

This centralised application for marketing authorisation concerns a generic application according to article 10(1) of Directive 2001/83/EC for Deferasirox Mylan 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.

A single bioequivalence study was conducted in fasting state in healthy volunteers; comparing the applicant's Deferasirox film coated tablets 360 mg with Exjade (deferasirox) 360 mg Film coated tablets of Novartis Europharm Limited.

Additionally, the applicant provided a bioequivalence study with the crushed tablets consumed with apple sauce.

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.

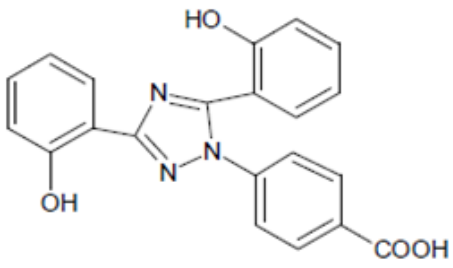
Other ingredients of the tablet core are: microcrystalline cellulose (PH 101 and PH 102), crospovidone (Type A), povidone (K30), poloxamer (P 188), colloidal anhydrous silica, and magnesium stearate. Opadry Orange 03F530071 is used as film-coating material, which contains hypromellose 2910 (6 mPas), titanium dioxide (E171), macrogol/PEG (6000), talc, iron oxide yellow and red iron oxide red.
The finished product is available in PVC/PVDC/Aluminium blisters and perforated unit-dose blisters, as well as in high density polyethylene (HDPE) bottles with white opaque polypropylene (PP) screw cap with aluminium seal 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



Deferasirox has very poor solubility in the majority of solvents. It is not a hygroscopic substance.
Deferasirox structure does not contain chiral or asymmetric carbon atoms.
Deferasirox exists in various polymorphic forms.
For deferasirox an Active Substance Master File (ASMF) has been provided by the active substance manufacturer.

Manufacture, process controls and characterisation

For deferasirox an Active Substance Master File (ASMF) has been provided by the active substance manufacturer. Brief description of the validated manufacturing process of the active substance is presented in the ASMF applicant's part provided by the finished product manufacturer. The brief description includes a satisfactory discussion on the proposed starting materials, including the used reagents and solvents has been provided together with a discussion about possible impurities into the final active substance.

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.

Representative certificates of analysis (CoA) have been provided, and the suppliers, the brief description of the synthetic pathway have also been provided. Starting material specifications include identification tests, and limits for assay, related impurities and other relevant physico-chemical parameters. Specifications and methods of analysis have been provided, which control the impurity content and relevant physical parameters of the intermediates. The specifications for the reagents and solvents used in the process are considered suitable.

The critical manufacturing steps have been identified. Adequate in-process controls have been established to control completion of reaction and loss on drying at the end of the respective stages, these have been adequately described, method descriptions have been presented.

The specifications and methods of analysis for the two intermediates have been provided, which control the impurity content and relevant physical parameters of the intermediates. Certificates of analysis have been provided for the intermediates to show that the proposed specifications are in line with obtained results. Fate and purge of reagents have been discussed.

The manufacturing process development has been very briefly described, but considering the simplicity of the process, this is considered acceptable.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of active substances. The active substance was characterized by IR, UV, NMR, mass spectroscopy, elemental analysis, thermal analysis and XRD. Sufficient data has been presented. The methods used for elucidation of structure are adequate. Typical spectra have been enclosed. The spectrum assignations are consistent with the declared chemical structure. Information on elemental analysis is also provided. The results confirm the theoretical elemental composition of the active substance. The active substance manufacturer consistently produces the same crystalline form of the active substance. Stability of the polymorphic form has been adequately discussed.

An evaluation of the potential related impurities of deferasirox that could be introduced via the manufacturing process or from degradation pathways has been conducted. Potential and actual impurities were well discussed with regards to their origin and characterised. Characterisation of specified related substances has been presented. The listed impurities are either routinely controlled in the active substance specification, or their absence has been satisfactorily demonstrated in production batches. The discussion of genotoxic impurities is acceptable.

All of the residual solvents used in the synthesis steps of the commercial process are routinely controlled.

A satisfactory elemental impurities risk assessment was conducted following the principles outlined in ICH Q3D.

Specification

Deferasirox has no European Pharmacopoeia monograph. The specifications include tests and limits for appearance, solubility (Ph. Eur.) identity (IR, HPLC), assay (HPLC), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.), related substances (HPLC and LC-MS/MS), residual solvents (GC) and identification of polymorph (PXRD).

The proposed parameters and impurities limits are acceptable, the latter correspond to the requirements of ICH Q6A, ICH Q3A ICH Q3C and ICH Q3D guidelines. 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.

Analytical procedures and reference standards

The analytical methods have been suitably described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference materials is provided.

Batch analysis

All presented batch analysis (9 batches) results conform to the API manufacturer's specifications. The active substance produced is of consistent quality. The results are within the specifications and consistent from batch to batch.

Container closure

Deferasirox is packed into an antistatic white low-density polyethylene (LDPE) bag, twisted and tied with a plastic fastener.
Compliance of the primary packaging material with the relevant regulations has been certified. The information presented on the packaging materials is sufficient and adequate.

Stability

Stability studies have been conducted in accordance with the ICH guidelines, at accelerated (40°C/75%RH) and long-term (25°C/60%RH) conditions. The studies have been initiated for 3 batches. The scale of batches corresponds to the proposed batch size, taking into account the yield range. The packaging material resembles the commercial packaging. The analytical methods are the same as for routine testing. The following parameters were tested during stability studies: description, loss on drying, impurities, assay.

All results comply with the requirements up to the presented time-points. No out-of-specification result has been measured.
Forced degradation studies have revealed that deferasirox degrades in acidic medium at 60°C, but no significant degradation can be observed in basic and oxidative media as well as under the effect of heat and light. The active substance is photostable.
Measurements were undertaken to demonstrate stability of the polymorphic form.
Based on the stability data presented all tested parameters were within the specifications and the proposed re-test period can be accepted.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical Development

The finished product is film-coated tablets containing 90, 180 or 360 mg of deferasirox as active substance and their appearance is as follows:

90 mg strength: a peach, film-coated, modified capsule shaped, biconvex tablet debossed with "  " on one side of the tablet and 'DF' on the other side. Approx. tablet dimensions 10.0 mm x 4.5 mm.

180 mg strength: a peach, film-coated, modified capsule shaped, biconvex tablet debossed with "  " on one side of the tablet and 'DF1' on the other side. Approx. tablet dimensions 12.8 mm x 6.0 mm.

360 mg strength: a peach, film-coated, modified capsule shaped, biconvex tablet debossed with "  " on one side of the tablet and 'DF2' on the other side. Approx. tablet dimensions 17 mm x 6.7 mm.

The qualitative composition of the core is identical to that of the reference product. The different strengths are dose-proportional. They can be differentiated based upon their size and their markings. No overages are used.
Based on the characterization of reference product i.e. Exjade® tablets 90 mg, 180 mg and 360 mg manufactured by Novartis Europharm Ltd., it was determined that the test product should have the following attributes:
1. The product has to be formulated as an immediate release tablets to be administered orally having deferasirox as the active ingredient and it has to be pharmaceutically equivalent to the reference product.
2. The formulation should have comparable dissolution profile with reference product.
3. The product should have satisfactory pharmaceutical stability.
4. Test product should be bioequivalent to the reference product.
5. The test product strengths - 90 mg, 180 mg and 360 mg should be formulated as dose weight proportional formulations in order to justify biowaiver of lower strengths - 90 mg and 180 mg.

Initially, the quality target product profile (QTPP) was defined based on the properties of the drug substance, characterization of reference product, consideration of the reference product label and intended patient population.

The excipients used in formulation were selected based on the excipients used in the reference product, excipient compatibility study and prior experience of product development.
Except for the film coating material, all of the excipients used are identical to those used in the reference product, and are conventional pharmaceutical ingredients that comply with the requirements of the European Pharmacopoeia. They are included in the formulation at suitable levels and for recognized purposes. The functionality related characteristics of the excipients have been adequately discussed in line with the findings of manufacturing process development, and included in their specification. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Appropriate TSE/BSE statements regarding safety of the excipients have been provided.
The film coating material is a proprietary material purchased from an established commercial supplier, to an agreed specification. The individual compendial components used in the manufacturing of Opadry coating material comply with the respective monograph in Ph. Eur. The colorants used in Opadry coating material comply with directive (EU) No. 231/2012. The iron content present in the chosen coating material does not significantly affect the iron binding capacity of the active substance.

Risk assessment was carried out throughout development to identify potentially high-risk formulation and process variables and to determine which studies were necessary to achieve product and process understanding.
Risk Assessment was performed to identify the formulation variables affecting the proposed critical quality attributes (CQAs). The identified formulation variables were studied at various levels and the optimized level of each variable was selected based on the desired values of the CQAs. An updated formulation risk assessment was found to be satisfactory as the high and medium formulation risks were reduced to low.

Following formulation risk assessment, a similar risk assessment was conducted to evaluate the risk associated with various process parameters. Formulations were prepared employing different levels of process variables and evaluated for the affected CQAs. The final range of process parameters was determined based on the results of these studies. Subsequently, the risk assessment was then updated after development to capture the reduced level of risk based on improved process understanding. Finally, an adequate control strategy of the material attributes and process parameters were proposed which also includes in-process controls and finished product specifications. Monitoring of the process will be continued throughout the product lifecycle and the control strategy will be adjusted based on the experience gained.

The chosen formulation and manufacturing process adequately accommodate active substance properties.
Optimization trials were undertaken by varying the concentration of the excipients in the formula. The batches were analyzed for weight variation, hardness, thickness, disintegration time, friability and dissolution profile. Based on the results, the final product composition was finalized.

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.
Deferasirox is a BCS class II compound which easily penetrates the relevant physiological barriers, and possesses poor solubility in the aqueous body fluids. During development of the dissolution method, surfactant had to be added to the dissolution medium to produce a measurable dissolved amount of the active substance. In spite of efforts taken to optimise dissolution parameters to accommodate the poor solubility of deferasirox, sink conditions could not be achieved for the 360 mg strength in all media, nor probably for the 180 mg strength. Nevertheless, the discriminatory power of the chosen method has been satisfactorily demonstrated.
The applicant has performed comparative bioequivalence study between Deferasirox 360 mg film coated tablets and the reference product Exjade (Deferasirox) 360 mg film coated tablets. The applicant confirmed that the composition and the manufacturing process of the test product formulation used in the bioequivalence study and the formulation proposed for commercial supplies to the European Economic Area is the same. The assay and impurities data of the batches used in the bioequivalence study have been provided. The difference in assay of the test and the reference products is less than 5%, as per the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1). The levels of impurities are similar. The biobatch has been produced at the proposed finished product manufacturing site. The source of active substance has been indicated. Comparative dissolution profiles of the test and reference products have been provided.
A biowaiver is requested for the lower strengths. The conditions necessary for a waiver are fulfilled. In order to unambiguously prove similar *in vitro* behaviour of the test and reference products, lower

strengths of the reference product have also been compared to the respective 90 mg and 180 mg test products and found comparable.

Furthermore, according to the SmPC, "*For patients who are unable to swallow whole tablets, the film-coated tablets may be crushed and administered by sprinkling the full dose onto soft food, e.g. yogurt or apple sauce (pureed apple).*" No compatibility study was required due to identical instructions in the reference product's SmPC; and no in-use stability was requested, as according to the SmPC "the dose should be immediately and completely consumed, and not stored for future use". Considering that according to the SmPC administration of crushed tablets is also proposed, comparative dissolution profiles of crushed and intact tablets have also been provided, additionally a bioequivalence study was performed comparing test and reference crushed in apple sauce.

In addition a new bioequivalence study (No. C18443) was submitted in response to the Day 120 LoQ. The study was performed with the additional mode of administration i. e. crushing the tablet, administered with soft food (apple sauce). Based on the results of the study with crushed Deferasirox 360 mg film-coated tablets (Mylan) and Exjade 360 mg filmovertrukne tabletter (Novartis) (language as written in the response documentation) met the bioequivalence criteria with regard to rate and extent of absorption under fasting conditions.

The product is presented in the following pack types:

- PVC/PVDC/Aluminium blister pack and unit-dose blisters.
- High density polyethylene (HDPE) bottle pack with opaque polypropylene (PP) screw closure

The packaging materials are commonly used for storage of oral film-coated tablets, and comply with the relevant EC directive requirements for packaging materials in contact with food. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product

The manufacturing process comprises granulation, blending, compression, coating as main steps and can be considered as a standard process.
The detailed narrative description of the process has been provided, as well as the flow chart of the process steps. The manufacturing conditions and operating parameters to be followed for the proposed commercial batch sizes are in line with the conclusions of the manufacturing process development as sufficiently detailed in the respective section.

In-process control (IPC) tests and criteria have been adequately detailed. The packaging materials of the intermediates and holding times, verified by stability studies, have been provided.

The manufacturing process has been validated for three batches per strength. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification, analytical procedures, batch analysis

The finished product release specifications include appropriate tests for this kind of dosage form: description (visual), identification (HPLC, UV), identification of colorants (colorimetry), dissolution (UV), assay (HPLC), related substances (HPLC), uniformity of dosage units (Ph. Eur.), and loss of drying (Ph. Eur.).

The specification covers all relevant parameters for the dosage form as described in the Ph. Eur. monograph. The proposed specification parameters and acceptance limits are acceptable and they are in line with those prescribed in the European Pharmacopoeia for this dosage form and also with the relevant ICH guidances (Q6A, Q3B, Q3D), batch data and stability results.

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 analytical methods are acceptably described. System suitability criteria are defined, calculation formulae, typical chromatograms and spectra have been provided. The analytical test methods applied were adequately validated in line with ICH Q2 (R1),and are suitable for their intended purpose. The stability indicating nature of the methods has been demonstrated by the forced degradation studies.

Batch analysis
The presented batch analysis results (3 batches of each strength) confirm 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. No additional impurity of deferasirox is observed in the finished product during manufacturing or during stability.
Satisfactory information regarding the reference standards has been presented.

The finished product is released on the market based on the above release proposed specifications, through traditional final product release testing.

Stability of the product

Finished product long-term (25°C/60% RH) and accelerated (40°C/75% RH) stability study
Stability data have been presented up to 18 months for long-term and up to 6 months for accelerated conditions. Acceptable bracketing design has been applied for the stability studies in bottles.
The tested parameters are within the specified limits. No significant changes or trends can be observed for any of the tested parameters at any of the tested conditions. The conditions used in the stability studies comply with the ICH stability guideline, stability data are available for representative batches (9 batches) of all strengths manufactured at the commercial site and packed in the commercial container closure systems i.e. the tablets were packed in the container closure system as proposed for marketing i.e. HDPE bottle pack and PVC/PVDC/aluminium blister pack.

Bulk stability study: data have been presented up to 12 months. The tested parameters are within the specified limits. No significant changes or trends can be observed for any of the tested parameters at any of the tested conditions, except for a slight increase in loss on drying.

In-use stability: despite a slight increase in loss on drying, all results comply with the requirements. Since the tablets packed in bottle packs comply with the proposed shelf-life specification at the end of the conducted in-use study, no in-use period is stated in the SmPC in line with EMA Q&A on quality Part 2.

Photostability study has been performed on one representative batch from each strength as per ICH Q1B Guideline- "Photo stability testing of new drug substances and products", and the results showed that the product is not sensitive to light.

Based on available stability data, the proposed shelf-life of 2 years without special storage conditions as stated in the SmPC (section 6.3 and 6.4) is acceptable.

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.

2.2.6 Recommendation(s) for future quality development

N/A

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.

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

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 Mylan manufactured by Mylan S.A.S 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 is expected to be similar.

2.3.3. Discussion on non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Absence of ERA has been acceptably justified by the applicant.

2.3.4. Conclusion on the non-clinical aspects

The application is approvable from a non-clinical perspective.

2.4. Clinical aspects

2.4.1. Introduction

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

Additionally, the applicant conducted a bioequivalence study with cross-over design under fasting conditions (light meal and with crushed tablets) in relation to section SmPC 4.2 of the reference product 'For patients who are unable to swallow whole tablets, the film-coated tablets may be crushed and administered by sprinkling the full dose onto soft food, e.g. yogurt or apple sauce.'.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of deferasirox based on published literature. The SmPC is in line with the SmPC of the reference product.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) is of particular relevance.

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 request was submitted for the additional 90 mg and 180 mg strengths according to the Bioequivalence Guideline (General biowaiver criteria).

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 in presence of surfactant.

The low solubility of the drug substance was confirmed also with the dissolution profiles without surfactant.

Although it has been demonstrated according to the Guideline on the Investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) that similar profiles are obtained with samples of the same dose (1x360 mg tablet vs 2x180 mg tablets vs 4x90 mg tablets in a vessel), sink conditions were visibly not achievable for all strengths.

In order to unequivocally prove similar in-vitro behaviour of the test and reference products, lower strengths of the reference product were compared to the respective 90 mg and 180 mg test products, confirming that low dissolution is drug substance rather than formulation related. Furthermore, considering the SmPC of the originator, since it allows the administration of crushed tablets is also proposed, comparative disintegration times of the tablets and dissolution profiles of crushed and intact tablets were also provided.

Further dissolution and disintegration tests were performed with Deferasirox Test and Reference (Exjade) showing similar dissolution profiles.

Clinical studies

To support the application, the applicant has submitted one pivotal bioequivalence study in fasting conditions.
Additionally, as part of the responses to the Day 120 LoQ , one supportive study (crushed tablets with light meal), was submitted in connection to section SmPC 4.2 of the reference product 'For patients who are unable to swallow whole tablets, the film-coated tablets may be crushed and administered by sprinkling the full dose onto soft food, e.g. yogurt or apple sauce.'.

Table 1. Tabular overview of clinical studies

Type of Study	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	Healthy subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	Not Applicable								
BE	Project No. C17305	Clinical Study Report & PK Report and Adverse Event Listing **Clinical Study (5.3.1.2)** Bioanalytical Report **Bioanalytical (5.3.1.4)** CRFs and Individual Subjects **Individual CRF (5.3.7)** Literature References **Literature References (5.4)**	**Primary objective:** To evaluate the oral bioequivalence of Deferasirox film coated tablets 360 mg of Mylan Laboratories Limited, India with Exjade® (deferasirox) 360 mg Film coated tablets of Novartis Europharm Limited Frimley Business Park Camberley GU16 7SR United Kingdom in normal healthy adult human subjects under fasting conditions. **Secondary objective:** To monitor the adverse events and to ensure the safety of the study subjects.	An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study.	Test Drug (T): Deferasirox film coated tablets 360 mg, oral Reference Drug (R): Exjade® (deferasirox) 360 mg Film coated tablets, oral	Planned - 40 subjects+ A maximum of 02 additional subjects Enrolled - 40 subjects+ 01 additional subject (standby-I) Dosed: Period-1: 40 Subjects Period-2: 38 Subjects Completed - 38 subjects Withdrawn: 02 subjects (subject numbers 01 & 06) Bio-sample analyzed – 38 Subjects Pharmacokinetic and statistical data analyzed – 37 subjects	Healthy, adult, human male subjects	Single-dose	Complete Abbreviated
BE	Project No. C18443	Clinical Study Report & PK Report and Adverse Event Listing **Clinical Study (5.3.1.2)** Bioanalytical Report **Bioanalytical (5.3.1.4)** CRFs and Individual Subjects **Individual CRF (5.3.7)** Literature References **Literature References (5.4)**	Primary Objective was to evaluate the oral bioequivalence of Deferasirox film coated tablets 360 mg of Mylan Laboratories Limited, India with Exjade® (deferasirox) 360 mg filmovertrukne tabletter deferasirox of Novartis Europharm Limited, Frimley Business Park, Camberley GU16 7SR, storbritannien, bretland, storbritannia in normal healthy adult human subjects under fasting conditions. Secondary Objective was to monitor the adverse events and to ensure the safety of the subjects.	A randomized, balanced, two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study in normal healthy adult human subjects under fasting conditions.	Test Drug (T): Deferasirox film coated tablets 360 mg, 1 x 360 mg, oral. Reference Drug (R): Exjade® 360 mg filmovertrukne tabletter, 1 x 360 mg, oral	Planned - 34 subjects + A maximum of 02 additional subjects, Enrolled - 34 subjects + 02 additional subjects (standby-I & standby-II). Dosed: Period-1: 34 subjects Period-2: 33 subjects Completed - 33 subjects. Withdrawn: 01 subject (subject number 25) Bio-sample analyzed – 33 Subjects Pharmacokinetic and statistical data analyzed - 33 subjects.	Healthy, adult, human subjects	Single-dose	Complete; Abbreviated
PK	Not Applicable								
PD	Not Applicable								
Efficacy	Not Applicable								

2.4.2. Pharmacokinetics

Study C17305: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study of Deferasirox film coated tablets 360 mg of Mylan Laboratories Limited, India with Exjade® (deferasirox) 360 mg Film coated tablets of Novartis Europharm Limited in normal healthy adult human subjects under fasting conditions.

Methods

Study design

Study C17305 was an open-label, randomized, balanced, single dose, two-period, two-treatment cross-over bioequivalence study in healthy adult human subjects under fasting conditions with a wash-out period of 7 days between the two administrations. The single oral dose of 360 mg film-coated tablet Test (treatment A) or Reference product (treatment B) was administered after 10.00 hours overnight fasting. Blood collections were performed 1.5 hour prior to the administration of study medication (0.00 hour – pre-dose) and post dose at 0.25, 0.50, 0.75, 1.00, 1.333, 1.667, 2.00, 2.333, 2.667, 3.00, 3.333, 3.667, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours in pre labelled K_3EDTA vacutainers.

Study periods:

Period I: 27 November 2017 (check-in) – 01 December 2017 (72h blood draw)

Period II: 04 December 2017 (check-in) – 08 December 2017 (last blood draw)

Test and reference products

Product Characteristics	Test Product	Reference Product
Name	Deferasirox film coated tablets 360 mg	Exjade® 360 mg filmovertrukne tabletter deferasirox
Strength	360 mg	360 mg
Dosage Form	Film coated Tablets	Film coated Tablets
Manufactured by	**Manufactured by:** Mylan Laboratories Limited	**Manufactured For:** Novartis Europharm Limited, Frimley Business Park, Camberley GU16 7SR, storbritannien, bretland, storbritannia.
Batch number/ Lot number	8062747	WP827
Batch Size (Biobatch)	150,000	Not available
Measured Content(s) (% of Label Claim)	99.9 % w/w	98.7 % w/w
Commercial Batch Size	Not applicable	Not available
Expiry Date	Dec 2018	01.2020
Location of Certificate of Analysis	5312-compar-ba-be-stud-rep, Appendix-16.1.7	5312-compar-ba-be-stud-rep, Appendix-16.1.7
Member State where the reference product is purchased from:	Not applicable	EU
This product was used in the following trials:	Study no.:C17305	Study no.:C17305

Population studied

The study population included healthy, non-smoking male volunteers aged between 18 to 45 years (included), with a body mass index (BMI) of ≥ 18.5 kg/m^2 and ≤ 30.0 kg/m^2 and weight ≥ 50.00 kg. The sample size calculation was properly conducted, the choice of population size was N=40. Two subjects were withdrawn, thus 38 subjects completed the study.

Protocol deviations/violations: one protocol deviation occurred during the study period, inclusion/exclusion of subject No. 31 due to loose motion in period 2 post-dose. The study validity remained unaffected.

Analytical methods

The plasma samples of subjects were analysed using LC/MS/MS method for Deferasirox in Human Plasma using High Performance and Ultra Performance Liquid Chromatography Method with Tandem mass spectrometry over a Concentration range of 0.250 µg/mL lower limit of quantification (LLOQ) to 32.618 µg/mL upper limit of quantification (ULOQ).

Bioanalytical assay: 13 December 2017 – 21 December 2017.

The analytical method for the determination of deferasirox in human plasma was validated. The validation, partial validations and analytical reports were submitted. CoAs of internal standards and analyte standard were presented. Stability of analyte in the plasma samples has been demonstrated. The reanalysis using incurred samples confirmed the reproducibility of study samples used in validated bioanalytical method.

During the bioanalysis 299 samples (15.82%) had to be reanalysed because of "QCs did not meet the acceptance criteria". Both assay methods were validated, and appropriate incurred sample reanalysis indicated that using UPLC and HPLC technique was acceptable as well.

The bioequivalence results were based on free deferasirox, in line with the requirement as the evaluation should be based on the parent compound.

Pharmacokinetic variables

Primary Variables:

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 Variables:

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

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

K_{el}: apparent first-order elimination or terminal rate constant calculated from a semi-log plot of the plasma concentration versus time curve.

$t_{1/2}$: the elimination or terminal half-life is calculated as $0.693/K_{el}$.

$AUC_{\_\%Extrap\_obs}$.: The residual area in percentage was determined by the formula $[(AUC_{0-inf} - AUC_{0-t})/ AUC_{0-inf}] \times 100$

The actual time of blood sample collection were used for estimation of pharmacokinetic parameters, using non-compartmental model of Phoenix® WinNonlin® version 6.3.

Statistical methods

Statistical analysis was performed on the data obtained assaying concentration of deferasirox in the plasma samples collected, using SAS® Software (Version 9.2); SAS Institute Inc., USA, actual time of blood sample collection were used for estimation of pharmacokinetic parameters, which was computed using non-compartmental model of Phoenix® WinNonlin® version 6.3.

Descriptive statistics were computed for all primary pharmacokinetic parameters.

The ln-transformed pharmacokinetic parameters C_{max} AUC_{0-t} and AUC_{0-inf} for Deferasirox were subjected to Analysis of Variance (ANOVA). The model was including Sequence, Formulation, Period and Subject (Sequence) as fixed effects. Sequence effect was tested using Subject (Sequence) as error term. An F-test was performed to determine the statistical significance of the Formulation and Period effects involved in the model at a significance level of 5% (alpha= 0.05) and Sequence effect involved in the model at a significance level of 10% (alpha= 0.10).

Bioequivalence criteria: Bioequivalence of the test product with that of the reference product under fasting condition was concluded if the 90% confidence intervals of geometric least square mean ratio of the test to reference product falls within the acceptance range of 80.00 % – 125.00% for C_{max} and AUC_{0-t} for deferasirox.

Although not pre-specified in the analysis plan, the results of the study have been presented with inclusion and also with exclusion of subject No. 31 who developed loose motion.

Results

Pivotal Study C17305

Pharmacokinetic measurements assessed were based on the parameters derived from the plasma concentration versus time data of 38 subjects who completed the clinical phase. The first statistical analysis was performed with inclusion of the subject No. 31 (loose motion in period 2 post-dose).

Table 2. Pharmacokinetic parameters for deferasirox, n=38 (non-transformed values)

Pharmacokinetic parameter n=38	**Test**		**Reference**	
	arithmetic mean geometric mean	**SD CV%**	**arithmetic mean geometric mean**	**SD CV%**
$AUC_{(0-t)}$ (µg.hr/mL)	**228.674** 218.759	± 70.5203 30.8	218.676 210.358	± 62.8184 28.7
$AUC_{(0-\infty)}$ (µg.hr/mL)	**236.574** 226.415	± 72.6629 30.7	226.113 217.877	± 63.6923 28.2
C_{max} (µg/mL)	**21.317** 20.697	± 4.6760 21.9	20.641 20.236	± 4.2178 20.4
T_{max}*(hr)	**3.667**	1.000 – 4.500	3.333	1.000 – 5.000
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 3. Statistical analysis for deferasirox, n=38 (ln-transformed values)

Pharmacokinetic parameter	**Geometric Mean Ratio Test/Reference**	**Confidence Intervals**	**CV%***
$AUC_{(0-t)}$ (µg.hr/mL)	**103.99 %**	**99.90 – 108.25 %**	**10.4**
C_{max} (µg/mL)	**102.28 %**	**96.23 – 108.71 %**	**15.8**
*** estimated from the Residual Mean Squares**			

Although 38 subjects completed the clinical phase of the study, after the first statistical analysis subject No. 31 was excluded from the PK and statistical analysis due to adverse event (loose motion in period 2 post-dose). The applicant presented the data with exclusion of this subject as well.

Table 4. Pharmacokinetic parameters for deferasirox (non-transformed values)

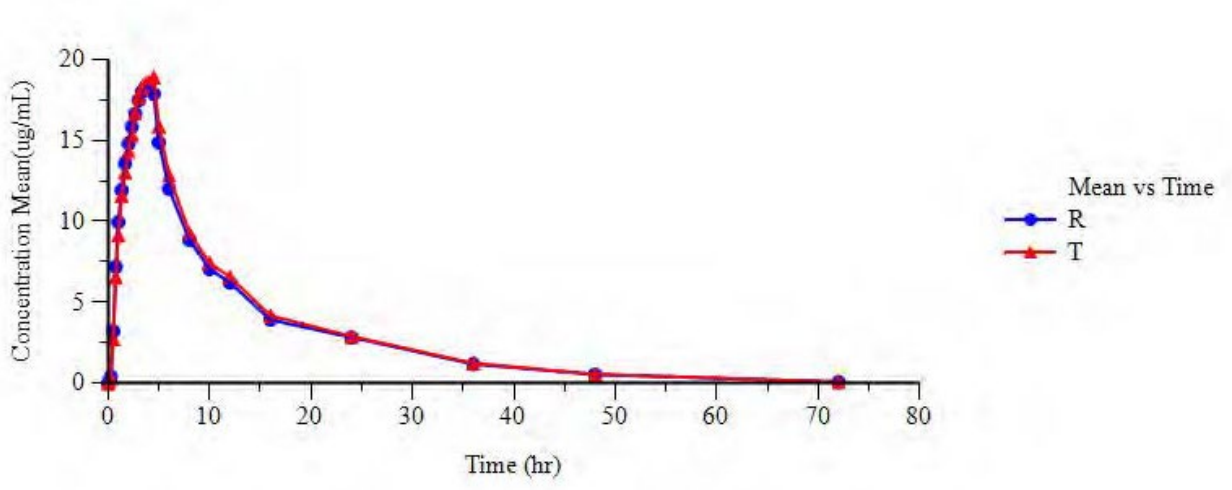
Pharmacokinetic parameter n=37	**Test**		**Reference**	
	arithmetic mean geometric mean	**SD CV%**	**arithmetic mean geometric mean**	**SD CV%**
$AUC_{(0-t)}$	**225.085**	±67.6729	216.512	±62.2914

Pharmacokinetic	**Test**		**Reference**	
(µg.hr/mL)	215.847	30.1%	208.362	28.8%
$AUC_{(0-\infty)}$	**233.041**	±70.0330	223.875	±63.0538
(µg.hr/mL)	223.512	30.1%	215.826	28.2%
C_{max} (µg/mL)	**21.221**	±4.7017	20.448	±4.1014
	20.594	22.2%	20.063	20.1%
T_{max}*(hr)	**3.667**	1.000 – 4.500	3.333	1.000 – 5.000
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

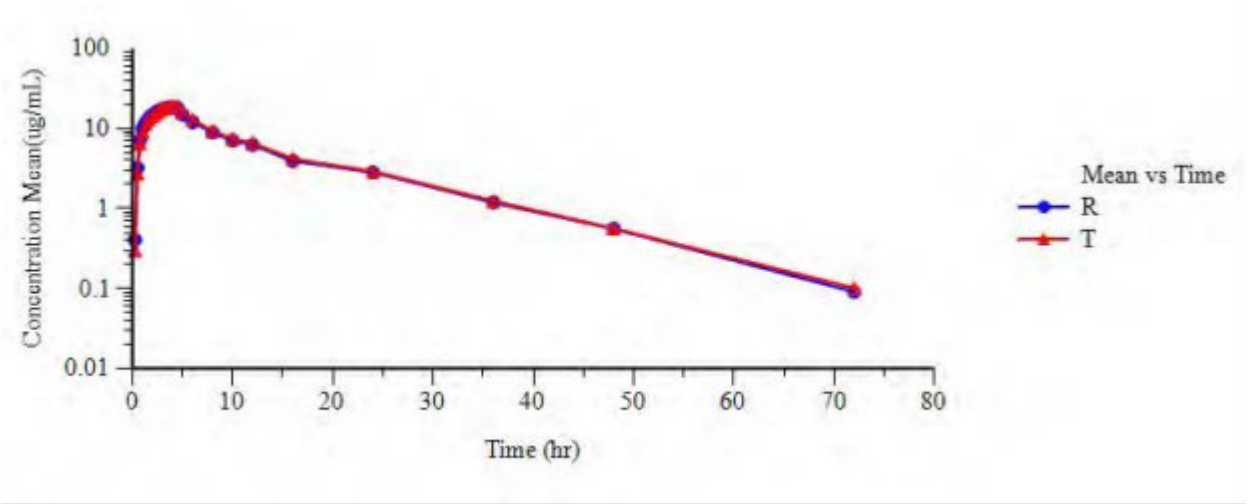
Table 5. Statistical analysis for deferasirox PK parameters, n=37 (ln-transformed values)

Pharmacokinetic parameter	**Geometric Mean Ratio Test/Reference**	**Confidence Intervals**	**CV%***
$AUC_{(0-t)}$ (µg.hr/mL	103.76 %	99.57 – 108.12 %	10.5
C_{max} (µg/mL)	102.84 %	96.65 – 109.42 %	15.9
* estimated from the Residual Mean Squares			

Linear plot (n=37):



Semi-log plot (n=37):



Supportive PK study No. C18443 (submitted as part of responses to the LoQ)

This is a randomized, balanced, two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study of Deferasirox film coated tablets 360 mg of Mylan Laboratories Limited, India with Exjade® (deferasirox) 360 mg filmovertrukne tabletter deferasirox of Novartis Europharm Limited, Frimley Business Park, Camberley GU16 7SR, UK, in normal healthy adult human subjects under fasting conditions.

The objective of the study was to evaluate oral bioequivalence of Test and Reference deferasirox products in thirty four subjects. Two experimental sessions were respectively undertaken from 18/12/2018 to 22/12/2018 (period-1), and from 26/12/2018 to 30/12/2018 (period-2). In each period, all subjects were required to fast overnight for at least 10.00 hours prior to dosing. On dosing day, approximately weighed 10 grams of apple sauce was dispensed on the spoon at least 3 hours prior to dosing and kept aside. A single oral dose of either Test or Reference tablet was crushed using a mortar and pestle. This crushed tablet was sprinkled over a spoonful of apple sauce and administered to the subjects with 240 mL of ambient temperature water.

Blood samples were collected for 72 hours in each period, and minimum of eight days washout interval was kept between the two periods. All plasma samples were stored at a temperature of -70°C at the clinical site until transferred on dry ice to analytical site.

Bioequivalence was concluded if the 90% confidence intervals of geometric least square mean ratio of the T/R product fell within the acceptance range of 80.00 % – 125.00% for C_{max} and AUC_{0-t} for Deferasirox. Primary log-transformed pharmacokinetic results are presented in Table 3.3.7.

Table 6. Statistical analysis for deferasirox PK parameters in study No. C18443, n=33 (ln-transformed values)

Pharmacokinetic parameter	**Geometric Mean Ratio Test/Reference**	**Confidence Intervals**	**CV%***
$AUC_{(0-t)}$ (µg.hr/mL)	97.48 %	93.68 – 101.45 %	9.6
C_{max} (µg/mL)	96.61 %	92.12 – 101.32 %	11.4
* estimated from the Residual Mean Squares			

Both the Geometric mean ratio and the Confidence interval were within the prespecified range for the primary PK parameters. Based on the results of this bioequivalence study with **crushed** deferasirox 360

mg film-coated tablets the **Test product met the bioequivalence criteria to Reference product** with regard to rate and extent of absorption under fasting conditions consumed with apple sauce.

According to PKWP's proposal, although bioequivalence of crushed Test and Reference products was justified, this study can only be considered as a supporting one. The applicant has demonstrated that the Reference product has the same lot number (WP827) as in the pivotal study, and the medicinal product has been authorised in the EU (EU/1/06/356/018).

Safety data

No serious adverse events were observed during the study C17305. By four subjects a total of six adverse events were reported over the course of the study, one AE during period-2 in-house and five events during post study safety evaluation.

All of the reported adverse events were mild in severity and possibly related to the study drug.

The details of AEs from the pivotal trial are presented in table 7 (Display of adverse events).

Table 7. Display of adverse events

Sub. No.	Treatment group	Study period	Adverse Event	MedDRA PT Term	SOC Term & Code	Dosing (Time & date)	Onset (Time & date)	Resolution (Time & date)	Severity	Causality	Concomitant medication given
31	T	Period-2	Loose motions	Diarrhoea, 10012735	Gastrointestinal disorders, 10017947	08:08 & 05 Dec 2017	11:14 & 05 Dec 2017	21:15 & 05 Dec 2017	Mild	Possible	Tab .SPORLAC-DS 2 in number not less than 240 million spores, orally with Batch No: DSTH16022, Exp. date: MAR 2018.
02	N/A	Post study	Increased WBC	White blood cell count increased, 10047943	Investigations, 10022891	N/A	08:57 & 08 Dec 2017	*N/A	Mild	Possible	Nil
02	N/A	Post study	Decreased ferritin	Serum ferritin increased, 10040250	Investigations, 10022891	N/A	08:57 & 08 Dec 2017	*N/A	Mild	Possible	Nil
15	N/A	Post study	Decreased ferritin	Serum ferritin increased, 10040250	Investigations, 10022891	N/A	09:51 & 08 Dec 2017	*N/A	Mild	Possible	Nil
32	N/A	Post study	Increased eosinophils	Eosinophil percentage increased, 10052222	Investigations, 10022891	N/A	08:06 & 08 Dec 2017	16:06 & 20 Jan 2018	Mild	Possible	Nil
32	N/A	Post study	Increased eosinophils (ABS)	Eosinophil count increased, 10014945	Investigations, 10022891	N/A	08:06 & 08 Dec 2017	16:06 & 20 Jan 2018	Mild	Possible	Nil

T: Test product, N/A: Not applicable, MedDRA: Medical Dictionary for Regulatory activities Version 20.1, SOC: System Organ Class. *N/A: Subject post study AE was considered as lost to follow up.

The requested data about the subjects' laboratory parameters and vital signs were provided by the applicant.

Conclusions

Based on the presented bioequivalence studies Deferasirox Mylan is considered bioequivalent with Exjade.

The results of study C17305 with the 360mg formulation can be extrapolated to other strengths, 90 mg and 180 mg, according to conditions in the Guidelines and following the in-vitro dissolution tests submitted.

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

The submitted bioequivalence study was considered relevant to support the generic documentation of the Deferasirox Mylan film-coated tablets. The study seemed adequately designed considering the number of randomized subjects, wash-out period, sampling periods, test and reference products. A pre-dose level was not detected in any samples, thus it can be concluded that the wash-out period was long enough to avoid carry-over effect. C_{max} was not observed in any subject in the first sample point. The point estimates and 90% confidence intervals for the ln-transformed pharmacokinetic variables C_{max} and AUC were within the conventional bioequivalence range of 80.00% - 125.00%. The sponsor presented PK and statistical report by including and with excluding subject No. 31 as well. The applicant showed that inclusion of subject No 31 did not have significant impact on the study results. Even if loose motion was not pre-defined as exclusion criteria in the protocol, leaving out subject No 31 from pharmacokinetic and statistical analysis seems to be acceptable.

ANOVA detected significant period effect for the log-transformed $AUC_{(0-t)}$ (p=0.0184) and $AUC_{(0-inf)}$ (p=0.0340). The applicant ruled out reasons like different positioning, timing and degree of physical activity, timing and composition of food/beverages ingested and explained the issue with possibility of different psychological status of the subjects that could lead to effect on blood concentration data. Nevertheless this significant period effect was not expected by the applicant to influence the comparison of test and reference products using 90% confidence interval. The applicant was requested to discuss further the influence of this significant period effect on the study outcome.

The applicant has adequately discussed that the decrease in intra-subject variability can lead to the increase of study power, hence the sensitivity of statistical tests may also increase. Consequently, the small differences between the periods may become significant. This explanation of the phenomenon seems to be acceptable and it can be concluded that the observed significant period effects in AUC-s have no influence on the outcome of the bioequivalence study.

Although, in principle, study C17305 could be considered sufficient to demonstrate the essential similarity between the Test and Reference products, there were some issues that needed to be resolved by the applicant. Taking into consideration the mode of administration described in the reference product SmPC, for patients suffering from swallowing difficulties, the tablets can be administered crushed and dispersed with food. Consequently, the applicant had to justify and demonstrate by appropriate *in vitro* or *in vivo* data that the bioavailability of the active substance is not affected with this additional mode of administration namely crushed and dispensed with light meal (apple sauce or yogurt).

The results of the newly conducted bioequivalence study (No. C18443) with crushed tablets administered with apple sauce indicate that this mode of administration does not have significant impact on the bioavailability of deferasirox, the increase in t_{max} and $t_{1/2}$ parameters seems negligible as well. Thus, crushed deferasirox 360 mg film-coated tablets Test product met the bioequivalence criteria to crushed 360 mg film-coated tablets Reference product with regard to rate and extent of absorption under fasting conditions when consumed with apple sauce. Moreover, line extension studies of Exjade (procedure X/43 film-coated tablets) justified that administration of film-coated tablets in crushed form with applesauce or in yoghurt results in comparable absorption. The applicant demonstrated that administration of crushed deferasirox film-coated tablets in apple sauce does not have a significant impact on the bioavailability of deferasirox, as compared to the intact deferasirox 360 mg film-coated tablets.

CHMP-PKWP provided the following input on PK

The applicant has addressed the possibility of 'crushing' by submitting an additional bioequivalence study comparing Test and Reference taken in crushed with apple sauce. Bioequivalence has been demonstrated, confirming that qualitative formulation differences did not result in different biopharmaceutic performance when crushed products where compared in vivo. As expressed in the respective recently revised PKWP Q&A document (Q & A 3.6 at https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/clinical-pharmacology-pharmacokinetics-questions-answers), this may be considered an expected outcome given already demonstrated bioequivalence with intact products.

In addition, in order to unequivocally prove similar *in vitro* behaviour of the test and reference products and accept the biowaiver for the lower strengths, comparison of the reference product to the respective 90 mg and 180 mg test products was requested, confirming that low dissolution is drug substance rather than formulation related (without surfactant). Furthermore, concerning the acceptability of the alternative administration for the lower strengths in relation to the SmPC of the originator, which allows administration of crushed tablets, comparative disintegration times of the test and reference intact tablets were also asked to be provided.

The observed significant period effect in AUCs' and their influence on the outcome of the bioequivalence study was discussed, considering that the decrease in intra-subject variability can lead to the increase of study power, hence increasing the sensitivity of statistical tests. Consequently, the small differences between the periods may become significant. The explanation and the conclusion of the applicant "as the observed significant period effect in AUC's did not impact on the study outcome" was considered acceptable.

During the bioanalysis, 299 samples (15.82%) had to be reanalysed because of "QCs did not meet the acceptance criteria". As per the explanation, the re-assay of the mentioned samples (299) were in accordance with the predefined SOP "CRC-SOP-BIO-TEC-0001" criteria. Due to gradual decrease the QC runs failed, and it was noted, that repeat analytical run versus original failed analytical run showed almost similar differences in the concentration data as in the QC's samples. The procedure of re-assay seems acceptable.

HPLC and UPLC were also used for the bioanalysis. Both assay methods were validated, and appropriately incurred sample reanalysis indicated that using UPLC and HPLC technique is acceptable as well. The applicant provided the case report forms of study subjects, and the accurate documentation of the medicine concomitantly administered a few hours after intake of the 2nd period investigation drug in patient No.31 reporting loose motion. All necessary data about the medication and further observation were detailed. Handling of this patient during the study seemed to be appropriate.

Further data about the subjects' laboratory parameters and vital signs were presented by the applicant.

The lower pre-study Creatinine clearance was not considered remarkable by the principal investigator of Subject No 31 (who had loose motions and was partly excluded from the statistical analyses). Based on the SmPC of the originator (Exjade®): "*During clinical studies, increases in serum creatinine of >33% on ≥2 consecutive occasions, sometimes above the upper limit of the normal range, occurred in about 36% of patients."*

Thus the slight increase in post-study creatinine level in this patient does not seem to have a clinical relevance either.

A total of three post study adverse events were reported by three subjects over the course of study No. C18443. These laboratory parameter deviations (Eo count / ALAT / Blood bilirubin increased) were mild in severity and possibly related to the study drug, however, the subjects were not interested to come for repeated safety sample collection therefore were considered as lost to follow-up.

The applicant confirmed that only free form of deferasirox was measured in the plasma samples which is in line with the guideline.

2.4.6. Conclusions on clinical aspects

To support this application, the applicant originally submitted one successful bioequivalence study (study C17305) with intact tablets, and in the LoQ response document one study with crushed tablets taken with apple sauce (study C18443) both in fasting conditions.

For the originator, the effect of food on the bioavailability of deferasirox has been demonstrated to be (i) formulation dependent and (ii) divergent dependent on the fat content of the meal. Since the formulation of the proposed Deferasirox Mylan film-coated tablets differs from that of the originator's film-coated tablets, the applicant provided an additional study to demonstrate similarity of the food effect. Based on the submitted data, light meal (apple sauce, yoghurt) has no influence on the bioavailability of Deferasirox Mylan 360 mg film-coated tablets, or of the Reference product. Bioequivalence criteria were met in study C18443, and the data sufficiently support the claim of essential similarity of tested crushed Deferasirox Mylan to the crushed reference medicinal product Exjade.

The CHMP considers that Deferasirox Mylan 360 mg, 180 mg and 90 mg film-coated tablets are approvable from a pharmacokinetic point of view.

2.5. Risk management plan

Safety concerns

Summary of safety concerns	
Important identified risks	Renal disorders (increased serum creatinine, acute renal failure, renal tubular disorders [acquired Fanconi's syndrome]) Increased liver transaminases / Hepatic failure Gastrointestinal hemorrhage and ulcers; esophagitis Hearing loss Lens opacities, retinal changes and optic neuritis Severe cutaneous adverse reactions (including Stevens-Johnson syndrome, Toxic epidermal necrolysis and Drug reaction with eosinophilia and systemic symptoms)
Important potential risks	Compliance with posology and biological monitoring Medication errors
Missing information	Long term safety in paediatric NTDT patients aged 10 to 17years

Pharmacovigilance plan

Routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The applicant committed to include specific adverse reaction follow-up checklists for the following risks post-approval before launch of the product:
- Renal disorders (increased serum creatinine, acute renal failure, renal tubular disorders [acquired Fanconi's syndrome])
- Increased liver transaminases and Hepatic failure
- Gastrointestinal hemorrhage and ulcers; esophagitis
- Hearing loss
- Lens opacities, retinal changes, and optic neuritis
- Severe skin reactions

Routine pharmacovigilance is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified risks		
Renal disorders (increased serum creatinine, acute renal failure, renal tubular disorders (acquired Fanconi's syndrome))	**Routine risk minimization measures:** SmPC Section 4.2 Posology and method of administration, 4.3 Contraindications, and 4.4 Special warnings and precautions for use. Relevant terms are included as ADRs Section 4.8 Undesirable effects. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities** Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up using a targeted checklist **Additional pharmacovigilance activities:** None
Increased liver transaminases/Hepatic failure	**Routine risk minimization measures:** SmPC Section 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use. Relevant terms are included as ADRs Section 4.8 Undesirable effects. **Additional risk minimization measures**: None	**Routine pharmacovigilance activities:** Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up using a targeted checklist **Additional pharmacovigilance activities:** None
Gastrointestinal hemorrhage and ulcers; esophagitis	**Routine risk minimization measures:** SmPC Section 4.4 Special warnings and precautions for use, and 4.5 Interaction with other medicinal products and other forms of interaction. Relevant terms are included as ADRs in SmPC Section 4.8 Undesirable effects. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities:** Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up using a targeted checklist. **Additional pharmacovigilance activities:** None
Hearing loss	**Routine risk minimization measures**	**Routine pharmacovigilance activities:**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	SmPC Section 4.4 Special warnings and precautions for use. Relevant terms are included as ADRs in Section 4.8 Undesirable effects. **Additional risk minimization measures:** None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up using a targeted checklist **Additional pharmacovigilance activities:** None
Lens opacities, retinal changes and optic neuritis	**Routine risk minimization measures** SmPC Section 4.4 Special warnings and precautions for use, 5.3 Preclinical safety data. Relevant terms are included as ADRs in Section 4.8 Undesirable effects **Additional risk minimization measures:** None	**Routine pharmacovigilance activities:** Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up using a targeted checklist **Additional pharmacovigilance activities:** None
SCARs (including SJS, TEN and DRESS)	**Routine risk minimization measures**: SmPC Section 4.4 Special warnings and precautions for use. Relevant terms are included as ADRs Section 4.8 Undesirable effects. **Additional risk minimization measures:** None	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: SJS/TEN Follow-up using a targeted checklist. DRESS None. **Additional pharmacovigilance activities:** None
Important potential risks		
Compliance with posology and biological monitoring	**Routine risk minimization measures:** SmPC Section 4.2 Posology and method of administration and 4.4 Special warnings and precautions for use. **Additional risk minimization**	**Routine pharmacovigilance activities:** Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None **Additional pharmacovigilance**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	measures: Educational materials for physicians and patients	**activities:** For the originator: Physician survey
Medication error	**Routine risk minimization measures:** SmPC Section 4.2 Posology and method of administration. **Additional risk minimisation measures:** Educational materials for physicians and patients	**Routine pharmacovigilance activities:** Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None **Additional pharmacovigilance activities:** For the originator: Physician survey
Missing information		
Long term safety in paediatric NTDT patients aged 10 to 17 years	**Routine risk minimization measures:** SmPC Section 4.2 Posology and method of administration, 4.4 Special warning and precautions for use **Additional risk minimization measures:** None	**Routine pharmacovigilance activities:** Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None **Additional pharmacovigilance activities:** For the originator: Review of data from Study CICL670E2422

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 is acceptable.

The applicant made a commitment to provide an updated RMP with specific adverse reaction follow-up checklists post-approval. A variation shall be submitted to the Agency before the launch of the product.

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.

2.7.2. Additional monitoring

This product does not require additional monitoring.

3. Benefit-risk balance

This application concerns a generic version of deferasirox film-coated tablets. The reference product Exjade is indicated for the treatment of iron overload (see detailed indication). 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 an open-label, randomized, balanced, single dose, two-period, two-treatment cross-over design. 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 was adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Deferasirox Mylan met the protocol-defined criteria for bioequivalence when compared with 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.

4. Recommendation

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Deferasirox Mylan is not similar to Revlimid, Zynteglo within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Outcome

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

Deferasirox Mylan 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 Mylan 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 Mylan 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

Prior to launch of Deferasirox Mylan 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 Mylan is marketed, all healthcare professionals and patients who are expected to prescribe, dispense and use Deferasirox Mylan are provided with the following educational package:

- 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 Mylan
    - 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)