RISK MANAGEMENT PLAN
For
Deferasirox
Version 4.1

RMP Version to be Assessed as Part of this Application:

RMP Version Number	4.1
Data Lock Point for this RMP	31-Jan-2024
Date of Final Sign Off	14-May-2024
Rationale for Submitting an Updated RMP	RMP updated in line with Exjade RMP version 21.2 published on 31-Jan-2024 on the EMA website and CHMP - PRAC joint assessment report, following response to RSI, dated 08-May-2024
Summary of Significant Changes in this RMP	The following significant changes were made in the current RMP: • RMP updated in line with Exjade RMP version 21.2 published on 31-Jan-2024 on the EMA website. • RMP updated in line with CHMP - PRAC joint assessment report, following response to RSI, dated 08-May-2024

Other RMP Versions Under Evaluation:

RMP Version Number	4.0
Submitted On	12-Apr-2024
Procedure Number	EMEA/H/C/005014 R/0013

Details of the Current RMP:

Version Number	3.0
Approved with Procedure	EMEA/H/C/005014
Date of Approval (Opinion Date)	22-Apr-2022

Approver	Dr. Eiko Soehlke, MD MPH, EEA QPPV
Signature	RMP has been reviewed and approved by the marketing authorisation applicant's QPPV and that the electronic signature is on file.
E-mail address of contact person	PV.RMP@Viatris.com

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical Classification System
CHMP	Committee for Medicinal Products for Human Use
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures – Human
CrCl	Creatinine clearance
DCP	Decentralised Procedure
DDD	Daily Defined Dose
DHPC	Direct Healthcare Professional Communication
DLP	Data Lock Point
DT	Dispersible tablets
dw	Dry weight
EEA	European Economic Area
EPAR	European Public Assessment Report
EU	European Union
EURD	European Union Reference Date
FCT	Film coated tablets
HCP	Healthcare Professional
ICSR	Individual Case Safety Report
LIC	Liver iron concentration
LLN	Lower limit of normal
MAA	Marketing Authorization Applicant
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRP	Mutual Recognition Procedure
NTDT	Non-Transfusion- Dependent Thalassemia
PAC	Patient Alert Card
PL	Package Leaflet
POM	Prescription only medicine
PPP	Pregnancy Prevention Programme
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PTC	Patient Treatment Course
PTD	Patient Treatment Days
PTM	Patient Treatment Months
PTY	Patient Treatment Years
PVA	Pharmacovigilance Agreement
QPPV	Qualified Person for Pharmacovigilance
SCD	Sickle cell disease
SmPC	Summary of Product Characteristics
ULN	Upper limit of normal
WHO	World Health Organization

PART I: PRODUCT(S) OVERVIEW

Table 1: Part 1.1-Product Overview

Active Substance(s) (INN or Common Name)	Deferasirox
Pharmacotherapeutic Group(s) (ATC Code)	ATC code: V03AC03 Pharmacotherapeutic group: Iron chelating agents
Marketing Authorisation Holder	Mylan Pharmaceuticals Ltd.
Medicinal Products to Which this RMP Refers	1
Invented Name(s) in the European Economic Area (EEA)	Deferasirox Mylan 90 mg film-coated tablets Deferasirox Mylan 180 mg film-coated tablets Deferasirox Mylan 360 mg film-coated tablets
Marketing Authorisation Procedure	EMEA/H/C/005014
Brief Description of the Product	Deferasirox is an orally active chelator that is highly selective for iron (III). It is a tridentate ligand that binds iron with high affinity in a 2:1 ratio. Deferasirox promotes excretion of iron, primarily in the faeces. Deferasirox has low affinity for zinc and copper and does not cause constant low serum levels of these metals.
Hyperlink to the Product Information:	PI available in section 1.3.1 of the dossier
Indication(s) in the EEA (Current)	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-

<table>
<tr><td></td><td>transfusion-dependent thalassaemia syndromes aged 10 years and older.</td></tr>
<tr><td>Dosage in the EEA (Current)</td><td>Route of administration: per oral (PO)
<u>Transfusional iron overload</u>
It is recommended that treatment be started after the transfusion of approximately 20 units (about 100 ml/kg) of packed red blood cells (PRBC) or when there is evidence from clinical monitoring that chronic iron overload is present (e.g. serum ferritin >1,000 µg/l). Doses (in mg/kg) must be calculated and rounded to the nearest whole tablet size.

<u>Non-transfusion-dependent thalassaemia syndromes</u>
Chelation therapy should only be initiated when there is evidence of iron overload (liver iron concentration [LIC] ≥5 mg Fe/g dry weight [dw] or serum ferritin consistently >800 µg/l). LIC is the preferred method of iron overload determination and should be used wherever available. Caution should be taken during chelation therapy to minimise the risk of over-chelation in all patients (see section 4.4)

In the EU, medicines containing deferasirox are available as film-coated tablets and dispersible tablets marketed under different tradenames as generic alternatives of deferasirox. Due to different pharmacokinetic profiles, a 30% lower dose of deferasirox film-coated tablets is needed in comparison to the recommended dose for deferasirox dispersible tablets.
<u>The corresponding doses for both formulations are shown in the table below:</u>

Transfusional iron overload
<table>
<tr><th></th><th>Film-coated tablets</th><th>Dispersible tablets</th></tr>
<tr><td>Starting dose</td><td>14 mg/kg/day</td><td>20 mg/kg/day</td></tr>
<tr><td>Alternative starting doses</td><td>7 mg/kg/day
21 mg/kg/day</td><td>10 mg/kg/day
30 mg/kg/day</td></tr>
<tr><td>Adjustment steps</td><td>3.5 - 7 mg/kg/day</td><td>5 - 10 mg/kg/day</td></tr>
<tr><td>Maximum dose</td><td>28 mg/kg/day</td><td>40 mg/kg/day</td></tr>
</table></td></tr>
</table>

<table>
<tr><td></td><td>NTDT syndromes:
<table>
<tr><th></th><th>Film-coated tablets</th><th>Dispersible tablets</th></tr>
<tr><td>Starting dose</td><td>7 mg/kg/day</td><td>10 mg/kg/day</td></tr>
<tr><td>Adjustment steps</td><td>3.5 - 7 mg/kg/day</td><td>5 - 10 mg/kg/day</td></tr>
<tr><td>Maximum dose</td><td>14 mg/kg/day</td><td>20 mg/kg/day</td></tr>
</table>
Note: Dispersible tablet dosage details of above table are as per Exjade RMP</td></tr>
<tr><td>Pharmaceutical Form(s) and Strengths (Current)</td><td>Deferasirox Mylan 90 mg film-coated tablets
Deferasirox Mylan 180 mg film-coated tablets
Deferasirox Mylan 360 mg film-coated tablets</td></tr>
<tr><td>Is the Product Subject to Additional Monitoring in the EU?</td><td>No</td></tr>
</table>

PART II: SAFETY SPECIFICATION

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

Not applicable.

Part II: Module SII - Non-clinical Part of the Safety Specification

Not applicable.

Part II: Module SIII - Clinical Trial Exposure

Not applicable.

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Not applicable.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

Not applicable.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Not applicable.

Part II: Module SV - Post-authorisation Experience

Not applicable.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

Not applicable.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Viatris has an approved RMP for deferasirox generic medicine for procedure EMEA/H/C/005014.

Table 2: SVII- Summary of 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 haemorrhage 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 17 years

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

As per RMP version 3.0 (DLP 14-Dec-2021, sign off date 25-Jan-2022), safety concern Severe cutaneous adverse reactions (including Stevens-Johnson syndrome, Toxic epidermal necrolysis and Drug reaction with eosinophilia and systemic symptoms) previously classified as important identified risk was removed from the list of safety concerns as per the brand lead RMP (version 19.0, dated 02-Feb-2021, procedure EMEA/H/C/000670/II/0075) which stated that "*MAH has proposed to remove the risk of "Severe cutaneous adverse reactions (including Stevens-Johnson syndrome, Toxic epidermal necrolysis and Drug reaction with eosinophilia and systemic symptoms)" from the RMP considering that this risk is fully characterized, no additional PhV activities, no additional risk minimization activities in place and the clinical measures (drug interruption) are fully integrated into clinical practice and adequately communicated in the SmPC (Clinical Overview). Thus, Severe cutaneous adverse reactions no longer fully meets the Good Pharmacovigilance Practice (GVP) Module V revision 2 criteria for inclusion of an important identified risk I the RMP*".

In RMP Version 21.2 for reference product Exjade published on 31-Jan-2024 by the EMA: the important potential risk of 'medication errors' was revised to 'medication errors due to switching between Exjade FCT/granules and generic versions of deferasirox DT. The MAH is proposing to re-word the safety concern Medication errors accordingly – from "Medication errors" to "Medication errors due to switching between deferasirox FCT (film-coated tablet)/granules and generic versions of deferasirox DT (dispersible tablet)."

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Not applicable.

SVII.3.2. Presentation of the Missing Information

Not applicable.

Part II: Module SVIII - Summary of the Safety Concerns

Table 3: SVIII- 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 haemorrhage and ulcers; esophagitis • Hearing loss • Lens opacities, retinal changes and optic neuritis
Important Potential Risks	• Compliance with posology and biological monitoring • Medication errors due to switching between deferasirox FCT/granules and generic versions of deferasirox DT.
Missing Information	• Long term safety in paediatric NTDT patients aged 10 to 17 years

PART III: PHARMACOVILIGANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

The Pharmacovigilance System Master File contains details of the system and processes that the MAH has in place to identify and characterize the risks recognised in the safety specification.

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

In line with the originator RMP, the MAH has put in place Specific adverse reaction follow-up checklists for the following risks:

- Renal disorders (increased serum creatinine, acute renal failure, renal tubular disorders [acquired Fanconi's syndrome])
- Increased liver transaminases and Hepatic failure
- Gastrointestinal haemorrhage and ulcers; esophagitis
- Hearing loss
- Lens opacities, retinal changes, and optic neuritis

The forms are provided in Annex 4 - Specific Adverse Drug Reaction Follow-up Forms of the RMP.

III.2 Additional Pharmacovigilance Activities

As current routine pharmacovigilance activities are sufficient, no additional pharmacovigilance activities are recommended.

III.3 Summary Table of Additional Pharmacovigilance Activities

None.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMISATION MEASURES

The safety information in the proposed product information is aligned to the reference medicinal product (Exjade).

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table 4: Part V.1- Description of routine risk minimisation measures by safety concern

Safety Concern	Routine Risk Minimisation Activities
Important Identified Risks	
Renal disorders (increased serum creatinine, acute renal failure, renal tubular disorders [acquired Fanconi's syndrome])	**Routine risk communication**: SmPC section 4.2, 4.3, 4.4 and 4.8 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: This item is appropriately communicated through current labelling: SmPC Section 4.2 Posology and method of administration, Section 4.3 Contraindications, and Section 4.4 Special warnings and precautions for use. Relevant terms are included as ADRs in Section 4.8 Undesirable effects. **Other risk minimisation measures beyond the Product Information**: Medicine's legal status: Prescription only medicine (POM), to be used by experienced physicians in the approved indications.
Increased liver transaminases/Hepatic failure	**Routine risk communication:** SmPC sections 4.2, 4.4 and 4.8 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** This item is appropriately communicated through current labelling: SmPC Section 4.2 Posology and method of administration, Section 4.4 Special warnings and precautions for use. Relevant terms are included as ADRs in Section 4.8 Undesirable effects. **Other risk minimisation measures beyond the Product Information**: Medicine's legal status: POM, to be used by experienced physicians in the approved indications
Gastrointestinal haemorrhage and ulcers; esophagitis	**Routine risk communication**: SmPC sections 4.4, 4.5 and 4.8

Safety Concern	Routine Risk Minimisation Activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: This item is appropriately communicated through current labelling: SmPC Section 4.4 Special warnings and precautions for use, and Section 4.5 Interaction with other medicinal products and other forms of interaction. Relevant terms are included as ADRs in SPC Section 4.8 Undesirable effects. **Other risk minimisation measures beyond the Product Information:** Medicine's legal status: POM, to be used by experienced physicians in the approved indications
Hearing loss	**Routine risk communication**: SmPC sections 4.4 and 4.8 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: This item is appropriately communicated through current labelling: SmPC Section 4.4 Special warnings and precautions for use. Relevant terms are included as ADRs in Section 4.8 Undesirable effects. **Other risk minimisation measures beyond the Product Information**: Medicine's legal status: POM, be used by experienced physicians in the approved indications.
Lens opacities, retinal changes and optic neuritis	**Routine risk communication**: SmPC sections 4.4, 4.8 and 5.3 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: This item is appropriately communicated through current labelling: 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. **Other risk minimisation measures beyond the Product Information**: Medicine's legal status: POM, be used by experienced physicians in the approved indications.
Important Potential Risks	
Compliance with posology and biological monitoring	**Routine risk communication**: SmPC Section 4.2

Safety Concern	Routine Risk Minimisation Activities
	Section 4.4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** This item is appropriately communicated through current labelling: SmPC Section 4.2 Posology and method of administration and Section 4.4 Special warnings and precautions for use. **Other risk minimisation measures beyond the Product Information**: Medicine's legal status: POM, to be used by experienced physicians in the approved indications.
Medication errors due to switching between deferasirox FCT/granules and generic versions of deferasirox DT	**Routine risk communication**: SmPC Section 4.2 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: This item is appropriately communicated through current labelling: SmPC Section 4.2 Posology and method of administration. **Other risk minimisation measures beyond the Product Information**: Medicine's legal status: POM, to be used by experienced physicians in the approved indications.
Missing Information	
Long term safety in paediatric NTDT patients aged 10 to 17 years	**Routine risk communication**: SmPC Section 4.2 Section 4.4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** This item is appropriately communicated through current labelling: SmPC Section 4.2 Posology and method of administration, and Section 4.4 Special warnings and precautions for use. **Other risk minimisation measures beyond the Product Information**: Medicine's legal status: POM, to be used by experienced physicians in the approved indications.

V.2 Additional Risk Minimisation Measures

This medicine has additional risk minimisation measures for the following risks:

- Compliance with posology and biological monitoring
- Medication errors due to switching between deferasirox FCT/granules and generic versions of deferasirox DT

The additional risk minimisation measures consist of:

- Educational materials for HCPs and patients

Objectives of Additional Risk Minimisation Activities:

To address the risk of "Compliance with posology and biological monitoring" and "Medication errors due to switching between deferasirox FCT/granules and generic versions of deferasirox DT", the applicant proposes HCP and Patient/Carer Guide to educate HCPs and patients/caregivers about specific risks and their early symptoms and the best course of action to be taken when these appear, beyond the recommendation contained in the Product Information.

Rationale for the Additional Risk Minimisation Activity:

In line with the reference product RMP, the MAH considers it is necessary to:
- educate HCPs and patients/caregivers about the appropriate dosing (including dose adjustment requirements in case of switch between Deferasirox FCT/granules and generic versions of deferasirox DT) and biological monitoring.
- provide a prescribing decision tool for physicians to support calculation of appropriate posology and tracking of biological monitoring (physicians' checklist).

Target Audience and Planned Distribution Path:

HCP/patients/carers

Plans for Evaluating the Effectiveness of the Interventions and Criteria for Success:

Effectiveness of risk minimisation measures for the safety concern will be measured by routine pharmacovigilance activities during PSUR preparation, as per the EURD list (if applicable) and signal detection activity as per internal procedures.

Results of Effectiveness Evaluation

After evaluation of all information available to Viatris within the period from 26-Sep-2022 to 25-Sep-2023, including ICSRs from Viatris' global safety database, global literature, PSUR outcome, outcome of signal detection activities, health authority websites, results of interventional and non-interventional studies and EudraVigilance data, no new significant data have become available that may change the safety or benefit-risk profile of deferasirox. The risk minimization measures in place for this product are considered adequate and no further actions are needed for the time being.

Rationale for Proposing to Remove Additional Risk Minimisation Measures:

Not applicable.

V.3 Summary Table of Pharmacovigilance and Risk Minimisation Activities by Safety Concern

Table 5: Part V.3- Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

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 minimisation 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 minimisation 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 haemorrhage 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 Section 4.8 Undesirable effects. **Additional risk minimisation 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 minimisation 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, and 5.3 Preclinical safety data. Relevant terms are included as ADRs Section 4.8 Undesirable effects. **Additional risk minimisation 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
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 minimisation measures:** Educational materials for physicians (which also includes a physicians' checklist) and patients regardless of indication.	Routine pharmacovigilance activities **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None
Medication errors due to switching between deferasirox FCT/granules and generic versions of deferasirox DT	**Routine risk minimization measures**: SmPC Section 4.2 Posology and method of administration. **Additional risk minimisation measures**: Educational materials for physicians (which also includes a physicians' checklist) and patients clarifying the dose	Routine pharmacovigilance activities **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	adjustment requirements in case of switch between deferasirox FCT/granules and generic versions of deferasirox DT.	
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**: None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Deferasirox Mylan film-coated tablets (Deferasirox)

This is a summary of the risk management plan (RMP) for Deferasirox Mylan film-coated tablets. The RMP details important risks of deferasirox, how these risks can be minimised, and how more information will be obtained about deferasirox' s risks and uncertainties (missing information).

Deferasirox Mylan film-coated tablet's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how it should be used.

This summary of the RMP for Deferasirox Mylan film-coated tablets should be read in the context of all the information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Deferasirox Mylan film-coated tablet's RMP.

I. The Medicine and What it is Used For

Deferasirox 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 film-coated tablets 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 film-coated tablets 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.

It contains deferasirox as the active substance and it is given by oral route of administration. In case of switching patients between deferasirox FCT/granules and generic versions of deferasirox DT, the dose of the deferasirox FCT/granules should be adjusted. The corresponding doses for both formulations are shown in the table below:

Transfusional iron overload

	Film-coated tablets	**Dispersible tablets**
Starting dose	14 mg/kg/day	20 mg/kg/day
Alternative starting doses	7 mg/kg/day	10 mg/kg/day

	21 mg/kg/day	30 mg/kg/day
Adjustment steps	3.5 - 7 mg/kg/day	5 - 10 mg/kg/day
Maximum dose	28 mg/kg/day	40 mg/kg/day

NTDT syndromes:

	Film-coated tablets	**Dispersible tablets**
Starting dose	7 mg/kg/day	10 mg/kg/day
Adjustment steps	3.5 - 7 mg/kg/day	5 - 10 mg/kg/day
Maximum dose	14 mg/kg/day	20 mg/kg/day

Note: Dispersible tablet dosage details of above table are as per Exjade RMP

Further information about the evaluation of Deferasirox Mylan film-coated tablets' benefits can be found in Deferasirox Mylan film-coated tablets EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/deferasirox-mylan.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Deferasirox Mylan film-coated tablets, together with measures to minimise such risks and the proposed studies for learning more about Deferasirox Mylan film-coated tablets' risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimises its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Deferasirox Mylan film-coated tablets is not yet available, it is listed under 'missing information' below.

In the case of Deferasirox Mylan film-coated tablets, these routine measures are supplemented with additional risk minimisation measures, mentioned under relevant risks below.

II.A List of Important Risks and Missing Information

Important risks of Deferasirox Mylan film-coated tablets are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken by patients. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Deferasirox Mylan film-coated tablets. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine/use in special patient populations etc.);

Table 6: Part VI.1- Summary of safety concerns

List of Important Risks and Missing Information	
Important Identified Risks	• Renal disorders (increased serum creatinine, acute renal failure, renal tubular disorders [acquired Fanconi's syndrome]) • Increased liver transaminases / Hepatic failure • Gastrointestinal haemorrhage and ulcers; esophagitis • Hearing loss • Lens opacities, retinal changes and optic neuritis
Important Potential Risks	• Compliance with posology and biological monitoring • Medication errors due to switching between deferasirox FCT/granules and generic versions of deferasirox DT
Missing Information	• Long term safety in paediatric NTDT patients aged 10 to 17 years

II.B Summary of Important Risks

Table 7: Part VI.2- Important Identified Risk: Renal disorders (increased serum creatinine, acute renal failure, renal tubular disorders [acquired Fanconi's syndrome])

Evidence for linking the risk to the medicine	In thalassemia patients 0.5% of patients are reported to develop renal tubular dysfunction and 3.1% of patients progressed to dialysis therapy and 8% had a reduced CrCI. Renal tubular abnormalities, including increased urinary excretion of proteins and of tubular enzymes, have been reported in 30% of 250 patients with β thalassemia. Progressive renal insufficiency, generally heralded by the appearance of increasing proteinuria, hypertension and haematuria occurs in 5-18% of patients with SCD and can require haemodialysis or renal transplantation and contributes to 18% of deaths in patients older than 40 years. Acute renal failure has been described as part of a multi-organ failure syndrome that accompanies pain crises in SCD patients and is present in 10% of patients hospitalized with SCD. Renal failure contributes to 18% of deaths in SCD

	patients older than 40 years. In SCD, 26% of 381 patients were reported to have proteinuria, 13% at or close to the nephritic range. It was reported that 2.3% of MDS patients have renal disorders. Myelodysplastic syndrome patients are generally elderly and have serum creatinine levels that are close to or slightly > ULN due to the normal aging process.
Risk group and risk factors	Analyses showed that patients receiving high doses of deferasirox DT (20 or 30 mg/kg) and a low iron intake from infrequent blood transfusions were more likely to develop creatinine increases. Elderly patients were more likely to develop creatinine values > ULN though, as explained above, the magnitude of increase in comparison to baseline was no higher in these patients. Patients with pre-existing renal conditions or patients who are receiving medicinal products that depress renal function may be at higher risk of complications including ARF. In clinical studies a relationship between iron status (liver iron and ferritin concentrations), the rate of iron removal and renal effects has been observed. As with other iron chelator treatment, the risk of toxicity may be increased when inappropriately high doses of deferasirox are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated.
Risk Minimisation Measures	**Routine risk minimisation 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 in Section 4.8 Undesirable effects. **Additional risk minimisation measures** None

Table 8: Part VI.2- Important Identified Risk: Increased liver transaminases /Hepatic failure

Evidence for linking the risk to the medicine	**Increased liver transaminases** Elevated liver transaminases have ben correlated with increased LIC in patients with β-thalassemia. Studies have shown that hepatomegaly is seen in 50% of patients with SCD, hepatitis in 11% of patients and approximately one third of SCD patients will have a form of hepatic dysfunction. **Hepatic failure** In patients aged > 6 years with beta-thalassemia, 4-6% had evidence of liver failure or cirrhosis. SCD patients can develop sickle cell crises and sequestration events affecting the liver causing massive hepatic enlargement with hepatic failure occurring in up to 10% of patients. Cirrhosis has been reported in 16 to 29% of SCD patients.
Risk group and risk factors	**Increased liver transaminases** None identified.

	Hepatic failure Patients with pre-existing hepatic impairment.
Risk Minimisation Measures	**Routine risk minimisation measures** SmPC Section 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use. Relevant terms are included as ADRs in Section 4.8 Undesirable effects. **Additional risk minimisation measures** None

Table 9: Part VI.2- Important Identified Risk: Gastrointestinal haemorrhage and ulcers; esophagitis

Evidence for linking the risk to the medicine	No information was found regarding the incidence of this event in the unexposed population.
Risk factors and risk groups	Patients who are taking deferasirox in combination with drugs that have known ulcerogenic potential, such as NSAIDs, corticosteroids or oral bisphosphonates, and in patients receiving anticoagulants.
Risk Minimisation Measures	**Routine risk minimisation 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 minimisation measures** None.

Table 10: Part VI.2- Important Identified Risk: Hearing loss

Evidence for linking the risk to the medicine	Hearing loss not attributed to chelation therapy has been reported in 28% of patients with beta-thalassemia. A study of 75 adults with SCD demonstrated that the prevalence of hearing loss was 41% and was higher than that of the general population.
Risk factors and risk groups	As with other iron chelator treatment, the risk of toxicity may be increased when inappropriately high doses are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated.
Risk Minimisation Measures	**Routine risk minimisation measures** SmPC Section 4.4 Special warnings and precautions for use. Relevant terms are included as ADRs in Section 4.8 Undesirable effects. **Additional risk minimisation measures** None

Table 11: Part VI.2- Important Identified Risk: Lens opacities, retinal changes and optic neuritis

Evidence for linking the risk to the medicine	The background incidence of eye abnormalities in patients with beta-thalassemia is poorly documented. However, several reports document patients with lenticular opacities who have never received chelation therapy though the overall incidence was not provided. Cataracts have not been

	reported in patients with SCD. In the predominantly elderly patients with MDS, senile cataracts are a relatively frequent event.
Risk factors and risk groups	As with other iron chelator treatments, the risk of toxicity may be increased when inappropriately high doses are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated.
Risk Minimisation Measures	**Routine risk minimisation 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 minimisation measures** None

Table 12: Part VI.3- Important Potential Risk: Compliance with posology and biological monitoring

Evidence for linking the risk to the medicine	Not applicable
Risk factors and risk groups	Patients who are non-compliant with posology and biological monitoring requirements in the SmPC.
Risk Minimisation Measures	**Routine risk minimisation measures** SmPC Section 4.2 Posology and method of administration and 4.4 Special warnings and precautions for use. **Additional risk minimisation measures** Educational materials for physicians' (which also has a physicians' checklist) and patients regardless of indication.

Table 13: Part VI.3- Important Potential Risk: Medication errors due to switching between deferasirox FCT/granules and generic versions of deferasirox DT

Evidence for linking the risk to the medicine	Not applicable
Risk factors and risk groups	Patients may be at risk of medication errors during switch between deferasirox FCT/granules and generic versions of deferasirox DT available on the market by different MAHs and as appropriate depending on the coexistence of these formulations at a national level.
Risk Minimisation Measures	**Routine risk minimisation measures** SmPC Section 4.2 Posology and method of administration. **Additional risk minimisation measures** Educational materials for physicians (which also includes a physicians' checklist) and patients clarifying the dose adjustment requirements in case of switch between deferasirox FCT/granules and generic versions of deferasirox DT.

Table 14: Part VI.4- Missing Information: Long term safety in paediatric NTDT patients aged 10 to 17 years

Risk Minimisation Measures	**Routine risk minimisation measures** SmPC Section 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use. **Additional risk minimisation measures** None

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Deferasirox Mylan.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Deferasirox Mylan.

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

In line with the originator RMP, the MAH has put in place specific adverse reaction follow-up checklists for the following risks:

- Renal disorders (increased serum creatinine, acute renal failure, renal tubular disorders [acquired Fanconi's syndrome])

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided.

Patient Details:

Patient's Initials	
Age/Date of birth	
Gender	
Weight	
Height	

Deferasirox information at the time of event:

Tradename	
Strength	
Batch number	
Expiry date	
Route of administration	
Dose mg/kg/day	
Dose frequency	
Start date	
Stop date	
Onset date for event	

Information on Dose of Deferasirox:

Dose in mg/kg/day	Dates of treatment (dd/mm/yyyy)	
	Start Date	Stop Date

Actions taken with the suspected medication: Check all that apply:

1) Was Deferasirox discontinued?

☐ **Yes** - Date of Deferasirox discontinuation: ___/___/____ (dd/mm/yyyy)

- Has serum creatinine returned to baseline after discontinuation? ☐ **Yes** ☐ **No** ☐ **Unknown**
- Has Deferasirox been restarted? ☐ **Yes** ☐ **No**

If **Yes,** restart date: ___/___/____ (dd/mm/yyyy), Dose:_____

Re-occurrence of serum creatinine increase? ☐ **Yes** ☐ **No** ☐ **Unknown**

☐ **No** - Has Deferasirox dose been reduced? ☐ **Yes** ☐ **No**

If **Yes,** reduction date: ___/___/____ (dd/mm/yyyy), Dose:_____

- Has serum creatinine returned to baseline after reduction? ☐ **Yes** ☐ **No** ☐ **Unknown**

2) Measurement of serum creatinine:

	Date	**Serum creatinine values**	**Unit**	**Reference Range**
[@ treatment start, if available]				
[during treatment #1, if available]				
[during treatment #2, if available]				
[@ time of event]				
*[follow-up measurement @ **+30d**]*				
*[follow-up measurement @ **+60d**]*				

3) Renal biopsy:

Has a renal biopsy been performed? ☐ **Yes** ☐ **No**

If **Yes**, please provide results

4) Measurement of serum ferritin:

	Date	**Serum ferritin values**	**Unit**	**Reference Range**
[@ treatment start, if available]				
[during treatment #1, if available]				
[during treatment #2, if available]				
[during treatment #3, if available]				
[@ time of event]				
[follow-up measurement]				

Event Description:

Did the patient present with any of the following signs or symptoms? **Check all that apply**

☐ Fever
☐ Dehydration
☐ Nausea/vomiting
☐ Loss of appetite
☐ Pain around costovertebral angle
Urinary urgency
☐ Infections
☐ Muscle cramps
☐ Dry/itchy skin
☐ Shortness of breath
☐ Hypertension
☐ Trouble sleeping
☐ Bradycardia
☐ Tachycardia
☐ Difficulty starting or maintaining urine stream
☐ Increased urinary output
☐ Hematuria/red cola colored urine
☐ Arthralgia
☐ Edema
☐ Lethargy
☐ Confusion
☐ Hypotension
☐ Burning sensation upon urinating
☐ Decreased urinary output
☐ Pain upon urinating
☐ Skin rash ☐
☐ Flank pain
☐ Change in size of urine stream
☐ None of the above

Were any of the following diagnostic tests performed? **Check all that apply and please specify which test(s) and include dates, results and reference range for pre- and post- treatment values:**

☐ Creatinine clearance ☐ 24-hour protein (proteinuria) ☐ Kidney biopsy

- ☐ BUN
- ☐ Serum creatinine
- ☐ Hemoglobin
- ☐ CPK
- ☐ Urinalysis (including microscopic)
- ☐ Albumin
- ☐ Serum total protein
- ☐ Myoglobin
- ☐ Electrolytes
- ☐ Pulmonary angiography
- ☐ CT scan
- ☐ Renal ultrasound
- ☐ Cystoscopy
- ☐ Echocardiogram

☐ Complement studies

☐ Urine protein/Urine creatinine

☐ Glomerular filtration rate (estimated/measured)

- ☐ Chest x-ray
- ☐ Metabolic Acidosis
- ☐ Antinuclear antibodies
- ☐ Liver function tests
- ☐ Erythrocyte Sedimentation rate
- ☐ Blood pressure
- ☐ C-reactive protein
- ☐ Lipid levels
- ☐ Coagulation studies
- ☐ Abdominal x-ray
- ☐ Magnetic resonance imaging
- ☐ Electrocardiogram
- ☐ None of the above

Relevant medical history (concurrent and pre-existing conditions)

(Please specify medical condition and date of onset)

Does the patient have a history of any of the following prior to the start of the suspect drug? **Check all that apply:**

- ☐ Congestive heart failure
- ☐ Diabetes mellitus (Type I or Type II)
- ☐ Reflux nephropathy
- ☐ Renal disease (including nephrolithiasis)
- ☐ Autoimmune disease (specify)
- ☐ Hypertension
- ☐ Trauma/burns
- ☐ Kidney or bladder problems/Stones
- ☐ Disease of the prostate
- ☐ Intravenous contrast material
- ☐ Multiple myeloma
- ☐ Urinary tract infection
- ☐ Thromboembolic disease
- ☐ Obstructive uropathy
- ☐ Sickle cell disease
- ☐ Hyperuricemia
- ☐ Renal arteries obstructions
- ☐ Drug allergies *(please specify)*
- ☐ Rhabdomyolysis
- ☐ Rhabdomyolysis
- ☐ Hemorrhage
- ☐ Exposure to chemical dyes
- ☐ Myocardial infarction
- ☐ Coronary artery disease
- ☐ Hypercalcemia
- ☐ History of renal transplant
- ☐ Hepatorenal syndrome
- ☐ Hemolytic uremic syndrome
- ☐ Dehydration
- ☐ Cystic kidney disease

☐ History if dialysis

☐ Other relevant history *(please specify)*

☐ None of the above

_____

_____

_____

Relevant family history

- ☐ chronic kidney disease
- ☐ kidney genetic abnormalities
- ☐ hearing loss/deafness
- ☐ kidney cancer

Was the patient taking any of the following drugs? Check all that apply:

☐ACE Inhibitors	☐Lithium	☐Quinolones	☐Immunosuppressants	☐Actaminophen
☐Amphotericin B	☐Foscarnet	☐Aminoglycosides	☐Diphenhydramine	☐Doxylamine
☐Rifampin				
☐Sulfonamides	☐Vancomycin	☐Adefovir,Cidofovir, Tenofovir, Indinavir, Acyclovir, Ganciclovir		
☐Benzodiazepines	☐Clopidogrel	☐Carmustine	☐Cisplatin	☐Interferon-alfa
☐Methotrexate	☐Mitomycin-C	☐Contrast dye	☐Diuretics	☐Drugs of Abuse **(specify):**
☐Herbals **(specify):**	☐PPIs	☐Allopurinol	☐Gold Therapy	☐Pamidronate
☐Phenytoin	☐Ranitidine	☐Zoledronate	☐Haloperidol	☐Quinine
☐Amitriptyline	☐Doxepin	☐Fluoxetine	☐Pentamidine	☐COX-2 Inhibitors
☐NSAIDS	☐Calcium	☐ Angiotension II Receptor Blockers		☐Vitamin D-3
☐Penicillins				

Reporter's Details:

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Name: Sign

- Increased liver transaminases and Hepatic failure

Patient Details:

Patient's Initials	
Age/Date of birth	
Gender	
Weight	
Height	

Deferasirox information at the time of event:

Tradename	
Strength	
Batch number	
Expiry date	
Route of administration	
Dose	
Dose frequency	
Start date	
Stop date	
Onset date for event	

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided.

Event Description:

1. Diagnosis and date of diagnosis_____

2. Did the patient present with any of the following signs or symptoms? **Check all that apply:**

☐ Jaundice ☐ Ascites ☐ Asterixis (flapping tremor)
☐ Dark urine ☐ Fever ☐ Altered mental status
☐ Pale stool ☐ Fatigue ☐ Abdominal pain (specify location)
☐ Pruritus ☐ Bleeding (specify location) ☐ Anorexia
☐ Nausea ☐ Spider angiomata ☐ Variceal Bleeding
☐ Caput medusa ☐ Peripheral edema ☐ Fetor hepaticus
☐ Gynecomastia ☐ Muscle wasting ☐ Other (specify)
☐ None

3. Were any of the following diagnostic tests performed?

►**If yes, please specify the dates and results including reference range and pre- and post- treatment values:**

☐ Liver function tests

- ☐ Serology & PCR testings for Hepatitis A, B, C &/or E virus
- ☐ Autoantibody tests
- ☐ Abdominal or hepatobiliary ultrasound (with or without Doppler's)
- ☐ Abdominal CT scan/MRI
- ☐ Liver biopsy
- ☐ Liver transplant (planned or completed)
- ☐ Other (specify)
- ☐ None

4. Does the patient have a history of any of the following prior to the start of the suspect drug? **Check all that apply and include date(s) of onset as well as status (i.e. active/inactive) and details:**

- ☐ Previously elevated liver enzymes
- ☐ Hepatitis
- ☐ Other hepatobiliary disease or dysfunction
- ☐ Autoimmune disease (specify type)
- ☐ Active or chronic pancreatitis
- ☐ Diabetes mellitus (Type I or II)
- ☐ Non-alcoholic steatohepatitis
- ☐ Cirrhosis
- ☐ Ascites
- ☐ Spider angiomata
- ☐ None
- ☐ Tattoos
- ☐ Transfusion or blood product administration
- ☐ Gilbert's disease
- ☐ Alcohol intake (quantify if possible)
- ☐ Drug abuse
- ☐ Foreign travel
- ☐ Active gall bladder disease
- ☐ Portal hypertension
- ☐ Variceal bleeding/esophageal varices
- ☐ Thrombocytopenia
- ☐ Other (specify)

5. Has the patient recently (i.e. within the past 6 months) taken any of the following? **Check all that apply:**

- ☐ Sulfonamides
- ☐ Valproic acid
- ☐ Metronidazole
- ☐ COX II inhibitors (e.g. celecoxib)
- ☐ Thiazide diuretics
- ☐ Nicotinic acid
- ☐ None
- ☐ Furosemide
- ☐ NSAIDS (e.g. ibuprofen)
- ☐ Acetaminophen/Paracetamol
- ☐ Tetracycline
- ☐ 6-Mercaptopurine
- ☐ Methotrexate
- ☐ ACE Inhibitors
- ☐ Estrogens (oral contraceptives)
- ☐ Amiodarone
- ☐ Steroids
- ☐ Statins
- ☐ Other (specify)

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Name: Sign

- Gastrointestinal haemorrhage and ulcers; esophagitis

Patient Details:

Patient's Initials	
Age/Date of birth	
Gender	
Weight	
Height	

Deferasirox information at the time of event:

Tradename	

Strength	
Batch number	
Expiry date	
Route of administration	
Dose	
Dose frequency	
Start date	
Stop date	
Onset date for event	

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Event Description:
Did the patient experience any of the following signs or symptoms before the GI bleed/ulcer developed? **Check all that apply & specify time to onset from first starting Deferasirox, time of occurrence during the day in relation to Deferasirox ingestion, severity, and frequency, if applicable**

Symptom	Time to onset from first starting Deferasirox	Time of occurrence during the day in relation to Deferasirox ingestion	Severity (mild, moderate, severe)	Frequency (e.g. daily, once weekly, three times monthly)
☐ Nausea				
☐ Abdominal pain				
☐ Epigastric tenderness/pain				
☐ Hematemesis				
☐ Hematochezia				
☐ Malaena				
☐ Vomiting				
☐ Dyspepsia				
☐ Other (specify):				

Provide the platelet count at baseline (start of Deferasirox) and at the time of the bleed? At baseline _____

At time of bleed _____

Were any of the following diagnostic tests/procedures performed? **Check all that apply and specify dates and results**

☐ *H. Pylori* ___/___/____ (dd/mm/yyyy) Results: _____

☐ Endoscopy ___/___/____ (dd/mm/yyyy) Results: _____

☐ Tissue/mucosal biopsy ___/___/____ (dd/mm/yyyy) Results: _____

☐ Other – please specify:

_____ ___/___/____ (dd/mm/yyyy) Results: _____

☐ None of the above

Patient History:

Does the patient have a history of any of the following? **Check all that apply**

☐ Epigastric pain
☐ Gastritis
☐ Gastrointestinal ulcer
☐ Bleeding disorders/abnormal coagulation tests
☐ None of the above
☐ Esophagitis
☐ Gastrointestinal bleed
☐ Hemorrhoids
☐ Other relevant history – please specify:
_____

Was the patient taking any of the following drugs at the time of event? **Check all that apply**

☐ Anticoagulants
☐ NSAIDs
☐ Aspirin (acetylsalicyclic acid)
☐ Antiplatelet drugs (platelet aggregation inhibitors)
☐ None of the above
☐ Bisphosphonates
☐ Steroids

Has the patient ever used any of the following drugs? **Check all that apply**

☐ Antacids
☐ H2 blockers
☐ Proton pump Inhibitors
☐ None of the above

Reporter's Details:
I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Name: Sign

- Hearing loss

Patient Details:

Patient's Initials	
Age/Date of birth	
Gender	
Weight	
Height	

Deferasirox information at the time of event:

Tradename	
Strength	
Batch number	
Expiry date	
Route of administration	
Dose	
Dose frequency	
Start date	
Stop date	
Onset date for event	

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Event Description:

Which of the following describes the hearing loss? **Check all that apply**

☐ **Unilateral hearing loss** or ☐ **Bilateral hearing loss**

☐ **Sensorineural hearing loss** or ☐ **Conductive hearing loss**

Further description of the event (if necessary):_____
_____
_____
_____

Were any relevant investigations performed (e.g. audiometry testing or reports from specialists if consulted)?

☐ **Yes**, Test:_____ Date:___/___/____ (dd/mm/yyyy) Results:_____
Test:_____ Date:___/___/____ (dd/mm/yyyy) Results:_____
Test:_____ Date:___/___/____ (dd/mm/yyyy) Results:_____
Test:_____ Date:___/___/____ (dd/mm/yyyy) Results:_____

☐ **No** ☐ **Unknown**

Patient History:

Does the patient have a history of **Ear problems** prior to the start of the suspect drug? ☐ **Yes** ☐ **No**

If yes, please specify: ☐ **Other ear disorders** (Please specify):

_____ _____
_____ _____
_____ _____
_____ _____

Follow-up:

1) **Was Deferasirox discontinued?**

☐ **Yes** - Was there any improvement in the hearing loss after discontinuation? ☐ **Yes** ☐ **No**
- Has Deferasirox been restarted? ☐ **Yes** ☐ **No**
If **Yes,** restart date: ___/___/____ (dd/mm/yyyy), Dose:_____
Re-occurrence of hearing loss? ☐ **Yes** ☐ **No**

☐ **No** - Has Deferasirox dose been reduced? ☐ **Yes** ☐ **No**
If **Yes,** reduction date: ___/___/____ (dd/mm/yyyy), Dose:_____
- Was there any improvement in the hearing loss after reduction? ☐ **Yes** ☐ **No**

2) **Measurement of serum ferritin**

	Date	**Serum ferritin values**	**Unit**	**Reference Range**
[@ treatment start, if available]				
[during treatment #1, if available]				
[during treatment #2, if available]				
[during treatment #3, if available]				
[@ time of event]				
[follow-up measurement]				

Reporter's Details:

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Name: Sign

- Lens opacities, retinal changes, and optic neuritis

Patient Details:

Patient's Initials	
Age/Date of birth	
Gender	
Weight	
Height	

Deferasirox information at the time of event:

Tradename	
Strength	
Batch number	
Expiry date	
Route of administration	
Dose	
Dose frequency	
Start date	
Stop date	
Onset date for event	

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided.

Event Description:

Which of the following describes the lens opacity? **Check all that apply**

☐ **Unilateral**
or
☐ **Bilateral**

☐ **Punctuate lens opacities**
or
☐ **Complete cataract formation**

Further description of the lens opacity (e.g. size): _____
_____
_____
_____

Were any relevant investigations performed (e.g. ophthalmology testing or reports from specialists if consulted)?
☐ **Yes**, Test:_____ Date:___/___/____ (dd/mm/yyyy) Results:_____
Test:_____ Date:___/___/____ (dd/mm/yyyy) Results:_____

Test:_____ Date:___/___/____ (dd/mm/yyyy) Results:_____
Test:_____ Date:___/___/____ (dd/mm/yyyy) Results:_____

☐ **No** ☐ **Unknown**

Relevant medical history (concurrent and pre-existing conditions)
(Please specify medical condition and date of onset)

Does the patient have a history of **Lens opacities / Cataracts** prior to the start of the suspect drug? ☐ **Yes** ☐ **No**

If yes, please specify: ☐ **Other eye disorders** (Please specify):

_____ _____
_____ _____
_____ _____
_____ _____

Follow-up:

1) Was Deferasirox discontinued?

☐ **Yes** - Was there any improvement in the lens opacity after discontinuation? ☐ **Yes** ☐ **No**
- Has Deferasirox been restarted? ☐ **Yes** ☐ **No**
If **Yes,** restart date: ___/___/____ (dd/mm/yyyy), Dose:_____
Re-occurrence of lens opacity? ☐ **Yes** ☐ **No**

☐ **No** - Has Deferasirox dose been reduced? ☐ **Yes** ☐ **No**
If **Yes,** reduction date: ___/___/____ (dd/mm/yyyy), Dose:_____
- Was there any improvement in the lens opacity after reduction? ☐ **Yes** ☐ **No**

2) Measurement of serum ferritin

	Date	**Serum ferritin values**	**Unit**	**Reference Range**
[@ treatment start, if available]				
[during treatment #1, if available]				
[during treatment #2, if available]				
[during treatment #3, if available]				
[@ time of event]				
[follow-up measurement]				

Reporter's Details:

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Name: Sign

Annex 6 – Details of Proposed Additional Risk Minimisation Activities (If Applicable)

Organization of material

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 theNational 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 deferasirox FCT/granules and generic versions of deferasirox DT

The risk of medication error is due to switching between deferasirox FCT/granules and generic deferasirox DT formulations available on the market by different MAHs and as appropriate depending on the coexistence of these formulations at a national level.

The MAH shall ensure that, 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 and
- Patient educational material

Additional periodic distributions should be performed, notably after substantial safety modifications of the product information justifying educational material updates, if applicable in the Member States.

Objective

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

Details of proposed educational program

The physician educational material should contain elements:

- The Summary of Product Characteristics
- Guide for healthcare professionals (which also includes a physicians' checklist)

The Guide for healthcare professionals shall contain the following key elements as appropriate depending on the coexistence of deferasirox formulations at a national level:

- Description of available deferasirox formulations on the market (e.g. dispersible tablets, film- coated tablets and granules) in the EU

    - Different posology regimen
    - Different conditions of administration
- Dose conversion table of Deferasirox film coated tablets/granules and Deferasirox dispersible tablets as a reference 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 7 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
    - 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 contains:

- Patient information leaflet
- Patient guide

The 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)