EU Risk Management Plan
for
[Deferasirox]
90mg, 180mg, 360mg film coated tablets

RMP version to be assessed as part of this application:

RMP Version number: 0.3

Data lock point for this RMP: 27.09.2021

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Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP: Not applicable

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Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	Deferasirox
Pharmacotherapeutic group(s) (ATC Code)	Iron chelating agents (V03AC03)
Marketing Authorisation Applicant	Pharmathen SA Medical Valley Invest AB Egis Pharmaceuticals PLC G.L. Pharma GmbH
Medicinal products to which this RMP refers	3
Invented name(s) in the European Economic Area (EEA)	For DK/H/3112/001-003/DC: DeferasiroxPharmathen (DK) For DK/H/3113/001-003/DC: Deferasirox Medical Valley (DK), For DK/H/3114/001-003/DC: DEFLOXOL (DK)
Marketing authorisation procedure	Decentralised
Brief description of the product	Chemical class: Pharmacotherapeutic group: Iron chelating agents, ATC code: V03AC03
	Summary of mode of action: 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.
	Important information about its composition: N/A
Hyperlink to the Product Information	*SmPC: refer to module 1.3.1* *PIL: refer to module 1.3.1* *Label: refer to module 1.3.1*
Indication(s) in the EEA	**Current:** [Deferasirox] 90, 180, 360 mg film-coated tablets 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] 90, 180, 360 mg 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

<table>
<tr><td></td><td>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] 90, 180, 360 mg 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.</td></tr>
<tr><td></td><td>Proposed: N/A</td></tr>
<tr><td>Dosage in the EEA</td><td>Current: Treatment with [Deferasirox] 90, 180, 360 mg film-coated tablets should be initiated and maintained by physicians experienced in the treatment of chronic iron overload.

<u>Posology</u>

<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. The goals of iron chelation therapy are to remove the amount of iron administered in transfusions and, as required, to reduce the existing iron burden. [Deferasirox] 90, 180, 360 mg film-coated tablets demonstrate higher bioavailability compared to the deferasirox dispersible tablet formulation (see SmPC section 5.2). In case of switching from dispersible tablets to film-coated tablets, the dose of the film-coated tablets should be 30 % lower than the dose of the dispersible tablets, rounded to the nearest whole tablet.

The corresponding doses for the different formulations are shown in the table below.

<u>Table 1</u> Recommended doses for transfusional iron overload

<table>
<tr><th></th><th>Film-coated tablets/granules</th><th>Dispersible tablets</th><th>Transfusions</th><th>Serum ferritin</th></tr>
<tr><td>Starting dose</td><td>14 mg/kg/day</td><td>20 mg/kg/day</td><td>After 20 units (about 100 mL/kg) of PRBC</td><td>or >1,000 µg/L</td></tr>
<tr><td rowspan="2">Alternative starting doses</td><td>21 mg/kg/day</td><td>30 mg/kg/day</td><td>> 14 mL/kg/month of PRBC (approx. > 4 units/month for an adult)</td><td></td></tr>
<tr><td>7 mg/kg/day</td><td>10 mg/kg/day</td><td>< 7 mL/kg/month of PRBC (approx. < 2 units/month for an adult)</td><td></td></tr>
<tr><td>For patients well managed on deferoxamine</td><td>One third of deferoxamine dose</td><td>Half of deferoxamine dose</td><td></td><td></td></tr>
<tr><td>Monitoring</td><td></td><td></td><td></td><td>Monthly</td></tr>
<tr><td>Target range</td><td></td><td></td><td></td><td>500-1,000</td></tr>
</table>
</td></tr>
</table>

				µg/L
Adjustment steps (every 3-6 months)	**Increase**			>2,500 µg/L
	3.5-7 mg/kg/day	5-10 mg/kg/day		
	Up to 28 mg/kg/day	Up to 40 mg/kg/day		
	Decrease			
	3.5-7 mg/kg/day	5-10 mg/kg/day		< 2,500 µg/L
	In patients treated with doses > 21 mg/kg/day	In patients treated with doses > 30 mg/kg/day		
	- When target is reached			500-1,000 µg/L
Maximum dose	**28 mg/kg/day**	**40 mg/kg/day**		
Consider interruption				**< 500 µg/L**

Starting dose
The recommended initial daily dose of [Deferasirox] 90, 180, 360 mg film-coated tablets is 14 mg/kg body weight.

An initial daily dose of 21 mg/kg may be considered for patients who require reduction of elevated body iron levels and who are also receiving more than 14 mL/kg/month of packed red blood cells (approximately > 4 units/month for an adult).

An initial daily dose of 7 mg/kg may be considered for patients who do not require reduction of body iron levels and who are also receiving less than 7 mL/kg/month of packed red blood cells (approximately < 2 units/month for an adult). The patient's response must be monitored and a dose increase should be considered, if sufficient efficacy is not obtained (see SmPC section 5.1).

For patients already well managed on treatment with deferoxamine, a starting dose of [Deferasirox] 90, 180, 360mg film-coated tablets that is numerically one third that of the deferoxamine dose could be considered (e.g. a patient receiving 40 mg/kg/day of deferoxamine for 5 days per week (or equivalent) could be transferred to a starting daily dose of 14 mg/kg/day of [Deferasirox] 90, 180, 360 mg film-coated tablets). When this results in a daily dose less than 14 mg/kg body weight, the patient's response must be monitored and a dose increase should be considered, if sufficient efficacy is not obtained (see SmPC section 5.1).

Dose adjustment
It is recommended that serum ferritin be monitored every month and that the dose of [Deferasirox] 90, 180, 360 mg be adjusted, if necessary, every 3 to 6 months based on the trends in serum ferritin. Dose adjustments may be made in steps of 3.5 to 7 mg/kg and are to be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of iron burden). In patients not adequately controlled with doses of 21 mg/kg (e.g. serum ferritin levels persistently above 2,500 µg/L and not showing a decreasing trend over time), doses of up to 28 mg/kg may be considered. The availability of long-term efficacy and safety data from clinical studies conducted with deferasirox dispersible tablets used at doses above 30 mg/kg is currently limited (264 patients followed for an average of 1 year after dose escalation). If only very poor haemosiderosis control is achieved at doses up to 21 mg/kg, a further increase (to a maximum of 28 mg/kg) may not achieve satisfactory control and alternative treatment options may be considered. If no satisfactory

control is achieved at doses above 21 mg/kg, treatment at such doses should not be maintained and alternative treatment options should be considered whenever possible. Doses above 28 mg/kg are not recommended because there is only limited experience with doses above this level (see SmPC section 5.1).

In patients treated with doses greater than 21 mg/kg, dose reductions in steps of 3.5 to 7 mg/kg should be considered when control has been achieved (e.g. serum ferritin levels persistently below 2,500 µg/L and showing a decreasing trend over time). In patients whose serum ferritin level has reached the target (usually between 500 and 1,000 µg/L) dose reductions in steps of 3.5 to 7 mg/kg should be considered to maintain serum ferritin levels within the target range. If serum ferritin falls consistently below 500 µg/L, an interruption of treatment should be considered (see SmPC section 4.4).

Non-transfusion-dependent thalassaemia syndromes
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.

Deferasirox film-coated tablets demonstrate higher bioavailability compared to the deferasirox dispersible tablet formulation (see SmPC section 5.2). In case of switching from dispersible tablets to film-coated tablets, the dose of the film-coated tablets should be 30 % lower than the dose of the dispersible tablets, rounded to the nearest whole tablet.

The corresponding doses for the different formulations are shown in the table below.

Table 2 Recommended doses for non-transfusion-dependent thalassaemia syndromes

	Film-coated tablets/granules	**Dispersible tablets**	**Liver iron concentration (LIC)***		**Serum ferritin**
Starting dose	**7 mg/kg/day**	**10 mg/kg/day**	≥ 5 mg Fe/g dw	or	> 800 µg/L
Monitoring					**Monthly**
Adjustment steps (every 3-6 months)	**Increase**		≥ 7 mg Fe/g dw	or	> 2,000 µg/L
	3.5-7 mg/kg/day	5-10 mg/kg/day			
	Decrease		< 7 mg Fe/g dw	or	≤ 2,000 µg/L
	3.5-7 mg/kg/day	5-10 mg/kg/day			
Maximum dose	**14 mg/kg/day**	**20 mg/kg/day**			
	7 mg/kg/day	**10 mg/kg/day**			
	For adults		not assessed	and	≤ 2,000 µg/L
	For paediatric patients				
Interruption			**< 3 mg Fe/g dw**	or	**< 300 µg/L**
Retreatment			**Not recommended**		

*LIC is the preferred method of iron overload determination.

	Starting dose The recommended initial daily dose of [Deferasirox] 90, 180, 360 mg film-coated tablets in patients with non-transfusion-dependent thalassaemia syndromes is 7 mg/kg body weight. *Dose adjustment* It is recommended that serum ferritin be monitored every month. After every 3 to 6 months of treatment a dose increase in increments of 3.5 to 7 mg/kg should be considered, if the patient's LIC is ≥ 7 mg Fe/g dw or if serum ferritin is consistently > 2,000 µg/L and not showing a downward trend and the patient is tolerating the medicinal product well. Doses above 14 mg/kg are not recommended, because there is no experience with doses above this level in patients with non-transfusion-dependent thalassaemia syndromes. In patients in whom LIC was not assessed and serum ferritin is ≤ 2,000 µg/L dosing should not exceed 7 mg/kg. For patients in whom the dose was increased to > 7 mg/kg dose reduction to 7 mg/kg or less is recommended when LIC is < 7 mg Fe/g dw or serum ferritin is ≤ 2,000 µg/L. *Treatment cessation* Once a satisfactory body iron level has been achieved (LIC < 3 mg Fe/g dw or serum ferritin < 300 µg/L), treatment should be stopped. There are no data available on the retreatment of patients who reaccumulate iron after having achieved a satisfactory body iron level and, therefore, retreatment cannot be recommended. For the dosage in special populations, please refer to section 4.2 of SmPC.
	Proposed: N/A
Pharmaceutical form(s) and strengths	**Current:** [Deferasirox] 90 mg film-coated tablets Each film-coated tablet contains 90 mg deferasirox. [Deferasirox] 180 mg film-coated tablets Each film-coated tablet contains 180 mg deferasirox. [Deferasirox] 360 mg film-coated tablets Each film-coated tablet contains 360 mg deferasirox.
	Proposed: N/A
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

[Deferasirox] 90, 180, 360mg film-coated tablets are a generic formulation [Article 10(1)] of *Exjade 125, 250, 500 mg dispersible tablets [Novartis Europharm Limited]*. Therefore, Modules SI to SVII of Part II are not applicable.

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

Not applicable.

Part II: Module SV-Post-Authorization Experience

Not applicable.

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

Not applicable.

Part II: Module SVII-Identified and potential risks

[Deferasirox] 90, 180, 360mg film-coated tablets are a generic formulation [Article 10(1)] of Exjade 125, 250, 500 mg dispersible tablets [*Novartis Europharm Limited*]. Based on the Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2), this module is not applicable for medicinal products seeking a marketing authorisation according to Article 10(1) of Directive 2001/83/EC, as amended, provided that the originator's product has an RMP and its safety profile is available.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: 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
Important Potential Risks	• Compliance with posology and biological monitoring • Medication errors
Missing Information	• Long term safety in pediatric NTDT patients aged 10 to 17 years

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond Adverse Drug Reactions (ADRs) reporting and signal detection:

Specific adverse reaction follow-up questionnaires for [Deferasirox] 90, 180, 360mg film-coated tablets are considered necessary for the following safety concerns:

- 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

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are proposed for Deferasirox.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

The MAH will provide educational material to all physicians who may be involved in treating patients with deferasirox.

Prior to launch of deferasirox, the Marketing Authorisation Holder (MAH) shall agree upon the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme with the National Competent Authorities concerned.

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

The MAH shall ensure that, at launch, in each Member State where [Deferasirox] is marketed, all healthcare professionals and patients who are expected to prescribe, dispense and use deferasirox are provided with the following **educational package** for all available formulations for all indications:

- **Physician educational material**
- **Patient information pack**

The **physician educational material** should contain:

- ❖ The Summary of Product Characteristics
- ❖ Guide for healthcare professionals
- ❖ Prescriber's Checklist

The **Guide for healthcare professionals** shall contain the following key elements:
• Description of available deferasirox formulations
• 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 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 annual auditory and ophthalmic testing
• The need for a guidance table highlighting pre-treatment measurements of serum creatinine, creatinine clearance, proteinuria, hepatic enzymes, ferritin.
• Recommendations for treatment of non-transfusion-dependent thalassaemia (NTDT) syndromes.

The **Prescriber's Checklist** should contain the following key elements:
• Brief information about recommended doses at the initiation of the treatment
• The requirement and frequencies of different biological monitoring factors
• Details about the necessity of dose adjustment during treatment
• Guidance on treatment interruption

The **patient information pack** should contain:

- ❖ 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 and the main differences associated with these formulations (i.e., different posology regimen, different conditions of administration notably with food)

V.1. Routine Risk Minimisation Measures

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

Safety concern	Routine risk minimisation activities
Important identified risk **Renal disorders (increased serum creatinine, acute renal failure, renal tubular disorders (acquired Fanconi's syndrome)**	***Routine risk communication:*** SmPC sections: 4.2, 4.3, 4.4, 4.8 ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** Making aware of physicians and monitoring the risk. ***Other routine risk minimisation measures beyond the Product Information:*** Prescription only medicine. **Proposed Pack sizes as per proposed SmPC:** transparent PVC/PVDC - Aluminium foil blisters with an instruction leaflet. Unit packs containing 30 or 90 film-coated tablets or multipacks containing 300 (10 packs of 30) film-coated tablets. Not all pack sizes may be marketed.
Important identified risk **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:*** Making aware of physicians and monitoring the risk ***Other routine risk minimisation measures beyond the Product Information:*** Prescription only medicine **Proposed Pack sizes as per proposed SmPC:** transparent PVC/PVDC - Aluminium foil blisters with an instruction leaflet. Unit packs containing 30 or 90 film-coated tablets or multipacks containing 300 (10 packs of 30) film-coated tablets. Not all pack sizes may be marketed
Important identified risk **Gastrointestinal hemorrhage and ulcers, esophagitis**	***Routine risk communication:*** SmPC sections: 4.4, 4.5 and 4.8 ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** Making aware of physicians and monitoring the risk

	Other routine risk minimisation measures beyond the Product Information: Prescription only medicine ***Proposed Pack sizes as per proposed SmPC:*** transparent PVC/PVDC - Aluminium foil blisters with an instruction leaflet. Unit packs containing 30 or 90 film-coated tablets or multipacks containing 300 (10 packs of 30) film-coated tablets. Not all pack sizes may be marketed
Important identified risk **Hearing loss**	***Routine risk communication:*** SmPC sections 4.4, 4.8 ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** Making aware of physicians and monitoring the risk ***Other routine risk minimisation measures beyond the Product Information:*** Prescription only medicine **Proposed Pack sizes as per proposed SmPC:** transparent PVC/PVDC - Aluminium foil blisters with an instruction leaflet. Unit packs containing 30 or 90 film-coated tablets or multipacks containing 300 (10 packs of 30) film-coated tablets. Not all pack sizes may be marketed.
Important identified risk **Lens opacities, retinal changes, and optic neuritis**	***Routine risk communication:*** SmPC sections 4.4, 4.8, 5.3 ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** Making aware of physicians and monitoring the risk ***Other routine risk minimisation measures beyond the Product Information:*** Prescription only medicine **Proposed Pack sizes as per proposed SmPC:** transparent PVC/PVDC - Aluminium foil blisters with an instruction leaflet. Unit packs containing 30 or 90 film-coated tablets or multipacks containing 300 (10 packs of 30) film-coated tablets. Not all pack sizes may be marketed
Important potential risk **Compliance with posology and biological monitoring**	***Routine risk communication:*** SmPC sections 4.2, 4.4 ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** Making aware of physicians and monitoring the risk ***Other routine risk minimisation measures beyond the Product Information:***

	Prescription only medicine ***Proposed Pack sizes as per proposed SmPC:*** transparent PVC/PVDC - Aluminium foil blisters with an instruction leaflet. Unit packs containing 30 or 90 film-coated tablets or multipacks containing 300 (10 packs of 30) film-coated tablets. Not all pack sizes may be marketed.
Important potential risk **Medication errors**	***Routine risk communication:*** SmPC section 4.2 ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** Making aware of physicians and monitoring the risk ***Other routine risk minimisation measures beyond the Product Information:*** Prescription only medicine **Proposed Pack sizes as per proposed SmPC:** transparent PVC/PVDC - Aluminium foil blisters with an instruction leaflet. Unit packs containing 30 or 90 film-coated tablets or multipacks containing 300 (10 packs of 30) film-coated tablets. Not all pack sizes may be marketed.
Missing information **Long term safety in pediatric NTDT patients aged 10 to 17 years**	***Routine risk communication:*** SmPC sections 4.2, 4.4 ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** Making aware of physicians and monitoring the risk ***Other routine risk minimisation measures beyond the Product Information:*** Prescription only medicine **Proposed Pack sizes as per proposed SmPC:** transparent PVC/PVDC - Aluminium foil blisters with an instruction leaflet. Unit packs containing 30 or 90 film-coated tablets or multipacks containing 300 (10 packs of 30) film-coated tablets. Not all pack sizes may be marketed.

V.2. Additional Risk Minimisation Measures

Additional risk minimisation

The MAH will provide educational material to healthcare professionals (HCPs) who may be involved in treating patients and patients being treated with [Deferasirox] 90, 180, 360mg film-coated tablets.

The appropriate material will be agreed upon with each National Competent Authority and be available prior to product launch nationally.
In addition, this medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures).

These additional risk minimisation measures are for the following risks:

• **Non-compliance of the posology and biological monitoring**
• **Medication errors due to switching between formulations**

The **physician educational material** should contain:

- ❖ The Summary of Product Characteristics
- ❖ Guide for healthcare professionals
- ❖ Prescriber's Checklist

The **Guide for healthcare professionals** shall contain the following key elements:
• Description of available deferasirox formulations
• 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 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 annual auditory and ophthalmic testing
• The need for a guidance table highlighting pre-treatment measurements of serum creatinine, creatinine clearance, proteinuria, hepatic enzymes, ferritin.
• Recommendations for treatment of non-transfusion-dependent thalassaemia (NTDT) syndromes.

The **Prescriber's Checklist** should contain the following key elements:
- Brief information about recommended doses at the initiation of the treatment
- The requirement and frequencies of different biological monitoring factors
- Details about the necessity of dose adjustment during treatment
- Guidance on treatment interruption

The **patient information pack** should contain:
- ❖ 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 and the main differences associated with these formulations (i.e., different posology regimen, different conditions of administration notably with food)

Objective and rational:
- To inform patients and caregivers about the risks of non-compliance of the posology and biological monitoring that needs to be performed before and during the treatment with deferasirox.
- To inform patients and caregivers about the risk of medication errors due to different formulations available on the market.
- To inform patients and caregivers about appropriate management of the risks to minimise its occurrence and its severity.

Compliance with posology and biological monitoring:
The results of the blood and urine tests to monitor kidney and liver function,and hearing and eye examinations should be recorded and regularly assessed for trends.

Medication errors:
Healthcare professionals and patients need to be aware of the risk of medication errors due to different formulations.

Proposed action:
Implementation (i.e. active or non-active) should be agreed on national basis, acknowledging that individual member states may have different market experiences and clinical practices. Exact format and content and way of distribution are to be discussed locally with the individual authorities prior to the launch.

Plans to evaluate the effectiveness of the interventions and criteria for success:
The success of risk minimisation activities in delivering these objectives needs to be evaluated throughout the lifecycle of a product to ensure that the burden of adverse reactions is minimised and hence the overall risk-benefit balance is optimised. The ultimate measures of success of a risk minimisation program are the safety outcomes. Such an evaluation should involve the comparison of epidemiologic measures of outcome frequency such as incidence rate or cumulative incidence of the current adverse reaction.

Removal of additional risk minimisation activities

Rationale for the removal
Additional minimization measures should be removed when frequency and incidence rates of the risks above improve, and it could be ensured that healthcare professionals are well informed about described measures.

V.3 Summary of risk minimisation measures

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Renal disorders (increased serum creatinine, acute renal failure, renal tubular disorders [acquired Fanconi's syndrome])	Routine risk minimization measures: Section 4.2, 4.3, 4.4, 4.8 of SmPC *Other routine risk minimisation measures:* Prescription only medicine *Additional risk minimization measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Specific adverse reaction follow-up questionnaire *Additional pharmacovigilance activities:* None
Increased liver transaminases/hepatic failure	Routine risk minimization measures: Section 4.2, 4.4, 4.8 of SmPC *Other routine risk minimisation measures:* Prescription only medicine	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Specific adverse reaction follow-up questionnaire

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimization measures: None	*Additional pharmacovigilance activities:* None
Gastrointestinal hemorrhage and ulcers, esophagitis	Routine risk minimization measures: Section 4.4, 4.5, 4.8 of SmPC *Other routine risk minimisation measures:* Prescription only medicine *Additional risk minimization measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Specific adverse reaction follow-up questionnaire *Additional pharmacovigilance activities:* None
Hearing loss	Routine risk minimization measures: Section 4.4, 4.8 of SmPC *Other routine risk minimisation measures:* Prescription only medicine *Additional risk minimization measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Specific adverse reaction follow-up questionnaire *Additional pharmacovigilance activities:* None
Lens opacities, retinal changes and optic neuritis	Routine risk minimization measures: Section 4.4, 4.8, 5.3 of SmPC *Other routine risk minimisation measures:* Prescription only medicine *Additional risk minimization measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Specific adverse reaction follow-up questionnaire *Additional pharmacovigilance activities:* None
Compliance with posology and biological monitoring	Routine risk minimization measures: Sections 4.2, 4.4 of SmPC *Other routine risk minimisation measures:* Prescription only medicine *Additional risk minimization measures:* Educational materials for physicians (Guide for HCPs & Prescriber's Checklist) and information pack for patients regardless of indication.	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* None
Medication errors	Routine risk minimization measures: Section 4.2 of SmPC *Other routine risk minimisation measures:* Prescription only medicine	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimization measures: Educational materials for physicians and information pack for patients for all the formulations and for all indications and appropriate dosing, to be distributed and prior to launch and after substantial safety modifications of the product information. Introductory notification letter to prescribers which includes a prescriber's guide and a patient's guide.	*Additional pharmacovigilance activities:* None
Long term safety in pediatric NTDT patients aged 10 to 17 years	Routine risk minimization measures: Sections 4.2, 4.4 of SmPC *Other routine risk minimisation measures:* Prescription only medicine *Additional risk minimization measures:* None	*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] 90, 180, 360 mg film-coated tablets**

This is a summary of the risk management plan (RMP) for [Deferasirox] 90, 180, 360 mg film-coated tablets. The RMP details important risks of [Deferasirox] 90, 180, 360 mg film-coated tablets, how these risks can be minimised, and how more information will be obtained about [Deferasirox]'s risks and uncertainties (missing information).

[Deferasirox]'s Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how [Deferasirox] 90, 180, 360 mg film-coated tablets should be used.

Important new concerns or changes to the current ones will be included in updates of [Deferasirox]'s RMP.

I. The medicine and what it is used for

[Deferasirox] 90, 180, 360 mg film-coated tablets is authorised 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] 90, 180, 360 mg 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] 90, 180, 360 mg 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 orally.

If important information that may affect the safe use of [Deferasirox] 90, 180, 360 mg film-coated tablets is not yet available, it is listed under 'missing information' below.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of [Deferasirox] 90, 180, 360 mg film-coated tablets, together with measures to minimise such risks and the proposed studies for learning more about [Deferasirox] 90, 180, 360 mg 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 patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of [Deferasirox] 90, 180, 360mg film-coated tablets, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, 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] 90, 180, 360mg film-coated tablets is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of [Deferasirox] 90, 180, 360mg film-coated tablets that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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] 90, 180, 360mg 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).

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 hemorrhage and ulcers; esophagitis • Hearing loss • Lens opacities, retinal changes and optic neuritis
Important Potential Risks	• Compliance with posology and biological monitoring • Medication errors
Missing Information	• Long term safety in pediatric NTDT patients aged 10 to 17 years

II.B Summary of important risks

Important Potential Risk: Compliance of the posology and biological monitoring	
Risk minimisation measures	Routine risk minimization measure: – Sections 4.2, 4.4 of SmPC *Other routine risk minimisation measures:* Prescription only medicine Additional risk minimization measures: Educational materials for physicians (Guide for HCPs & Prescriber's Checklist) and information pack for patients regardless of indication.
Important Potential Risk: Medication errors	
Risk minimisation measures	Routine risk minimization measure: – Section 4.2 of SmPC Additional risk minimization measures: Educational materials for physicians and information pack for patients for all the formulations and for all indications and appropriate dosing, to be distributed and prior to launch and after substantial safety modifications of the product information. Introductory notification letter to pharmacists explaining the switch between formulations. Introductory notification letter to prescribers which includes a prescriber's guide and a patient's guide.

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] 90, 180, 360 mg film-coated tablets.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for [Deferasirox] 90, 180, 360 mg film-coated tablets.

Part VII: Annexes

Annex 1 – EudraVigilance Interface

Not applicable.

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Not applicable.

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not applicable.

Annex 4 - Specific adverse drug reaction follow-up form

Targeted Follow-up Checklist for [Deferasirox] 90, 180 & 360 mg film-coated tablets Serum Creatinine Increase

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

Information on Dose of Deferasirox 360 mg film-coated tablets:

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] 90, 180 & 360 mg film-coated tablets discontinued?

☐ **Yes** - Date of [Deferasirox] 90, 180 & 360 mg film-coated tablets discontinuation: ___/___/____(dd/mm/yyyy)
- Has serum creatinine returned to baseline after discontinuation? ☐ **Yes** ☐ **No** ☐ **Unknown**
- Has [Deferasirox] 90.180 & 360 mg film-coated tablets been restarted? ☐ **Yes** ☐ **No**
If **Yes,** restart date: ___/___/____ (dd/mm/yyyy), Dose:_____
Re-occurrence of serum creatinine increase? ☐ **Yes** ☐ **No** ☐ **Unknown**

☐ **No** - Has [Deferasirox] 90, 180 & 360 mg film-coated tablets 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]				

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 [Deferasirox] 90, 180 & 360 mg film-coated tablets? **Check all that apply:**

☐ Renal disease
☐ Diabetes mellitus
☐ Autoimmune disease
☐ Sepsis
☐ Congestive heart failure
☐ Hypertension
☐ Volume depletion
☐ Diagnostic and therapeutic procedures

☐ Disease of the prostate
☐ Other relevant history ***(please specify)***:
_____
_____
_____
_____
_____

☐ None of the above

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	☐PPIs	☐Allopurinol	☐Gold Therapy	☐Pamidronate
☐Phenytoin	☐Ranitidine	☐Zoledronate	☐Haloperidol	☐Quinine
☐Amitriptyline	☐Doxepin	☐Fluoxetine	☐Pentamidine	☐COX-2 Inhibitors
☐NSAIDS	☐Penicillins			

Targeted Follow-up Checklist for [Deferasirox] 90, 180 & 360 mg film-coated tablets Gastrointestinal Ulcers & Bleeds

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] 90, 180 & 360 mg film-coated tablets, time of occurrence during the day in relation to [Deferasirox] 90, 180 & 360 mg film-coated tablets ingestion, severity, and frequency, if applicable**

Symptom	Time to onset from first starting [Deferasirox] 90, 180 & 360 mg film-coated tablets	Time of occurrence during the day in relation to [Deferasirox] 90, 180 & 360 mg film-coated tablets	Severity (mild, moderate, severe)	Frequency (e.g. daily, once weekly, three times monthly)
☐ Nausea				
☐ Abdominal pain				
☐ Epigastric tenderness/pain				
☐ Hematemesis				
☐ Hematochezia				
☐ Vomiting				
☐ Dyspepsia				
☐ Other (specify):				

Provide the platelet count at baseline (start of [Deferasirox] 90, 180 & 360 mg film-coated tablets) 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
☐ 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

Targeted Follow-up Checklist for [Deferasirox] 90, 180 & 360 mg film-coated tablets Hearing Loss

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] 90, 180 & 360 mg film-coated tablets discontinued?**

☐ **Yes** - Was there any improvement in the hearing loss after discontinuation? ☐ **Yes** ☐ **No**
- Has [Deferasirox] 90, 180 & 360 mg film-coated tablets been restarted? ☐ **Yes** ☐ **No**
If **Yes,** restart date: ___/___/____ (dd/mm/yyyy), Dose:_____
Re-occurrence of hearing loss? ☐ **Yes** ☐ **No**

☐ **No** - Has [Deferasirox] 90, 180 &360 mg film-coated tablets 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]				

Targeted Follow-up Checklist for [Deferasirox] 90, 180 & 360 mg film-coated tablets Lens Opacities / Cataracts

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] 90, 180 & 360 mg film-coated tablets discontinued?**

☐ **Yes** - Was there any improvement in the lens opacity after discontinuation? ☐ **Yes** ☐ **No**
- Has [Deferasirox] 90, 180 & 360 mg film-coated tablets been restarted? ☐ **Yes** ☐ **No**
If **Yes,** restart date: ___/___/____ (dd/mm/yyyy), Dose:_____
Re-occurrence of lens opacity? ☐ **Yes** ☐ **No**

☐ **No** - Has [Deferasirox] 90, 180 & 360 mg film-coated tablets 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]				

Targeted Follow-up Checklist for [Deferasirox] 90, 180 & 360 mg film-coated tablets Liver injury checklist

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

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 ☐ 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 test
☐ Abdominal or hepatobiliary ultrasound
☐ Abdominal CT scan
☐ Liver biopsy
☐ Liver transplant (planned or completed)
☐ Other (specify)
☐ None

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 ☐ Tattoos
☐ Hepatitis ☐ Transfusion or blood product administration
☐ Other hepatobiliary disease or dysfunction ☐ Gilbert's disease
☐ Autoimmune disease ☐ Alcohol intake
☐ Active pancreatitis ☐ Drug abuse
☐ Diabetes mellitus (Type I or II) ☐ Foreign travel
☐ Non alcoholic steatohepatitis ☐ Active gall bladder disease
☐ None ☐ Other (specify)

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

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

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities

The Member State must ensure that all conditions or restrictions with regard to the safe and effective use of the medicinal product described below are implemented:

The MAH will provide educational material to all physicians who may be involved in treating patients with deferasirox.

Prior to launch of [Deferasirox], the Marketing Authorisation Holder (MAH) shall 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 (dispersible tablets and film-coated tablets/granules)

The MAH shall ensure that, at launch, in each Member State where [Deferasirox] is marketed, all healthcare professionals and patients who are expected to prescribe, dispense and use [Deferasirox] are provided with the following **educational package** for all available formulations for all indications:

- **Physician educational material**
- **Patient information pack**

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

The **physician educational material** should contain:

- **The Summary of Product Characteristics**
- **Guide for healthcare professionals**
- **Prescriber's Checklist**

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

- Description of available deferasirox formulations (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]
    - 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 **Prescriber's Checklist** should contain the following key elements:
- Brief information about recommended doses at the initiation of the treatment
- The requirement and frequencies of different biological monitoring factors (serum ferritin, liver iron concentration, serum creatinine, creatinine clearance and/or plasma cystatin C, proteinuria, serum transaminases, bilirubin, alkaline phosphatase, body weight/ height, auditory and ophthalmic testing, sexual development status on paediatric patients, concomitant medications testing).
- Details about the necessity of dose adjustment during treatment
- Guidance on treatment interruption (in case serum ferritin levels are achieved or any abnormalities have raised)

Prior to launch of deferasirox film-coated tablets, healthcare professionals will receive introductory notification letters as follows:

- **Pharmacists** - a detailed letter explaining the switch between formulations
- **Prescribers** - a letter including the following dossiers:
    - A **prescribers' guide** informing about the switch between formulations in order to address the important potential risk of medication error for deferasirox
    - A **patient's guide** informing about the possibility of co-existing formulations in the EU market, and the differences concerning their administration, in order to address the important potential risk of medication error for deferasirox

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).

Annex 7 - Other supporting data (including referenced material)

1. Exjade EPAR- Assessment report, EMA/639290/2017 (07/09/2021).
2. Exjade- Summary of Product Characteristics.
3. [Deferasirox] 90, 180, 360mg film-coated tablets Summary of Product Characteristics.
4. [Deferasirox] 90, 180, 360mg film-coated tablets Patient Information Leaflet.

Annex 8 – Summary of changes to the risk management plan over time

Not applicable for pre-approval versions.