EU Risk Management Plan
for
Deferasirox Accord 90/180/360 mg film-coated tablets
(Deferasirox)

RMP version to be assessed as part of this application:

RMP Version number	7.0
Data lock point for this RMP	02-Jul-2024
Date of final sign off	10-Jul-2024

Rationale for submitting an updated RMP: This RMP has been updated in-line with Rapporteurs Preliminary Assessment Report (PAR) of Deferasirox Accord film-coated tablets 90/180/360 mg (EMEA/H/C/005156/R/0011).

Summary of significant changes in this RMP: Significant changes have been made in following section of RMP: Part VII (Annex 6).

Other RMP versions under evaluation: Not Applicable

Details of the currently approved RMP:

Version Number	Approved with procedure	Date of approval (opinion date)
6.0	EMEA/H/C/005156/IB/0003	15-Mar-2023

QPPV Name: Ms. Agata Gesiewicz

QPPV Signature: [redacted]

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Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	Deferasirox
Pharmacotherapeutic group(s)(ATC Code)	**Pharmacotherapeutic group(s):** Iron chelating agents **ATC code:** V03AC03
Marketing Authorisation Holder	Accord Healthcare S.L.U., Spain
Medicinal products to which this RMP refers	3
Invented name(s) in European Economic Area (EEA)	Deferasirox Accord 90 mg film-coated tablets Deferasirox Accord 180 mg film-coated tablets Deferasirox Accord 360 mg film-coated tablets
Marketing authorisation procedure	Centralised Procedure (EMEA/H/C/005156)
Brief description of the product	Chemical class: Achiral, tridentate triazole derived from salicylic acid
	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 Deferasirox Accord 90 mg film-coated tablets

	Each film-coated tablet contains 90 mg deferasirox *Excipients with known effect* Each 90 mg tablet also contains 27 mg of lactose (as monohydrate) and 2.95 mg of castor oil. Deferasirox Accord 180 mg film-coated tablets Each film-coated tablet contains 180 mg deferasirox *Excipients with known effect* Each 180 mg tablet also contains 54 mg of lactose (as monohydrate) and 5.9 mg of castor oil. Deferasirox Accord 360 mg film-coated tablets Each film-coated tablet contains 360 mg deferasirox *Excipients with known effect* Each 360 mg tablet also contains 108 mg of lactose (as monohydrate) and 11.8 mg of castor oil.
Hyperlink to the Product Information	Refer Module 1.3.1 for Product Information
Indication(s) in the EEA Current	Deferasirox Accord is indicated for the treatment of chronic iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older. Deferasirox Accord is also indicated for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the following patient groups: - in paediatric patients with beta thalassaemia major with iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) aged 2 to 5 years, - in adult and paediatric patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (<7

<table>
<tr><td></td><td>ml/kg/month of packed red blood cells) aged 2 years and older,
- in adult and paediatric patients with other anaemias aged 2 years and older.
Deferasirox Accord is also indicated for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia (NTDT) syndromes aged 10 years and older.</td></tr>
<tr><td>Dosage in the EEA
Current</td><td><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.
Deferasirox film-coated tablets demonstrate higher bioavailability compared to the deferasirox dispersible tablet formulation. 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 both formulations are shown in the table below:
<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>
</table>
</td></tr>
</table>

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

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

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

Recommended doses for transfusional iron overload

	Film-coated tablets	**Transfusions**	**Serum ferritin**
Starting dose	**14 mg/kg/day**	After 20 units (about 100 ml/kg) of PRBC	Or >1,000 µg/l
Alternative starting doses	21 mg/kg/day	>14 ml/kg/month of PRBC (approx. >4 units/month for an adult)	
	7 mg/kg/day	<7 ml/kg/month of PRBC (approx. <2 units/month for an adult)	
For patients well managed on deferoxamine	One third of deferoxamine dose		
Monitoring			**Monthly**
Target range			**500-1,000 µg/l**
Adjustment steps (every 3-6 months)	**Increase**		**>2,500 µg/l**
	3.5-7 mg/kg/day Up to 28 mg/kg/day		
	Decrease		**<2,500 µg/l**
	3.5-7 mg/kg/day In patients treated with doses >21 mg/kg/day		
	-When target is reached		**500-1,000 µg/l**
Maximum dose	**28 mg/kg/day**		

	Consider interruption		**<500 µg/l**

Starting dose:

The recommended initial daily dose of deferasirox film-coated tablets is 14 mg/kg body weight.

An initial daily dose of 21 mg/kg of deferasirox Accord film coated tablets 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 of deferasirox Accord film coated tablets 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.

For patients already well managed on treatment with deferoxamine, a starting dose of deferasirox 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 film-coated tablets). When these 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.

Dose adjustment:

It is recommended that serum ferritin be monitored every month and that the dose of deferasirox Accord film coated tablets 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. 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 and to minimise the risk of overchelation. If serum ferritin falls consistently below 500 µg/l, an interruption of treatment should be considered.

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. 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 both formulations are shown in the table below:

	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]

Recommended doses for non-transfusion-dependent thalassaemia syndromes

	Film-coated tablets	**Liver iron concentration (LIC)***		**Serum ferritin**
Starting dose	**7 mg/kg/day**	≥5 mg Fe/g dw	or	>800 µg/l
Monitoring				**Monthly**
	Increase	≥7 mg Fe/g dw	or	

Adjustment step (every 3-6 months)	3.5-7 mg/kg/day		or	**>2,000 µg/l**
	Decrease 3.5-7 mg/kg/day	<7 mg Fe/g dw		**≤2,000 µg/l**
Maximum dose	**14 mg/kg/day** For adult patients			
	7 mg/kg/day For paediatric patients			
	7 mg/kg/day For both adults and paediatric patients	not assessed	and	≤2,000 µg/l
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 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 to assess the patient's response to therapy and to minimise the risk of overchelation. 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 of deferasirox accord film coated tablets 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 of deferasirox accord film coated tablets 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. Method of administration For oral use.
Pharmaceutical form(s) and strengths Current:	Film coated tablets, 90 mg; 180 mg; 360 mg
Is the product subject to additional monitoring in the EU?	No

Part II: Safety specification

Module SI – Epidemiology of the indication(s) and target population(s)

Not applicable

Module SII – Non-clinical part of the safety specification

Not applicable

Module SIII – Clinical trial exposure

Not applicable

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

Module SV – Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable

Module SVI – Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Not applicable – there is no potential for misuse for illegal purposes.

Module SVII – Identified and potential risks

The safety concerns of this RMP are in-line with EPAR - Risk-management-plan summary of Exjade (Deferasirox), version 21.2, dated 18-Sep-2023, published by EMA on 30-Jan-2024. There is no change proposed by MAH in these safety concerns mentioned in Module SVIII.

Hence, this section remains "Not applicable".

SVII.1 Identification of safety concerns in the initial RMP submission

Not applicable.

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

Not applicable

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

Module SVIII – Summary of the safety concerns

Table 2: Summary of safety concerns

Important identified risks	• Renal disorders (increased serum creatinine, acute renal failure (ARF), renal tubular disorders [acquired Fanconi's syndrome]) • Increased liver transaminases / Hepatic failure • Gastrointestinal hemorrhage 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 film coated tablets/granules and generic versions of deferasirox dispersible tablets
Missing information	• Long term safety in paediatric NTDT patients aged 10 to 17 years

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file are sufficient for the safety concerns mentioned in "Module SVIII - Summary of the safety concerns".

Specific adverse reaction follow-up checklists are in place for the following risks:

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

Purpose: For collection and reporting of safety information while use of deferasirox.

Targeted Follow-up questionnaire have been appended in Annex 4 of this RMP.

III.2 Additional pharmacovigilance activities

None proposed.

III.3 Summary Table of additional Pharmacovigilance activities

None proposed

Part IV: Plans for post-authorisation efficacy studies

Not applicable

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

V.1 Routine Risk Minimisation Measures

Table 3: 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 (ARF), renal tubular disorders [acquired Fanconi's syndrome])	Routine risk communication: SmPC sections 4.2, 4.3, 4.4, 4.8, 4.9, 5.2 and 5.3 PIL section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Contraindication use in patients with estimated creatinine clearance <60 ml/min are included in SmPC section 4.3 • Recommendation to monitoring renal function test and deferasirox dose adjustment are included in SmPC section 4.4 and PIL section 2. Other routine risk minimisation measures beyond the Product Information: Prescription only status of the product.
Increased liver transaminases / Hepatic failure	Routine risk communication: SmPC sections 4.2, 4.4 and 4.8 PIL sections 2, 3 and 4

Safety concern	**Routine risk minimisation activities**
	Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation to monitoring of liver function test are included in SmPC section 4.4 and PIL section 2. • Recommendation on not to use deferasirox in patients with severe hepatic impairment are included in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Prescription only status of the product.
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: • Advise to monitor signs and symptoms of gastrointestinal ulceration and haemorrhage during deferasirox therapy are included in SmPC section 4.4 • Information on close clinical monitoring when deferasirox is concomitantly used with substances that have known ulcerogenic potentials, such as NSAIDs,

Safety concern	Routine risk minimisation activities
	corticosteroids or oral bisphosphonates are include in SmPC section 4.4 and 4.5 Other routine risk minimisation measures beyond the Product Information: Prescription only status of the product.
Hearing loss	Routine risk communication: SmPC sections 4.4 and 4.8 of PIL section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Information to perform auditory (decreased hearing) testing at regular period of intervals as described in SmPC section 4.4 • Advise to dose reduction or stop the treatment if disturbances are observed during the deferasirox treatment, included in section 4.4 Other routine risk minimisation measures beyond the Product Information: Prescription only status of the product.
Lens opacities, retinal changes and optic neuritis	Routine risk communication: SmPC sections 4.4, 4.8 and 5.3

Safety concern	**Routine risk minimisation activities**
	Routine risk minimisation activities recommending specific clinical measures to address the risk: • Information to perform ophthalmic testing (including fundoscopy) at regular period of intervals is included in SmPC section 4.4 • Advise to dose reduction or stop the treatment if disturbances are observed during the deferasirox treatment included in section 4.4 Other routine risk minimisation measures beyond the Product Information: Prescription only status of the product.
Important Potential Risks	
Compliance with posology and biological monitoring	Routine risk communication: SmPC sections 4.2 and 4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Deferasirox dose and dose adjustment for transfusional iron overload and non-transfusion-dependent thalassaemia syndromes are included in SmPC section 4.2 • Biological laboratory test monitoring for serum creatinine, serum transaminases

Safety concern	Routine risk minimisation activities
	and serum ferritin are included in SmPC section 4.4 Other routine risk minimisation measures beyond the Product Information: Prescription only status of the product.
Medication errors due to switching between Deferasirox film coated tablets/granules and generic versions of deferasirox dispersible tablets	Routine risk communication: SmPC Section 4.2 PIL Section 3 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Dose information of switching from dispersible tablets to film-coated tablets is included in SmPC Section 4.2. Other routine risk minimisation measures beyond the Product Information: Prescription only status of the product
Missing information	
Long term safety in paediatric NTDT patients aged 10 to 17 years	Routine risk communication: SmPC sections 4.2 and 4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Information on deferasirox dosing in paediatric patients with non-transfusion-

Safety concern	Routine risk minimisation activities
	dependent thalassaemia syndromes is included in SmPC section 4.2 and 4.4 • Advise to monitor laboratory test of liver iron concentration and serum ferritin as per frequency included in SmPC section 4.2 and 4.4. Other routine risk minimisation measures beyond the Product Information: Prescription only status of the product.

V.2 Additional Risk Minimisation Measures

Additional Risk Minimisation Measures have been proposed for following risks in-line with innovator medicinal product Exjade (deferasirox).

- Compliance with posology and biological monitoring
- Medication errors due to switching between Deferasirox film-coated tablets/granules and generic versions of deferasirox dispersible tablets

Proposed additional risk minimisation measures are listed below and are summarised in Annex *6*.

❖ **<u>Guide for Healthcare Professionals</u>** (which also includes a prescriber checklist)

Objectives:

To increase an awareness of healthcare professionals regarding risk of non-compliance of the posology and biological monitoring and medication errors due to switching between Deferasirox film-coated tablets/granules and generic versions of deferasirox dispersible tablets.

Rationale for the additional risk minimisation activity:

To minimise the risks of non-compliance of the posology and biological monitoring and

medication errors due to switching between Deferasirox film-coated tablets/granules and generic versions of deferasirox dispersible tablets.

To provide a prescribing decision tool for physicians to support calculation of appropriate posology and tracking of biological monitoring (prescriber checklist)

Target audience and planned distribution path:

Physicians and other healthcare professionals who may prescribe Deferasirox Accord and pharmacists

Plans to evaluate the effectiveness of the interventions and criteria for success:

Routine pharmacovigilance including analysis of ADR reports to assess compliance with Product Information recommendations will allow assessing and judging the success of the risk minimisation measures.

❖ **Patient education material**

Objectives:

To increase an awareness of patients regarding the risk of non-compliance of the posology and biological monitoring and medication errors due to switching between Deferasirox film-coated tablets/granules and generic versions of deferasirox dispersible tablets.

Rationale for the additional risk minimisation activity:

To minimise the risks of non-compliance of the posology and biological monitoring and medication errors due to switching between Deferasirox film-coated tablets/granules and generic versions of deferasirox dispersible tablets.

Target audience and planned distribution path:

Patients who are taking the Deferasirox Accord, their care takers and Physicians and other healthcare professionals who may prescribe Deferasirox Accord, and pharmacists

Plans to evaluate the effectiveness of the interventions and criteria for success:

Routine pharmacovigilance including analysis of ADR reports to assess compliance with Product Information (PI) recommendations will allow assessing and judging the success of the risk minimisation measures.

V.3 Summary of risk minimisation measures

Table 4: 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 (ARF), renal tubular disorders [acquired Fanconi's syndrome])	Routine risk minimisation measures: • SmPC sections 4.2, 4.3, 4.4, 4.8, 4.9, 5.2 and 5.3 • PIL section 2 and 4 • Contraindication use in patients with estimated creatinine clearance <60 ml/min are included in SmPC section 4.3 • Recommendation to monitoring renal function test and deferasirox dose adjustment are included in SmPC section 4.4 and PIL section 2. • Prescription only status of the product Additional risk minimisation measures: None	Routine pharmacovigilance beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up checklist has been proposed for this safety concern. Additional pharmacovigilance activity: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Increased liver transaminases / Hepatic failure	Routine risk minimisation measures: • SmPC sections 4.2, 4.4 and 4.8 • PIL sections 2, 3 and 4 • Recommendation to monitoring of liver function test are included in SmPC section 4.4 and PIL section 2. • Recommendation on not to use deferasirox in patients with severe hepatic impairment are included in SmPC section 4.4. • Prescription only status of the product. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up checklist has been proposed for this safety concern. Additional pharmacovigilance activity: None
Gastrointestinal hemorrhage and ulcers; esophagitis	Routine risk minimisation measures: • SmPC sections 4.4, 4.5 and 4.8 • Advise to monitor signs and symptoms of gastrointestinal ulceration and haemorrhage during	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up checklist has been proposed for this safety concern.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	deferasirox therapy are included in SmPC section 4.4 • Information on close clinical monitoring when deferasirox is concomitantly used with substances that have known ulcerogenic potentials, such as NSAIDs, corticosteroids or oral bisphosphonates are include in SmPC section 4.4 and 4.5 • Prescription only status of the product. Additional risk minimisation measures: None	Additional pharmacovigilance activity: None
Hearing loss	Routine risk minimisation measures: • SmPC sections 4.4 and 4.8 of • PIL section 2 and 4 • Information to perform auditory (decreased hearing) testing at regular period of intervals as	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up checklist has been proposed for this safety concern.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	described in SmPC section 4.4 • Advise to dose reduction or stop the treatment if disturbances are observed during the deferasirox treatment, included in section 4.4 • Prescription only status of the product. Additional risk minimisation measures: None	Additional pharmacovigilance activity: None
Lens opacities, retinal changes and optic neuritis	Routine risk minimisation measures: • SmPC sections 4.4, 4.8 and 5.3 • Information to perform ophthalmic testing (including fundoscopy) at regular period of intervals is included in SmPC section 4.4 • Advise to dose reduction or stop the treatment if disturbances are observed during the deferasirox	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up checklist has been proposed for this safety concern. Additional pharmacovigilance activity: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	treatment included in section 4.4 • Prescription only status of the product. Additional risk minimisation measures: None	
Important Potential Risks		
Compliance with posology and biological monitoring	Routine risk minimisation measures: • SmPC sections 4.2 and 4.4 • Deferasirox dose and dose adjustment for transfusional iron overload and non-transfusion-dependent thalassaemia syndromes are included in SmPC section 4.2 • Biological laboratory test monitoring for serum creatinine, serum transaminases and serum ferritin are included in SmPC section 4.4 • Prescription only status of the product.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None: Additional pharmacovigilance activity: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: Educational materials for physicians (which also includes a prescriber checklist) and patients	
Medication errors due to switching between Deferasirox film coated tablets/granules and generic versions of deferasirox dispersible tablets	Routine risk minimisation measures: • SmPC Section 4.2 • PIL Section 3 • Dose information of switching from dispersible tablets to film-coated tablets is included in SmPC Section 4.2. • Prescription only status of the product. Additional risk minimisation measures: • Educational materials for physicians (which also includes a prescriber checklist) and patients	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activity: None
Missing information		
Long term safety in paediatric NTDT	Routine risk minimisation measures: • SmPC sections 4.2 and 4.4	Routine pharmacovigilance activities beyond adverse

Safety concern	Risk minimisation measures	Pharmacovigilance activities
patients aged 10 to 17 years	• Information on deferasirox dosing in paediatric patients with non-transfusion-dependent thalassaemia syndromes is included in SmPC section 4.2 and 4.4 • Advise to monitor laboratory test of (liver iron concentration and serum ferritin as per frequency included in SmPC section 4.2 and 4.4. • Prescription only status of the product. Additional risk minimisation measures: None	reactions reporting and signal detection: None Additional pharmacovigilance activity: None

Part VI: Summary of the risk management plan

Summary of risk management plan for Deferasirox Accord 90/180/360 mg film-coated tablets (deferasirox)

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

Deferasirox Accord 90/180/360 mg film-coated tablet's product information and its package leaflet give essential information to healthcare professionals and patients on how Deferasirox Accord 90/180/360 mg film-coated tablets should be used.

This summary of the RMP for Deferasirox Accord 90/180/360 mg film-coated tablets should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of European Public Assessment Report for Deferasirox.

Important new concerns or changes to the current ones will be included in updates of Deferasirox Accord 90/180/360 mg film-coated tablet's RMP.

I. The medicine and what it is used for

Deferasirox Accord is indicated for the treatment of chronic iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older.

Deferasirox Accord is also indicated for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the following patient groups:

- In paediatric patients with beta thalassaemia major with iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) aged 2 to 5 years,
- In adult and paediatric patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells) aged 2 years and older,

- In adult and paediatric patients with other anaemias aged 2 years and older.

Deferasirox Accord is also indicated for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older.

It contains deferasirox as the active substance and it is given by oral route.

Further information about the evaluation of Deferasirox Accord 90/180/360 mg film-coated tablets' benefits can be found in Deferasirox Accord 90/180/360 mg 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-accord

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

Important risks of Deferasirox Accord 90/180/360 mg film-coated tablets, together with measures to minimise such risks and the proposed studies for learning more about Deferasirox Accord 90/180/360 mg film-coated tablet's 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 Product Information (PI) 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 Accord 90/180/360 mg film-coated tablets, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

[redacted]

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment and signal management activity, 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 Accord 90/180/360 mg 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 Accord 90/180/360 mg 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 administered. 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 Accord 90/180/360 mg 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);

Important identified risks	• Renal disorders (increased serum creatinine, acute renal failure (ARF), renal tubular disorders [acquired Fanconi's syndrome]) • Increased liver transaminases / Hepatic failure • Gastrointestinal hemorrhage 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 film coated tablets/granules and generic versions of deferasirox dispersible tablets

Missing information	• Long term safety in paediatric NTDT patients aged 10 to 17 years

II.B Summary of important risks with additional risk minimization measures

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important Identified Risks: Renal disorders (increased serum creatinine, acute renal failure (ARF), renal tubular disorders [acquired Fanconi's syndrome])	
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.2, 4.3, 4.4, 4.8, 4.9, 5.2 and 5.3 • PIL section 2 and 4 • Contraindication use in patients with estimated creatinine clearance <60 ml/min are included in SmPC section 4.3 • Recommendation to monitoring renal function test and deferasirox dose adjustment are included in SmPC section 4.4 and PIL section 2. • Prescription only status of the product Additional risk minimisation measures: • None
Important Identified Risks: Increased liver transaminases / Hepatic failure	
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.2, 4.4 and 4.8 • PIL sections 2, 3 and 4 • Recommendation to monitoring of liver function test are included in SmPC section 4.4 and PIL section 2.

	• Recommendation on not to use deferasirox in patients with severe hepatic impairment are included in SmPC section 4.4. • Prescription only status of the product. Additional risk minimisation measures: • None
Important Identified Risks: Gastrointestinal hemorrhage and ulcers; esophagitis	
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.4, 4.5 and 4.8 • Advise to monitor signs and symptoms of gastrointestinal ulceration and haemorrhage during deferasirox therapy are included in SmPC section 4.4 • Information on close clinical monitoring when deferasirox is concomitantly used with substances that have known ulcerogenic potentials, such as NSAIDs, corticosteroids or oral bisphosphonates are include in SmPC section 4.4 and 4.5 • Prescription only status of the product. Additional risk minimisation measures: • None
Important Identified Risks: Hearing loss	
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.4 and 4.8 • PIL sections 2 and 4

	• Information to perform auditory (decreased hearing) testing at regular period of intervals as described in SmPC section 4.4 • Advise to dose reduction or stop the treatment if disturbances are observed during the deferasirox treatment, included in section 4.4 • Prescription only status of the product. Additional risk minimisation measures: • None
Important Identified Risks: Lens opacities, retinal changes and optic neuritis	
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.4, 4.8 and 5.3 • Information to perform ophthalmic testing (including fundoscopy) at regular period of intervals is included in SmPC section 4.4 • Advise to dose reduction or stop the treatment if disturbances are observed during the deferasirox treatment included in section 4.4 • Prescription only status of the product. Additional risk minimisation measures: • None
Important Potential Risk: Compliance with posology and biological monitoring	
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.2 and 4.4 • Deferasirox dose and dose adjustment for transfusional iron overload and non-transfusion-dependent thalassaemia syndromes are included in SmPC section 4.2

	• Biological laboratory test monitoring for serum creatinine, serum transaminases and serum ferritin are include in SmPC section 4.4 • Prescription only status of the product. Additional risk minimisation measures: Educational materials for physicians (which also includes a prescriber checklist) and patients
Important Potential Risk: • Medication errors due to switching between Deferasirox film coated tablets/granules and generic versions of deferasirox dispersible tablets	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2 • PIL Section 3 • Dose information of switching from dispersible tablets to film-coated tablets is included in SmPC Section 4.2. • Prescription only status of the product. Additional risk minimisation measures: Educational materials for physicians (which also includes a prescriber checklist) and patients
Missing information: Long term safety in paediatric NTDT patients aged 10 to 17 years	
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.2 and 4.4 • Information on deferasirox dosing in paediatric patients with non-transfusion-dependent thalassaemia syndromes is included in SmPC section 4.2 and 4.4

	• Advise to monitor laboratory test of (liver iron concentration and serum ferritin as per frequency included in SmPC section 4.2 and 4.4. • Prescription only status of the product. 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 Accord 90/180/360 mg film-coated tablets.

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

There are no studies required for Deferasirox Accord 90/180/360 mg film-coated tablets.

Annex 4 – Specific adverse drug reaction follow-up forms

This annex contains the specific adverse event targeted follow-up checklists used to collect additional data for the following deferasirox RMP risks:

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

Targeted follow-up checklists:

Deferasirox Serum Creatinine Increase checklist

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

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

[redacted]

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]				

<u>Patient History:</u>

Does the patient have a history of any of the following prior to the start of Deferasirox?

Check all that apply

☐ Renal disease ☐ Congestive heart failure

☐ Diabetes mellitus ☐ Hypertension

☐ Autoimmune disease ☐ Disease of the prostate

☐ Other relevant history *(please specify)* ☐ None of the above

[redacted]

Concomitant medication:

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

☐ ACE inhibitors ☐ Diuretics ☐ Analgesics (e.g. COX-2 Immunosuppressants inhibitors, NSAIDs) ☐ None of the above

List details for the above drugs as appropriate:

Drug	Route of administration	Dosing regimen or daily dose	Dates of treatment *(dd/mm/yyyy)*		Indication for use
			Start date	Stop date	

Renal Impairment or Failure checklist

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

☐ Fever	☐ Increased urinary output	☐ Pain upon urinating
☐ Dehydration	☐ Decreased urinary output	☐ Discolored urine
☐ Arthralgia	☐ Difficulty starting or maintaining urine stream	☐ Pain around costovertebral angle
☐ Edema	☐ Urinary urgency	☐ Lethargy
☐ Skin rash	☐ Infections	☐ Confusion
☐ Flank pain	☐ Burning sensation upon urinating	☐ 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	☐ Albumin	☐ CT scan
☐ Serum creatinine	☐ Serum total protein	☐ Renal ultrasound
☐ Hemoglobin	☐ Myoglobin	☐ Cystoscopy
☐ CPK	☐ Electrolytes	☐ Echocardiogram
☐ Urinalysis	☐ Glomerular filtration rate	☐ Chest X-ray
☐ Metabolic Acidosis	☐ Blood pressure	☐ Abdominal X-ray
☐ Antinuclear antibodies	☐ C-reactive protein	☐ Magnetic resonance imaging
☐ Liver function tests	☐ Lipid levels	☐ Electrocardiogram
☐ Sedimentation rate	☐ Coagulation studies	☐ None of the above

Patient History:

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	☐ Multiple myeloma	☐ Exposure to chemical dyes
☐ Diabetes mellitus (Type I or Type 11)	☐ Urinary tract infection	☐ Myocardial infarction
☐ Reflux nephropathy	☐ Thromboembolic disease	☐ Coronary artery disease
☐ Renal disease (including nephrolithiasis)	☐ Obstructive uropathy	☐ Hypercalcemia
☐ Autoimmune disease	☐ Sickle cell disease	☐ History of renal transplant
☐ Hypertension	☐ Hyperuricemia	☐ Hepatorenal syndrome
☐ Extensive burns	☐ Renal arteries obstructions	☐ Hemolytic uremic syndrome
☐ Kidney or bladder problems/Stones	☐ Drug allergies *(please specify)*	☐ Dehydration
☐ Disease of the prostate	☐ Injury (crush or extensive blunt)	☐ Rhabdomyolysis
☐ Intravenous contrast material	☐ Hemorrhage	☐ Polycystic kidney disease
☐ Other relevant history *(please specify)*		☐ None of the above

_____

_____

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

☐ ACE inhibitors	☐ Diuretics	☐ Analgesics (e.g. COX-2 inhibitors, NSAIDS)
☐ Immunosuppressants	☐ Antineoplastic agents	
☐ Lithium	☐ Vitamin D3	☐ Antimicrobials (e.g. penicillin, sulfonamides)
☐ Calcium	☐ Herbal medication *(please specify)*	
☐ Aminoglycosides	☐ Amphotericin	☐ Mercury
☐ Angiotensin II receptor blockers	☐ Diuretics	☐ Gold
☐ Foscarnet	☐ None of the above	

_____

_____

[redacted]

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

_____

_____

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)*

_____

_____

Deferasirox Gastrointestinal Ulcers & Bleed checklist

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				
☐ 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

[redacted]

Patient History:

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

☐ Epigastric pain ☐ Esophagitis

☐ Gastritis ☐ Gastrointestinal bleed

☐ Gastrointestinal ulcer ☐ Hemorrhoids

☐ Bleeding disorders/abnormal coagulation tests

☐ Other relevant history - *please specify:* ☐ None of the above

_____

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

☐ Anticoagulants ☐ Bisphosphonates

☐ NSAIDs ☐ Steroids

☐ None of the above

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

☐ Antacids ☐ Proton pump Inhibitors

☐ H2 blockers ☐ None of the above

Deferasirox Hearing Loss checklist

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:

_____

[redacted]

_____

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]				

Deferasirox Lens Opacities/Cataracts checklist

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 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: _____

Results: _____

☐ **No**

☐ **Unknown**

Patient History:

Does the patient have a history of Lens opacities / Cataracts prior to the start of the suspect drug?

☐ Yes ☐ No

[redacted]

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]				

Annex 6 – Details of proposed additional risk minimisation activities

Prior to the launch of Deferasirox Accord in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed to increase an awareness of healthcare professionals regarding risk of non-compliance of the posology and biological monitoring and medication errors due to switching between Deferasirox film-coated tablets/granules and generic versions of deferasirox dispersible tablets.

The risk of medication error is due to switching between Deferasirox film coated tablets/granules and generic versions of deferasirox dispersible tablets 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 Accord is marketed, all healthcare professionals and patients/carers who are expected to prescribe / dispense / use Deferasirox Accord have access to/are provided with the following educational package:

- Guide for Healthcare Professionals (which also includes a prescriber checklist)
- Patient education material

The physician educational material contains:

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

<u>Guide for Healthcare Professionals</u>

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 (e.g. dispersible tablets, film-coated tablets and granules) in the EU.
    - Different posology regimen

[redacted]

- Different conditions of administration
- Dose conversion table when switching from one formulation to another (Deferasirox film-coated tablets/granules and generic versions of deferasirox dispersible tablets.

- 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 over chelation 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 education material

Patient Education Material

Patient education material 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)